BENHA MEDICAL JOURNAL bmj

Print ISSN 1110-208X.

Online ISSN 2357-0016

Original article

Significance of AXL Expression in Chronic Pancreatitis and Pancreatic Ductal Adenocarcinoma (an Immunohistochemical Study)

Ebtehal M. Abdel-Aal[a] , Nehal S. Abd El Wahab[a], Heba M. Rashad[a] , Mona A. Aboelkheir[a], Shrouk E. Gamil[a], Shaymaa S. Ahmed[b]

[a] Pathology Department, Faculty of Medicine Benha University, Egypt.

[b] Pathology Department, National Liver Institute, Menofia University, Egypt.

Corresponding to:

Dr. Shrouk E. Gamil.
Pathology Department, Faculty of Medicine Benha University, Egypt.

Email:
shroukelsaied27@gmail.com

Received: 29 March 2025

Accepted:14 May 2025

Abstract:

Background: Chronic pancreatitis is a well-established risk factor of pancreatic cancer. Pancreatic ductal adenocarcinoma is the most common histo-type of pancreatic cancer and considered the third leading cause of cancer deaths in the US. Different markers were used as diagnostic methods for PDAC as CA19-9 which have low sensitivity and specificity. AXL is a receptor tyrosine kinase (RTK) belonging to the tumor-associated macrophage (TAM) protein family that is involved in tumorigenesis and progression of many cancers. Aim: To evaluate the significance of (AXL) expression in chronic pancreatitis & PDAC and to compare & correlate (AXL) expression with the available clinicopathological data. **Material and methods:** This is a retrospective study using microarray technique carried upon selected formalin-fixed paraffin-embedded biopsy specimens of 50 PDAC cases and 10 cases of chronic pancreatitis. Clinicopathological characteristics of the examined cases were correlated with immunohistochemistry of AXL. **Results:** There is a significant statistical correlation between PDAC and chronic pancreatitis as regard expression of AXL with more frequency of positive expression among carcinoma cases (P=0.002). There is a significant statistical correlation between AXL scoring and different histological grade of studied cases, tumor necrosis, perineural invasion and TNM stage of pancreatic ductal adenocarcinoma (P value= 0.001, 0.006, 0.002 and P=0.05 respectively). **Conclusion:** The expression of AXL is more in PDAC than chronic pancreatitis cases indicating that AXL could have a role in the development of PDAC. AXL showed a significant correlation with tumor grade, tumor necrosis, with sensitivity 84%, specificity 90% and accuracy 89%.

Keywords: Pancreatic ductal adenocarcinoma; chronic pancreatitis; AXL; immunohistochemistry.

Introduction

The yearly incidence of chronic pancreatitis (CP) is increasing, and the overall CP hospitalization cost has increased by 1.4 times during the last 7 years, indicating that CP remains a heavy health burden [(1)].

Pancreatic cancer (PC) is the 12th most common cancer worldwide [(2)]. It ranks as the 12th commonest cancer in men and the 11th commonest cancer in women [(3)].

In the United States, the cancer death rate for pancreatic cancer has increased slightly (by 0.2% per year) since the mid-2000s according to the American Cancer Society [(4)].

In Egypt, pancreatic cancer is the 11th most common cancer with an incidence rate of about 2.2% among Egyptian cancer patients [(5).]

Genetic and epigenetic abnormalities [(٦),] dysregulation of the epithelial-mesenchymal (EMT) transition, immunological response, and inflammation- all contribute to the development of pancreatic ductal adenocarcinoma (PDAC) [(7)]. KRAS, cyclin-dependent kinase inhibitor 2A (CDKN2A)/P16, mothers against decapentaplegic homolog 4 (SMAD4), and tumor protein 53 (TP53)- are the most frequently impacted by somatic mutations in this neoplasm [(8)].

Although different markers are used as diagnostic methods for pancreatic ductal adenocarcinoma such as; carbohydrate antigen 19-9 (CA 19-9), their low sensitivity and specificity necessitates the importance of searching for other markers [(9).]

AXL receptor tyrosine kinase (AXL) is a receptor tyrosine kinase (RTK) belonging to the tumor-associated macrophage (TAM) protein family along with two other members: tyrosine-protein kinase receptor (TYRO3) and proto-oncogene tyrosine-protein kinase MER (MERTK) receptors [(10).]

A trial to assess the role of AXL in pancreatic ductal adenocarcinoma and its function in distinguishing it from chronic pancreatitis is necessary. The aim of this study to evaluate the possible significance of (AXL) immunohistochemical expression in chronic pancreatitis & pancreatic ductal adenocarcinoma and correlate its expression with different clinicopathological parameters.

Material and methods

Study group:

This is a retrospective study using microarray technique carried upon selected formalin-fixed paraffin-embedded biopsy specimens of ٥٠ pancreatic ductal adenocarcinoma (PDAC) cases, 10 cases of chronic pancreatitis and 6 cases of normal pancreatic tissue as a control group, retrieved from the archives of the Pathology Department, National Liver Institute, Menoufia University and from the archives of the Pathology Department of Benha Faculty of Medicine in the period from January 2019 to December 2023. Approval from the ethics committee from Benha faculty of Medicine {M.S.17.8.2023}. The specimens were obtained by the Whipple procedure. Inclusion criteria: The cases selected were PDAC and chronic pancreatitis on the basis of the availability of the blocks for serial cutting and histological examination. Exclusion criteria: cases of other types of pancreatic cancer rather than PDAC cases and cases with previous history of chemotherapy.

Histopathological studies:

Hematoxylin and eosin (H&E) stained slides were used to identify viable, representative areas of each sample which is circled with a pilot pen. Tissue cores with a diameter of 1.5µ from the predefined regions of each specimen in donor paraffin block were punched manually using a tissue arrayer's needle set provided by the tissue microarrayer instrument manufacturing company (Breecher Instrument, USA). We arrayed the cores in triplicate on a recipient paraffin block, into a ready-made hole.

Two observers reviewed the microscopic sections from all the cases, unaware of their diagnosis. The studied parameters included histological grade according to College of American Pathologists (CAP), tumor necrosis, lympho-vascular& perineural invasion, resection margins, regional lymph nodes and TNM pathological stage according to WHO [11].

AXL immunohistochemical study:

immunohistochemical staining, two positive slides were prepared:

Slides were immunostained according to manufacturer's instructions using a standard labelled streptavidin-biotin system ***(Dako Cytomation, Denmark, A/S).*** Antigen retrieval was performed using high? PH EDETA buffer solution for 20 min followed by 20 min cooling at room temperature. The slides were immunostained with AXL rabbit polyclonal antibody (ES6771, ELK Biotechnology, USA) at a dilution of 1:50, at 4°C overnight. Application of secondary antibody by using 1-2 drops of biotinylated polyvalent secondary antibody was done. Finally, the detection of bound antibody was accomplished using a prepared substrate-chromogen solution (that contained one drop of DAB (CELL MARQUE, Rev.3.0. CMC958080030, USA) chromogen for 1 min. The slides were counter-stained with Mayer's hematoxylin (Abcam, ab220365) for 30–60 seconds. Mounting the cover slip, using Dibutylphthalate Polystyrene Xylene (DPX) mounting medium was performed [12]. Negative control was performed by omitting the primary antibody and positive control was human tonsils.

Interpretation of AXL expression:

The expression was considered positive if any pancreatic ductal cells showed brownish cytoplasmic staining. The assessment was done using immunoreactive score (IRS) as follows: the intensity of cytoplasmic staining was scored (no staining = 0, weak staining = 1, moderate staining = 2, strong staining = 3) and for the extent of stained cells by percentage (0-100%). The final IRS was the product of the intensity score multiplied by the extent score. The value line of score between high (201-300), moderate (101-200) and low (1-100) [12].

Statistical analysis:

The clinico-pathological data were recorded on a report form. These data were tabulated and analyzed using the computer program Statistical Package for Social Science (SPSS version 26 for windows; SPSS Inc., Chicago, Illinois, USA) to obtain:

Descriptive statistics were calculated for the data in the form of Mean and standard deviation for quantitative data and Frequency and distribution for qualitative data. P value is considered significant if <0.05. Receiver-operating characteristic curve (ROC) curve- was used to assess validity of AXL immunohistochemical expression by detecting sensitivity, specificity and accuracy to differentiate between PDAC and chronic pancreatitis cases.

Results:

Clinicopathological results:

The age of the examined chronic pancreatitis cases varied from 46 to 69 years with mean of 58.8±7.28.

The age of the studied PDAC cases ranged from 34 to 76 years with the mean of 57.86±10.4. Twenty-seven cases (54%) were below 60 years old while 23 cases (46%) were above 60 years old. Tumor size of studied pancreatic ductal adenocarcinoma cases ranged from 2.5 to 8 cm. The grade distribution in pancreatic ductal adenocarcinoma cases was mostly grade II (44%). Most cases did not show necrosis (86.0%). Most cases of pancreatic duct adenocarcinoma showed no lympho-vascular invasion (70%) but most cases showed perineural invasion (94%). Most cases showed free resection margin (70%). Most cases showed positive lymph nodes (72%). Most cases were stage II (62%), **(Table 1).**

Immunohistochemical results (figure 1 A, B, C and D):

In control cases, AXL showed no expression.

In chronic pancreatitis cases, AXL H score varied from 0 to 30 with mean of 10.2±10.2. AXL H score grading was distributed as following; 3 cases (23.1%) showed low expression and 7 cases (43.8%) showed negative expression.

AXL showed cytoplasmic expression in malignant cells of PDAC cases. AXL H score varied from 0 to 290 with mean of 144.7±92.23. AXL H score grading was distributed as following; 15 cases were high expression, 16 cases were moderate expression, 10 cases were low expression and 9 cases were negative expression.

A Statistically significant variance between PDAC and chronic pancreatitis as regard expression of AXL with more frequency of positive expression among carcinoma cases. Also, high and moderate expression was detected among carcinoma cases only (P-value equal 0.002), **(Table 2).**

A statistically significant association was found between AXL scoring and tumor grade, tumor necrosis, perineural invasion and pathological TNM staging (P value= 0.001, 0.006, 0.002 and P=0.05 respectively). While a statistically insignificant association has been found between AXL scoring and patient age, sex, tumor size, lympho-vascular invasion, resection margin and lymph node status of studied pancreatic ductal adenocarcinoma cases (P value=0.584, 0.549, 0.990, 0.794, 0.951 and 0.473 respectively), (**Table 3)**.

Area under curve for H score in differentiating between chronic pancreatitis cases versus PDAC cases was excellent (AUC=0.986, 95% CI: 0.818-0.974) with the best detected cut off point is 15 yielding sensitivity 84% and specificity 90%. Positive predictive value (PPV) was 45%, negative predictive value (NPV) was 100% and accuracy was 89%.

Table (1): Clinicopathological results of studied PDAC cases :

Clinicopathological Parameter		Number	Percentage%
Age	<60 years	23	54
	≥60 years	27	46
Sex	Male	32	64
	Female	18	36
Tumor size	<4 cm	20	40
	≥4 cm	30	60
Histological grade	Grade I	10	20
	Grade II	22	44
	Grade III	18	36
Necrosis	Negative	43	86
	Positive	7	14
Lympho-vascular invasion	Absent	35	70
	Present	15	30
Perineural invasion	Negative	3	6
	Positive	47	94
Resection margin	Free	35	70
	Involved	15	30
Lymph node involvement	N0	14	28
	N1	23	46
	N2	13	26
TNM staging	**I**	0	0
	II	31	62
	III	19	38
Total		50	100

Abbreviations….

PDAC: Pancreatic ductal adenocarcinoma CP: chronic pancreatitis. AXL; Receptor tyrosine kinase.

Table (2) Comparison of AXL expression between studied groups:

AXL expression	Total number=60	PDAC N	Chronic pancreatitis N	Test of significance
High	15	15	0	
Moderate	16	16	0	χ^2=15.03
Low	13	10	3	P=0.002*
Negative	16	9	7	

χ^2=Chi-Square test, *statistically significant

Table (3) Relation between AXL expression and all clinicopathological features among PDAC cases:

	Total number=50	AXL expression High	Moderate	Lo	Negative	Test of significance
Age groups						
<60	27	9(33.3%)	9(33.3%)	6(22.2%)	3(11.1%)	χ^2=1.94
≥60	23	6(26.1%)	7(30.4%)	4(17.4%)	6(26.1%)	P=0.584
Sex						
Male	32	11(34.4%)	8(25%)	7(21.9%)	6(18.8%)	χ^2=2.11
Female	18	4(22.2%)	8(44.4%)	3(16.7%)	3(16.7%)	P=0.549
Tumour size						χ^2=0.116
<4 cm	20	6(30%)	6(30%)	4(20%)	4(20%)	P=0.990
≥4 cm	30	9(30%)	10(33.3%)	6(20%)	5(16.7%)	
Histologic Grade						
Grade I	10	0	0	5(50%)	5(50%)	χ^2=35.72
Grade II	22	3(13.6%)	13(59.1%)	3(13.6%)	3(13.6%)	P<0.001*
Grade III	18	12(66.7%)	3(16.7%)	2(11.1%)	1(5.6%)	
Necrosis						
Negative						
Positive	43	9(20.9%)	15(34.9%)	10(23.3%)	9(20.9%)	χ^2=12.31
	7	6(85.7%)	1(14.3%)	0	0	P=0.006*
Lymphovascular						χ^2=1.03
invasion	35	11(31.4%)	10(28.6%)	8(22.9%)	6(17.1%)	P=0.794
Absent	15	4(26.7%)	6(40%)	2(13.3%)	3(20%)	
Present						
Perineural invasion		0	0	0(0)	3(100%)	χ^2=14.53
Negative	3	15(31.9%)	16(34.0%)	10(21.3%)	6(12.8%)	P=0.002*
Positive	47					
Resection margin						χ^2=0.351
Free	٣٥	10(28.6%)	11(31.4%)	7(20%)	7(20%)	P=0.951
Involved	١٥	5(33.3%)	5(33.3%)	3(20%)	2(13.3%)	
LN grade						
N0	14	2(14.3%)	5(35.7%)	2(14.3%)	5(35.7%)	χ^2=5.57
N1	23	8(34.8%)	7(30.4%)	5(21.7%)	3(13%)	P=0.473
N2	13	5(38.5%)	4(30.8%)	3(23.1%)	1(7.7%)	
Pathological TNM staging						
I	0	0	0	0	0	
II	31	9(29%)	7(22.6%)	6(19.4%)	9(29%)	χ^2=7.82
III	19	6(31.6%)	9(47.4%)	4(21.1%)	0	P=0.05*

χ^2=Chi-Square test ,*Statistically significant

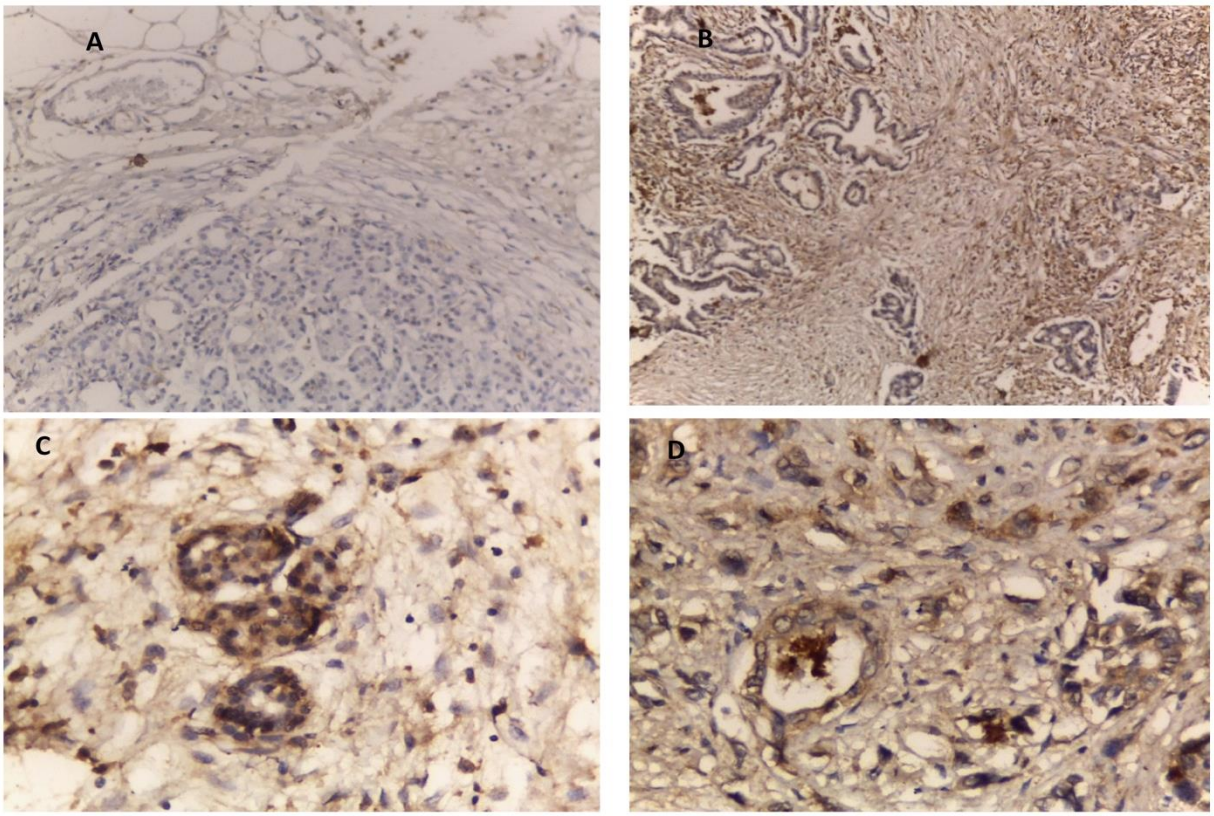

Figure (1 A) A case of chronic pancreatitis showed no AXL cytoplasmic expression in the ductal cells (ABC, x200).
Figure (1 B) A case of PDAC (grade I) showed low AXL intensity involving 60% of core with H score=60 (ABC, x200).
Figure (1 C) A case of PDAC (grade II) showed moderate AXL intensity involving 65% of core with H score=130 (ABC, x200).
Figure (1 D) A case of PDAC(grade III) showed high AXL intensity involving 90% of core with H score= 270 (ABC, x200).

Discussion:

In the United States, the cancer death rate for pancreatic cancer has increased slightly (by 0.2% per year) and the mortality of pancreatic cancer is predicted to increase over time, reaching the second-highest overall cancer mortality rate by 2030 [4].
In Egypt, pancreatic cancer is the 11th most common cancer with incidence rates varied greatly by urban and rural areas and by district of residence in the Nile Delta region of Egypt. Incidence rates were 1.3 times higher in urban compared to rural areas [5].
Together with two other members of the tumor-associated macrophage (TAM) protein family, tyrosine-protein kinase receptor (TYRO3) and proto-oncogene tyrosine-protein kinase MER (MERTK) receptors, AXL receptor tyrosine kinase (AXL) is a receptor tyrosine kinase (RTK) [10].

AXL has various cellular processes including proliferation, invasiveness, migration, epithelial-to-mesenchymal transition, angiogenesis, and immune modulation that are critical for the development, growth, and spread of tumors [13].
In this study, positive immunostaining for AXL was detected in the cytoplasm of pancreatic ductal adenocarcinoma (82%) but not in the 6 control cases of normal pancreatic tissue. As regard the chronic

pancreatitis, the marker gives faint staining or no staining and this difference was statistically significant one (P=0.002) which matched with Martínez-Bosch et al., [12] who found that AXL was not expressed in normal pancreatic tissue or chronic pancreatitis. Also, matched with the study of Vázquez-Bellón et al [14] who found that AXL was not detected in normal pancreatic tissue or chronic pancreatitis. This indicates that AXL has a role in pathogenesis of PDAC as AXL is a driver of diverse cellular processes that are critical for the development, growth, and spread of tumors, including proliferation, invasiveness and migration, epithelial-to-mesenchymal transition, angiogenesis, and immune modulation. However, Song et al., [15] found that non-neoplastic pancreatic ductal tissue samples showed a focally distributed mild AXL staining. This may be due to different antibody clones used and different number of cases.

In this work, AXL expression was significantly related to the tumor grade (P<0.001). This is consistent with Martínez-Bosch, N., et al., (2022), Yuan J, et al., (2024) and Oz, O., et al., (2023) [12,16&17] who stated that significant associations were found between AXL and tumor grade in pancreatic ductal adenocarcinoma (P<0.0001). Disagreeing with Yu, W., et al ., (2019) [18] who found that AXL expression was not significantly associated with the tumor grade (P=0.546). This may be due to technical variation, different tissue processing and different antibody clones used. The increased expression of AXL in high-grade indicates that AXL has a critical role in the development, growth, and spread of tumors, including proliferation, invasiveness and migration.

In this work, AXL expression was significantly related to the tumor necrosis (p=0.006). This is consistent with Yu, W., et al ., (2019) [18] who stated that significant associations were found between AXL and tumor necrosis in pancreatic ductal adenocarcinoma (P<0.001).

There was a high statistical significant relation between AXL expression and perineural invasion in our study (P=0.002) matching with Oz, O., et al., (2023) [17] who found that AXL positivity was significantly related to perineural invasion in their cases ($P < 0.000$). Disagreeing with Yu, W., et al ., (2019) [18] who found that AXL expression was not significantly associated with perineural invasion (P=0.466) due to different primary antibodies used among both studies, different interpretation method and different tumor behavior.

Positive association of AXL with tumor necrosis and perineural invasion could indicate that AXL has a role in tumor proliferation, invasiveness, migration and angiogenesis. AXL has been implicated as a cancer driver and correlated with poor survival in PDAC.

AXL expression in this study was highly statistically significant with pathological TNM staging (P=0.05) parallel to Yu, W., et al ., (2019) [18] who found that AXL expression was significantly related to higher tumor stage (P=0.041). Also, this is matched with Oz, O., et al., (2023) [17] who found in their studies of tumors including pancreatic ductal adenocarcinoma that the expression of AXL is interestingly and significantly related to the advanced stage ($P = 0.007$) indicating that AXL plays a critical role in invasiveness and migration as it activates matrix metalloproteinases. Disagreeing with Zito Marino, F., et al., (2022) [19] who found that AXL expression was not significantly associated with the TNM staging (P=0.646) which may be due to the different interpretation method.

This study showed insignificant statistical relation between AXL expression and the tumor size (P=0.990) matching with Oz, O., et al., (2023) [17] study who stated that no relationship was seen between AXL expression and the tumor size. Also, this is matched with Rayford, A., et al., (2024)[20] who found that there was no relationship

between AXL expression and tumor size (P = 0.043)

This study showed insignificant statistical relation between AXL expression and lympho-vascular invasion (P=0.794) and lymph node status (P=0.473) matching with Yu, W., et al ., (2019) [18] study who stated that no relationship was seen between AXL expression and lymphovascular invasion (P= 0.593) or lymph node status (P= 0.692) due to different primary antibodies used among both studies, different interpretation method and different tumor behavior.This study showed insignificant statistical relation between AXL expression and resection margin (P=0.951) matching with Song, L., et al., (2024) [15] study who stated that no relationship was seen between AXL expression and resection margin (P= 0.593), (Table 2).

By using ROC curve to determine the validity of AXL immunohistochemical expression in differentiation between chronic pancreatitis and pancreatic ductal adenocarcinoma, sensitivity was 84%, specificity was 90% and accuracy was 89% for this differentiation matching with Yuan, J., et al (2024) [16] .

Conclusion:

There is a significant difference between pancreatic duct carcinoma and chronic pancreatitis as regard expression of AXL with more frequency of positive expression among carcinoma cases, so, AXL could have a role in the development of PDAC.

AXL showed significant correlation with tumor grade, tumor necrosis, perineural invasion and pathological TNM staging, so, it could have a role in tumor progression and aggressiveness.

AXL has a notable role in differentiation between chronic pancreatitis & pancreatic ductal adenocarcinoma cases.

References:

1. Cai QY, Tan K, Zhang XL, Han X, Pan JP, Huang ZY, et al. Incidence, prevalence, and comorbidities of chronic pancreatitis: A 7-year population-based study. World journal of gastroenterology. 2023 Aug 14;29(30):4671.
2. Iqbal M, Khawaja UA, Soomro U, Rizvi SA, Rizvi ZH. Pancreatic adenocarcinoma in the elderly–recurrence and survival: A physician's challenge. Advances in Cancer Biology-Metastasis. 2023 Jul 1;7:100092.
3. Samaan JS, Abboud Y, Oh J, Jiang Y, Watson R, Park K, et al. Pancreatic cancer incidence trends by race, ethnicity, age and sex in the United States: a population-based study, 2000–2018. Cancers. 2023 Jan 31;15(3):870.
4. Li Z, Zhang X, Sun C, Li Z, Fei H, Zhao D. Global, regional, and national burdens of early onset pancreatic cancer in adolescents and adults aged 15–49 years from 1990 to 2019 based on the global burden of Disease Study 2019: a cross-sectional study. International Journal of Surgery. 2024 Apr 1;110(4):1929-40.
5. Abdelwahed ZM, Darwish SA, Elmashad NM, Tawfik HA. Clinico-Epidemiological Study of Pancreatic, Gall Bladder and Biliary Tract Cancers at Clinical Oncology Department Tanta University Hospitals. Egyptian Journal of Cancer and Biomedical Research. 2023 Sep 1;7(3):85-95.
6. Khanbabaei H, Ebrahimi S, García-Rodríguez JL, Ghasemi Z, Pourghadamyari H, Mohammadi M, et al. Non-coding RNAs and epithelial mesenchymal transition in cancer: molecular mechanisms and clinical implications. Journal of Experimental & Clinical Cancer Research. 2022 Sep 16;41(1):278.
7. Ciernikova S, Earl J, Garcia Bermejo ML, Stevurkova V, Carrato A, Smolkova B. Epigenetic landscape in pancreatic ductal adenocarcinoma: on the way to overcoming drug resistance?. International journal of molecular sciences. 2020 Jun 8;21(11):4091.
8. Masugi Y. The desmoplastic stroma of pancreatic cancer: multilayered levels of heterogeneity, clinical significance, and therapeutic opportunities. Cancers. 2022 Jul 5;14(13):3293.
9. Breitenecker K, Heiden D, Demmer T, Weber G, Primorac AM, Hedrich V, et al. Tumor-Extrinsic Axl Expression Shapes an Inflammatory Microenvironment Independent of Tumor Cell Promoting Axl Signaling in Hepatocellular Carcinoma. International Journal of Molecular Sciences. 2024 Apr 10;25(8):4202.
10. Morimoto K, Yamada T, Sawada R, Azuma K, Goto Y, Harada T, et al. Predictive value of p53 and AXL immunostaining for the efficacy of immune checkpoint inhibitor-based therapy after osimertinib treatment in patients with

epidermal growth factor-mutant non-small cell lung cancer. Cancer Immunology, Immunotherapy. 2023 Jun;72(6):1699-707.
11. Schouten TJ, Daamen LA, Dorland G, van Roessel SR, Groot VP, Besselink MG, et al. Nationwide validation of the 8th American Joint Committee on Cancer TNM staging system and five proposed modifications for resected pancreatic cancer. Annals of Surgical Oncology. 2022 Sep;29(9):5988-99.
12. MARTÍNEZ-BOSCH, Neus, et al. Soluble AXL is a novel blood marker for early detection of pancreatic ductal adenocarcinoma and differential diagnosis from chronic pancreatitis. *EBioMedicine*, 2022, 75.Williams EA, Vegas I, El-Senduny FF, Zhang J, Mata DA, Hiemenz MC, et al. Pan-cancer genomic analysis of AXL mutations reveals a novel, recurrent, functionally activating AXL W451C alteration specific to myxofibrosarcoma. The American journal of surgical pathology. 2024 Jun 1;48(6):699-707.
13. Vázquez-Bellón N, Martínez-Bosch N, de Frutos PG, Navarro P. Hallmarks of pancreatic cancer: spotlight on TAM receptors. Ebiomedicine. 2024 Sep 1;107.
14. Song L, Chen Z, Li Y, Ran L, Liao D, Zhang Y, et al. Trend and forecast analysis of the changing disease burden of pancreatic cancer attributable to high fasting glucose in China, 1990–2021. Frontiers in Oncology. 2024 Oct 18;14:1471699.
15. Yuan J, Wang Z, Pan Z, Li A, Zhang Z, Cui F. DPNN-ac4C: a dual-path neural network with self-attention mechanism for identification of N4-acetylcytidine (ac4C) in mRNA. Bioinformatics. 2024 Nov;40(11):btae625.
16. OZ, Ozden, et al. Prognostic significance of ımmunhistochemical axl expression in pancreas ductal adenocarcinomas. *Indian Journal of Pathology and Microbiology*, 2023, 66.3: 533-539.Yu W, Ge X, Lai X, Lv J, Wang Y. The up-regulation of Axl is associated with a poor prognosis and promotes proliferation in pancreatic ductal adenocarcinoma. International Journal of Clinical and Experimental Pathology. 2019 May 1;12(5):1626.
17. Zito Marino F, Della Corte CM, Ciaramella V, Erra S, Ronchi A, Fiorelli A, et al. AXL and MET tyrosine kinase receptors co-expression as a potential therapeutic target in malignant pleural mesothelioma. Journal of Personalized Medicine. 2022 Dec 2;12(12):1993.
18. Rayford A, Gärtner F, Ramnefjell MP, Lorens JB, Micklem DR, Aanerud M, et al. AXL expression reflects tumor-immune cell dynamics impacting outcome in non-small cell lung cancer patients treated with immune checkpoint inhibitor monotherapy. Frontiers in Immunology. 2024 Aug 21;15:1444007.

To cite this article: Ebtehal M. Abdel-Aal, Nehal S. Abd El Wahab, Heba M. Rashad, Mona A. Aboelkheir, Shrouk E. Gamil, Shaymaa S. Ahmed. Significance of AXL Expression in Chronic Pancreatitis and Pancreatic Ductal Adenocarcinoma (an Immunohistochemical Study). BMFJ 2025;42(7):969-977.