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Investigation of Lysosomal Membrane-Associated Glycoprotein 3 (LAMP3) on Cancer Stomach Stromal Cells: an Immunohistochemistry Study

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Abstract

One of the tetraspanin superfamily membranes and membrane protein (III) is lysosomal membrane-associated glycoprotein 3 (LAMP3). It is tied up with lysosomes and can detect different types of cancer. Tumor stromal cells in the primary stage can induce tumorigenesis in numerous kinds of cancer, and stimulate metastatic growth by supplying the pre-metastatic niche. However, it can promote invasion and metastasis. The blocks were cut into histological sections and then discordant into two parts to be stained by a common histological hematoxylin and eosin stain and immunohistochemistry technique by using the LAMP3 marker kit. The high score intensity of this marker was recorded in advanced stages (III & IV), diffuse subtypes. Also, concerning age and gender, it was positively expressed in patients aged > 55 and in males more than females, respectively. Furthermore, poorly graded tumors and invasion depth (pT3 and pT4), involving lymph nodes (N1, N2, and N3) were highly positively expressed. It is the first study in Iraq concerning this type of marker for stromal stomach cancer, and it could be a good marker for early diagnosis.

Keywords: LAMP3, exosome, stromal cell, stomach cancer, lysosome

التحري عن البروتين السكري المرتبط بغشاء الجسيمات الحالة (3) على الخلايا الحشوية السرطانية المعدية: دراسة نسجية مناعية كيميائية

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الخلاصة

يعد البروتين السكري المرتبط بغشاء الجسيمات الحالة 3 (LAMP3) عضو من ضمن عائلة التتراسبانين والبروتينات الغشائية (III). ,ومن خلال ارتباطه بالجسيمات الحالة يمكن الكشف عن أنواع مختلفة من السرطان. تمتلك الخلايا الحشوية السرطانية في المراحل المبكرة من المرض المقدرة على تكوين الورم من خلال توفير الاعشاش السرطانية ما قبل عملية النمو الانتشاري، وتحفيز زيادة النمو الانتشاري، وعمق الورم في العضو في أنواع عديدة من السرطان. قطعت البلوكات الشمعية إلى مقاطع نسجية، ومن ثم تقسيمها إلى قسمين لغرض تصبيغها بصبغة الهيماتوكسيلين والإيوسين، والصبغة النسجية المناعية الكيميائية باستخدام المُعَلِّم LAMP3. تم تسجيل شدة تصبيغ عالية لهذا المُعَلِّم في المراحل المتقدمة (III & IV)، والنوع المنتشر. أما فيما يتعلق بالعمر والجنس، فقد سجل المرضى الذين تزيد أعمارهم عن 55 عامًا تعبيراً عالياً مقارنة مع المرضى الذين تقل أعمارهم عن 55 عاماً، اما الذكور فقد كان التعبير الايجابي للمُعَلِّم أكثر مقارنة بالإناث. فضلاً عن ذلك، سجل التمايز الضعيف، وعمق الغزو للورم (pT3 & pT4)، وتضمين الغدد الليمفاوية (N1 وN3, N2) شدة تعبير عالية للمُعَلِّم. تعد هذه الدراسة اول دراسة في العراق فيما يخص استخدام هذا المُعَلِّم للخلايا الحشوية السرطانية المعدية، اذ من الممكن ان يكون معلماً جيدًا للتشخيص المبكر لهذا النوع من السرطان.

1. Introduction

The most common reason for cancer-associated deaths universally is stomach cancer. It was announced as the fifth most prevalent cancer and the fourth essential cause of cancer death worldwide in 2020, and the ninth most common type of cancer in Iraq [1,2]. Colon and stomach are a remarkable disease and keep beard to the surgeons and ever after the early diagnosis of gastrointestinal cancer with elevated incidence [3]. A compared study from (1990 to 2021) [4] found that over one million cases of SC in terms of (mortality and incidence) elevated in 2021 compared with 1990, with (954,373.60) deaths and (22,786,633.10) disability-adjusted life years (DALYs). Although, the standardized age frequency rates, the standardized age death rates, and the standardized age DALY rates reduce by (42%) from 49 - 35%, (49%) from 55 - 43%, and (53%) from 58 - 47%, respectively. As for males compared to females for the previous factors, males recorded higher rates than females. Smoking in (East Asia and North America) had a high encumbrance of SC, whereas the diets high-sodium in (Central Europe) proficient elevated SC encumbrance in 2021 [5].

This type of cancer must be disclosed in the early stage, but it is so hard to diagnose with the slight symptoms. However, it is not discovered until it reaches the advanced stage [5]. Stomach cancer is still a paramount health affair worldwide, even though; the therapy has seen progress in the technology of radiotherapy, surgical, and chemo-therapy. For these reasons, it is important and considerable to detect an efficient biomarker to define the clinicopathological significance and stomach cancer patient's prognosis strictly [6].

The exosome is a vesicle with extremely diversified membrane-boundary phospholipid liberated by all kinds of cells [7]. It emits its content from the cell's surface to the extracellular medium as body fluids (cerebrospinal fluid, ascites, blood urine, saliva, tears, and milk) [8]. It is considered a superficies membrane that holds very important proteins: the transmembrane proteins, cytoskeleton, antigen-presenting, signal transduction, the transporters membrane, and adhesion molecules [9]. It includes all types of molecular constituents of the descent cell: (cytokines, proteins, all types of RNA, metabolites, growth factors, lipids, and single and double strands of DNA) [10]. It contributes to an abundant of processes physiologically and pathologically, such as immunity, angiogenesis, programmed cell death, the migration of cells, and inflammation [11], because its proteins which are bind to the receptors of the cell

surface and fuse with the cell membrane to transmit its components [12].

Exosomes can also coordinate different intracellular pathways by signaling. It can be used as a biomarker for many diseases such as neurodegenerative, tumors, cardiovascular, immunity, and fetal abnormality [12]. It opens new horizons towards finding a treatment for disease and improves the survival of patients by early detection of exosomes. Thus, to avoid the overdiagnosis or overtreatment risks of treatments [13].

There are many studies of exosome proteins (proteomic), which have classified these proteins into two groups: internal reference as Alix-a mammalian cell cytosolic protein, and HSP70- chaperones highly homologous, which encode the N- terminal nucleotide-binding domain (NBD) where ATP connect and change the global shape and structure to an open condition, which are enormous found in the derived of the exosomes from different sources of cell. It can be utilized to disconnect and distinguish the crude products of exosomes [14]. Also, ubiquitous proteins exist in all exosomes and participate in the structural physique and effective proteins that demonstrate particular functions and features. Furthermore, the proteins of the tetraspanin superfamily, transported membrane, fusion (Annexins and Rabs), heat shock, and cytoskeletal proteins are the structural proteins. It can be used as an important biomarker for cancer. For instance, adhesion molecule of epithelial cell (CD326), B7 homolog 1 (CD274), receptor of epidermal growth factor as ErbB-1, formation of the blood vessel protein as PDGF, mucin 1 (MUC1), alpha-fetoprotein (AFP), cluster of differentiation 109 (CD109), prostate-specific antigen (PSA), and glypican-1 (GPC-1)] [15].

Stomach cancer is a type of cancer that must be disclosed in the early stage, but it is so hard to diagnose with the slight symptoms, however, it is not discovered until reaches the advanced stage [6]. stomach cancer is still a paramount health affair worldwide, even though; even though the therapy has seen progress in the technology of radiotherapy, surgical, and Chemo-therapy. For these reasons, it is important and considerable to detect an efficient biomarker to define the clinicopathological significance and stomach cancer patient's prognosis strictly [7].

One of the tetraspanin (TM4SF) family is LAMP3 (a family of conserved membrane proteins that regulate cell motility, morphology, signaling, plasma membrane dynamics, and protein trafficking), and a kind of membrane protein (III) is N-glycosylation conversion. It is tied up with lysosomes and can participate in different kinds of cancer [15]. Syntenin-1 is one of the important proteins in exosome, it has many functional proteins composed of a (tandem PDZ- PSD-95/Dlg/ZO-1 domain), which organizes many functions in a cancer cell as (Epithelial-mesenchymal transition- EMT, invasion, angiogenesis, migration, cancer cell metastasis, and proliferation) [17]. So, this LAMP3 can be a potential marker for detecting cancer. The contrasty of cancer comes from the tumor microenvironment-TME. It helps to realize the growth of tumors and the development of therapy effectiveness [18]. Tumor ambience is very complicated. Many factors influence it, such as stromal cells and immunity, which frustrate or promote the impacts of genetic epithelial modulation [19]. The TME consists of (tumor cells, stromal tumor cells, the cells of endothelial and immunity with a non-cellular combination of proteins in the extracellular matrix) [20]. These cells can play an important role in estimating cancer (diagnostic and prognostic) [21]. They are a key factor in many types of cancers, such as breast cancer. It influences the initiation of cancer, development, immunotherapy response, and cancer clinical outcome. It has been identified in the previous scarce years [22]. In the primary stage of tumor, stromal cells can induce tumorigenesis in numerous types of cancers [23]. Also, these stromal cells stimulate

metastatic growth by supplying the pre-metastatic niche [24]. However, it can stimulate invasion and metastasis of tumor cells to other organs while maintaining survival and proliferation, therefore being effective in colonizing in metastatic sites [12]. However, this study aimed to appreciate the expression of - LAMP3- in stromal cancer cells in stomach cancer patients in Iraq.

2. Methods

2.1 *The Collection of Samples*

This study is retrospective researchconducted from February 2019 to November 2021. The complete number of specimens obtained was sixty. Forty-five blocks were taken randomly as stomach cancer samples, and fifteen blocks of gastric sleeve surgery as a control group from the Gastroenterology and Hepatology Teaching Hospital.

2.2 Tissue sections staining

All blocks were cut by microtome in 4 µm. Histological sections were placed on positively charged slides. Routine staining by using hematoxylin and eosin (H&E), and Immunohistochemistry (IHC) technique by using Recombinant Human LAMP3 protein (Catalog#11271-H08H) LAMP3-antibody (mouse monoclonal antibody) (Dilution1 1:50-1:200; SinoBiological) were used for all tissue section. The first step was accomplished by removing paraffin and rehydration. Then, tissue sections are immersed in hydrogen peroxide to block endogenous peroxidase activity. Specimens were incubated with antibody for 2 h 25 ℃. Biotinylated goat anti-rabbit Immunoglobulin G (IgG) was added and incubated for 15 min. Streptavidin-peroxidase reagent was also put on all slides and then stained by Mayer's hematoxylin. All these steps are executed by the manufacturing company. The expression of LAMP3 was estimated depending on the staining intensity of and stained percentage of stromal cells: as the following scores 0–4 (0 / no, 1/ weak, 2/ moderate, 3 / intense, 4/ high intensity), with immune-positive cells percentage to given scores 0–4 (0 / 0%, 1 / 10%, 2/ 20-30%, 3/ 40%-50%, 4/ 60-100%). For detection, the expression of the slides negative and positive control used and accomplished depended on Abcam protocol by utilizing Human liver cancer tissue in (Figure 1 A and B).

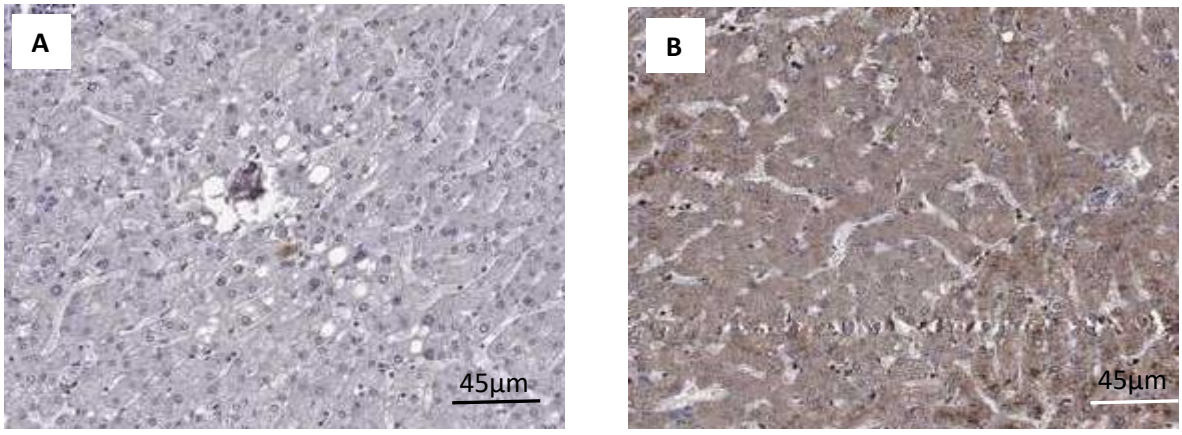

Figure 1: Negative and Positive control of cancer cells in human liver (A and B), scale bar 45 µm, 40X.

3. The Statistical Analysis

Chi-square (X^2) was implemented by Statistical Package for Social Science (SPSS) version -25) to find the linkage between clinic-pathological and the expression of the marker in stromal cells. Then, all data were compared with those of the control group. The level of significance in ≤ 0.01 (P-values) value was significantly considered.

4. Results

In this study control group includes 9 (60%) of healthy females and and, 6 (40%) of healthy males The total numbers of patients' females are recorded as 28 (62.22%), while the total numbers of males are registered as 17 (37.77%). In control and patients' cases, age from (22-75 years) is divided into similar or less than 55 and larger than 55. the total number of control and patients' cases are registered at 4 (26.66%), and 14 (31.11%), similar or less than 55, respectively, whilst those larger than 55 years are recorded at 11 (73.33%), 31 (68.88%), respectively. There is a different distribution in histopathological subtypes among patients as follows: intestinal type: 19 (42.22%), diffuse type: 22 (48.88%), whereas mixed type: 4 (8.88%). Most grades were poorly differentiated, which were registered in 23 (51.11%) cases, while primary differentiated were 3 (6.66%) and moderately recorded in 19 (42.22%). Furthermore, there is a change in the Invasion depth of tumor (pT2) and (pT3 and pT4) in about 11 (24.44%), and 34 (75.55%), respectively. The total number of patients that involve lymph nodes was registered as 41 (91.11%), while patients without lymph node involvement were 4 (8.88%). Patients' cases are divided into advanced stages (III and IV), and early stages (II) depending on tumor, node, and metastasis (TNM). Most cases are stages (III & IV) in about 29 (64.44%), while the stage (II) was 16 (35.55%), as shown in Table 1.

Table 1: The distribution of specimens concerns clinic-pathological parameters

Clinicopathological Parameters	Divisions		Frequency (%)
1. Age	≤ 55	Control	4 (26.66%)
		Patients	14 (31.11%)
	> 55	Control	11 (73.33%)
		Patients	31 (68.88%)
2. Gender	Female	Control	9 (60%)
		Patients	28 (62.22%)
	Male	Control	6 (40%)
		Patients	17 (37.77%)
3. Histopathological types	Patients	Diffuse	22 (48.88%)
		Intestinal	19 (42.22%)
		Mix	4 (8.88%)
4. Tumor Graded	Specimens	Primary	3 (6.66%)
		Moderate	19 (42.22%)
		Poor	23 (51.11%)
5. Tumor depth invasion	Specimens	(pT2)	11 (24.44%)
		(pT3& pT4)	34 (75.55%)
6. Tumar involvement in lymph node	Specimens	(N0)	4 (8.88%)
		(N1,2&3)	41 (91.11%)
7. TNM	Specimens	(II)	16 (35.55%)
		(III&IV)	29 (64.44%)

4.1 The expression of LAMP3 on stromal cancer cell

The statical analysis showed that high score intensity of this marker in patients at score +4 in about 21(46.6%), whereas positive scores were found at scores (+1, +2, and +3) in about 6 (13.3%), 8 (17.7%), 9 (20%), respectively. Conversely, in control groups, there is a negative expression for this marker at the scores (+2, +3, and +4) in about 0 (100%), while it is recorded in about 1 (2.2%) at score 0, and 6 (13.3%) at score +1. This result gives rise to a significant link between two groups in the manifestation of the studied immunohistochemical stain at stromal cancer cell at $P \leq 0.01$, $P = 0.001$, accordingly seen in Table 2 and Figures 2, 3, 4, 5, and 6.

Table 2: Stromal cancer cell manifestation of (LAMP3) in control and patient groups.

Manifestation of LAMP3		Specimens with (SC)	Control	P-value (*Chi-square P-value is significant (P ≤ 0.01)
Negative	Score (0)	1 (2.2%)	11 (24.4%)	P=0.001*
	Score +1	6 (13.3%)	4 (8.8%)	
Positive	Score +2	8 (17.7%)	0 (0%)	
	Score +3	9 (20%)	0 (0%)	
	Score +4	21(46.6%)	0 (0%)	
Total number/ number (ratio)		45 (99.8%)	15 (33.2%)	

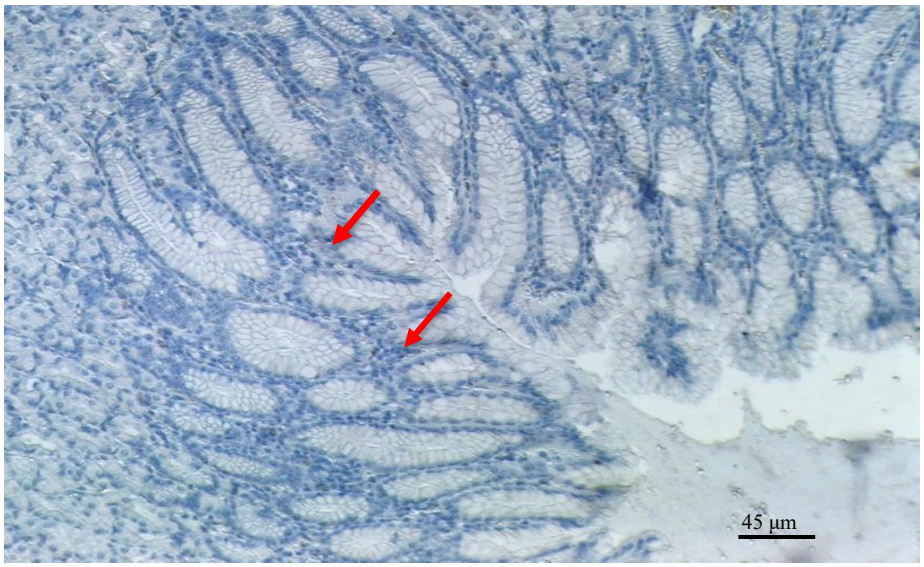

Figure 2: Normal tissue in the stomach (at score 0) shows the intensity of the immunohistochemistry staining LAMP3 marker and the negative manifestation of (LAMP3); none of the stromal cancer cells stained with a brown color (red arrow). (scale bar 45µm, 40X).

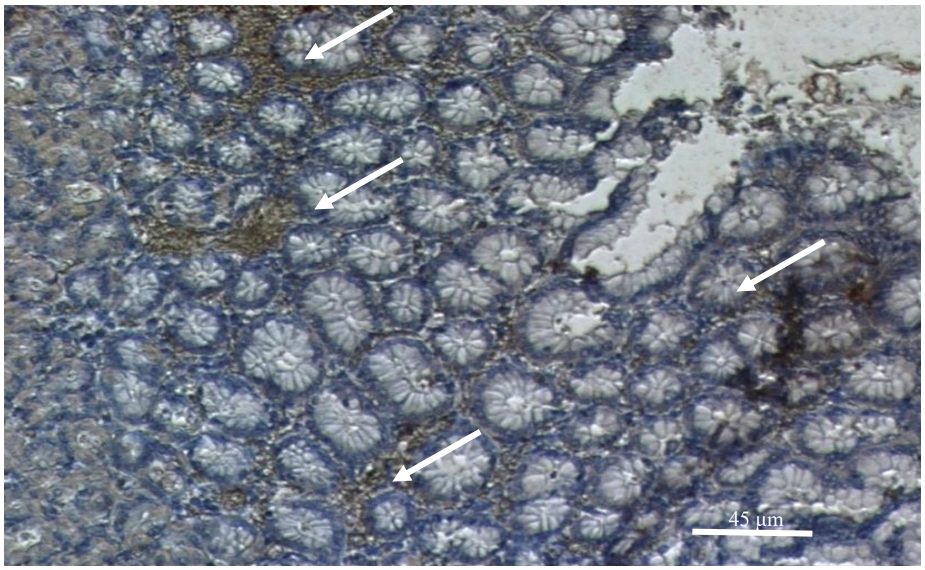

Figure 3: The tissue of the stomach (at score +1) shows the intensity of the immunohistochemistry staining LAMP3 marker the positive manifestation of (LAMP3), stromal cancer cell stained with brown- color (white arrow), (scale bar 45µm, 40X).

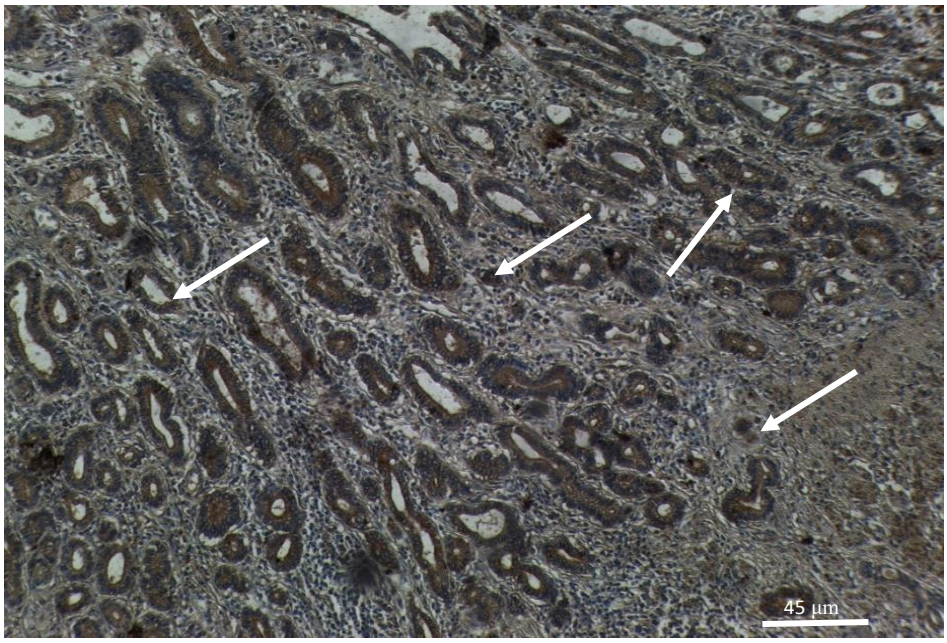

Figure 4: The tissue stomach (at score +2) shows the intensity of the immunohistochemistry staining LAMP3 marker the positive manifestation of (LAMP3), stromal cancer cell stained with brown- color (white arrow). (scale bar 45µm, 40X).

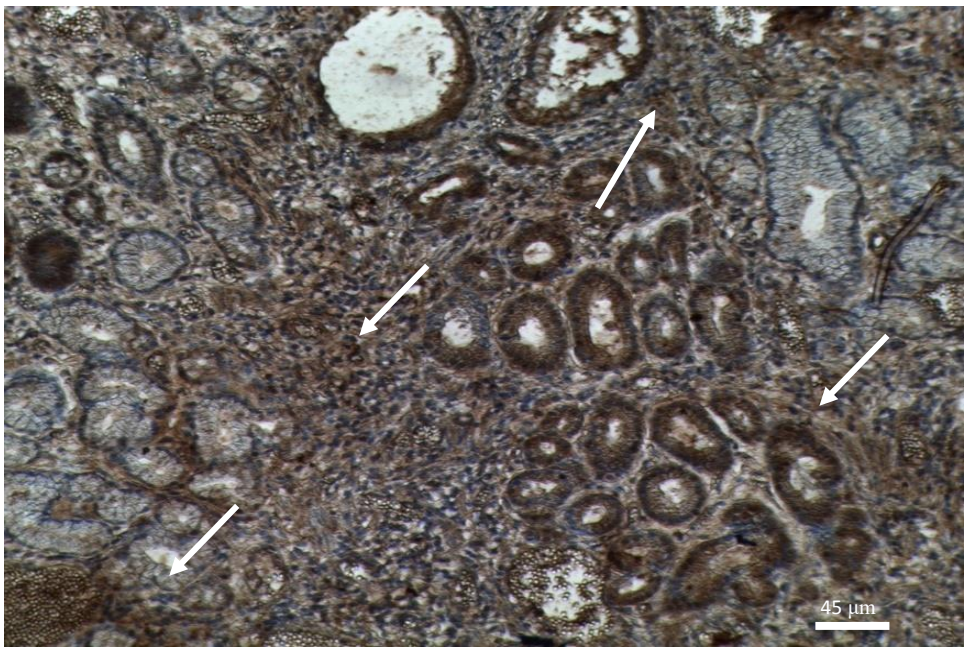

Figure 5: The tissue stomach (at score +3) shows the intensity of the staining LAMP3 marker, the positive manifestation of (LAMP3), and stromal cancer cells stained with brown-colored (white arrows). (scale bar 45µm, 40X).

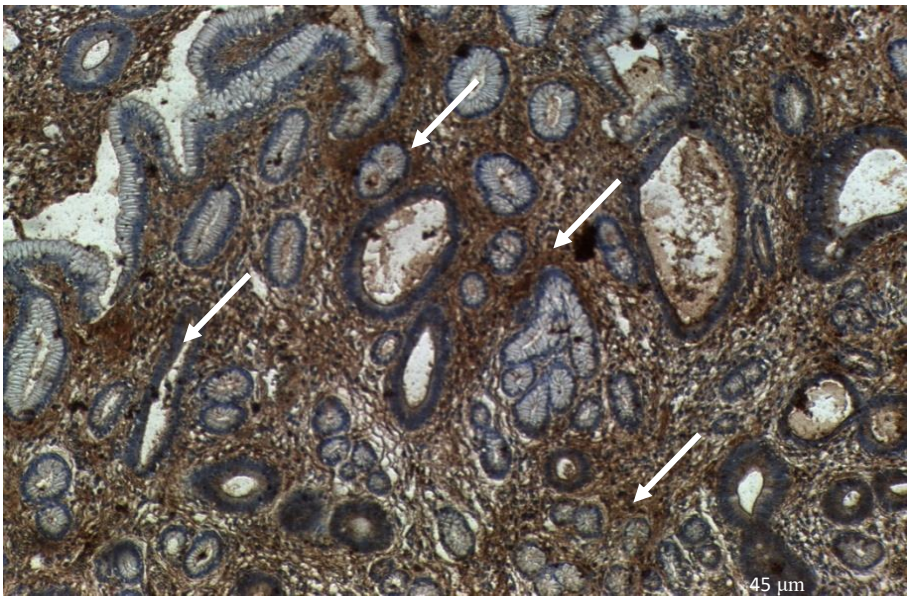

Figure 6: The tissue of the stomach (at score +4) shows the intensity of the immunohistochemistry staining LAMP3 marker the positive manifestation of (LAMP3), stromal cancer cell stained with brown -color (white arrow). (scale bar 45µm, 40X).

This study studied the relationship between the marker expressed with clinicpathological parameters. Concerning the age-positive, 11 (24.44%) of patients less than or equal to 55 years were recorded, and 3 (6.66%) were negative. Conversely, for patients more than 55 years, 30 (66.66%) were positive but 1 (2.22%). P-value = 0.493, larger than 0.01. This result reflects no significant link between age and the manifestation of this immunohistochemistry marker. It found that 23 (51.11%) of patients' males were expressed of LAMP3 and 5 (11.11%) as negative expressed. 14 (31.11%) female patients as LAMP3-positive expressed, but 3 (6.66%) were recorded as LAMP3-negative expressed. This indicated that there wasn't a significant link between gender and the manifestation of the marker, P- values were greater than (0.01), it was 0.286.

There was a significant link between the histopathological subtype and the manifestation of the marker, and the P-value was 0.0044. Diffuse subtype positive was registered 20 (44.44%), while negative diffuse subtype pigmentation 2 (4.44%). Furthermore, intestinal and mixed subtype positive pigmentation recorded 19 (42.22%) and 4 (8.88%), respectively, and there wasn't any record in these two subtypes for negative pigmentation in about 0 (0%). A significant association was seen in the grade of tumor (primary, moderately, and poorly) in about 3 (6.66%),17 (37.77%), and 23 (51.11%) as a positive expression to markers, and 2 (4.44%) for moderately as negative expression at P≤ 0.01 (P= 0.00174). The clinicopathological parameter invasion depth was highly positively expressed in pT3 and pT4, with 75.55% and 8.88% negative expression, while 22.22% positive record of pT 2 and 2.22% as negative expression. This statistically makes a significant link at P ≤ 0.01 (p=0.00187). Involving lymph nodes was a low expression of this marker at N0, which was recorded at 8.88%, whereas N1,2 and 3 were positively expressed at 91.11%. These differences made a significant correlation in p-value (p=0.0001) at P ≤ 0.01. The advanced stage (TNM) high was recorded at 64.44% for III and IV, and the lower recording for II at 35.55% with a P-value=0.0049.

Table 3: The correlation of clinicopathological parameters with the expression of LAMP3

Clinicopathological parameters		Manifestation **of LAMP3**		**P-value** (* P-value is significant ($P \leq 0.01$) as Chi-square)
		Negative specimens (ratio)	**Positive specimens (ratio)**	
Age	≤ 55	3 (6.66%)	11 (24.44%)	0.493
	>55	1 (2.22%)	30 (66.66%)	
Gender	Male	5 (11.11%)	23 (51.11%)	0.286
	Female	3 (6.66%)	14 (31.11%)	
Histopathological subtype	Diffuse	2 (4.44%)	20 (44.44%)	0.0044*
	Intestinal	0 (0%)	19 (42.22%)	
	Mix	0 (0%)	4 (8.88%)	
Grade of tumor	Primary	0 (0%)	3 (6.66%)	0.00174*
	Moderately	2 (4.44%)	17 (37.77%)	
	Poorly	0 (0%)	23 (51.11%)	
Invasion depth of tumor	pT 2	1 (2.22%)	10 (22.22%)	0.00187*
	pT3 & pT4	4 (8.88%)	34 (75.55%)	
Involvement of lymph node	N0	0 (0%)	4 (8.88%)	0.001*
	(N1,2 and 3)	0 (0%)	41 (91.11%)	
TNM	(II)	0 (0%)	16 (35.55%)	0.0049*
	(III and IV)	0 (0%)	29 (64.44%)	

5. Discussion

Stomach cancer is an evident issue in the world, even with the reduced records of incidence in (the United Kingdom and the United States). Japan, Chile, and parts of South Africa show a high incidence of this type of cancer [1]. It is the ninth and the second most common gastrointestinal malignancy after colorectal carcinoma in Iraq [2]. In Iraq, gastric intestinal cancers are considered (10.16%) of the total listed cases [24,28]. Depending on BCRG data in the years (2005-2008), stomach cancer mattress tenth in the whole population in males and ninth in females [25] and remains the ninth most common type of cancer in 2022 [1,2]. The Koh *et al*.; Liu *et al*.; and Britannica studies match the result of this study, which found that a high incidence was recorded in females compared with males, as demonstrated in Table 1. This high incidence of this cancer may refer to numerous factors. Firstly, the wars that Iraq suffered from (the Iraq-Iran war, the Gulf War, and the usage of uranium weapons in the southern part of Iraq). Secondly, the impurity effect of (oil wheel fire in the southern of Basrah, cars and generators for electricity production). Thirdly, deterioration of physiological and immunity roles with age progress can elevate the incidence of cancer [26,27,31]. This corresponds with the results that found patients aged more than 55 years are high, recording 31 (68.88%) of all cases, as shown in Table 1. The study of Abbas declares that there are many changes in the immune system in patients with prostate cancer. Tumor activity increases in the serum pre-operation and reduces in serum early and late phase post-operation in patients [20]. A deficiency in vitamin A (VitA) is one of the important factors, which could impact the medical evolution and analysis of breast cancer patients [28]. Natural bioactive compounds are the most powerful and active in health. These compounds could inhibit many types of cancer (with no side effects seen) [29]. Furthermore, natural bioactive compounds are

powerful and functional in primary health care. These compoundssuch as dandelion, can be used as an inhibiter for different types of cancer without any effective sides [30]

The exosome is a very small vesicle of about (30-150 nm) diameter, which excretes many biological substances. It contributes to transmitting intracellular signals [31,32]. It is found in body fluids and secreted by all types of cells [25]. It has a major role in many biological processes in normal and cancerous cells [25,26]. It transports signals between cancer cells to induce (the growth of tumors, metastasis, invasion, angiogenesis, innervation of tumors, and resistance to chemotherapeutic drugs) [28,36]. Histopathological subtypes and the expression of the markers are stringent for proper treatment and diagnosis of many types of cancer. It gives essential information about the behavior of the tumor, such as its aggressiveness, metastasis, and response to treatment [40]. For instance, a study by Choi and Thung on Hepatocellular carcinoma (HCC) focused on the importance of using histological subtypes and genetics to diagnose this type of cancer [42]. . Furthermore, intestinal and mixed subtype positive pigmentation recorded 19 (42.22%) and 4 (8.88%), respectively, and there wasn't any record in these two subtypes for negative pigmentation. A significant association was seen in the grade of tumor (primary, moderate, and poor). The clinicopathological parameter invasion depth was highly positively expressed in pT3 and pT4. Involving lymph nodes showeda low expression of this marker at N0, whereas N1,2 and 3 positively expressed at 91.11%. These differences made a significant correlation in p-value at $P \leq 0.01$. This marker's advanced stage (TNM) expression is in Table 3. Also, the result matches with the results of Hu *et al*., [29], which found that there was a positive expression of LAMP3 in tumor cells correlated with clinicopathological parameters in (subtype, grade, TNM stages and involvements of lymph nodes) and declared that this marker could be a prospective marker.

Exosome marker LAMP3, also known as a cluster of differentiation 63 [CD63], is a tetraspanins member that includes numerous superfamily proteins of the cell surface. It contributed to different processes in different types of cells (differentiation, activation of cells, adhesion, and invasion of tumor) [30]. It was highly expressed in many types of cancers (breast, colon, melanoma, lung, and ovary) [31]. The studies of Wei *et al*.; Mahdi *et al*.; Ascar and Fadhal , revealed that marker has a prospective role in controlling the progression of hepatocellular carcinoma (HCC), which opens a potential newfangled in targeted therapy. Furthermore, LAMP3 can be utilized as a marker to prognose the (HCC) [32,33,34]. New studies need to be found on the (diagnostic, prognostic, and predictive estimate) of many potential biomarkers in different types of cancer, such as breast cancer and other women-affected malignancies [35,36]. Van Niel, *et al*., and Jeyapriya, *et al*., showed that this marker was highly expressed in the TNM stage, T stage, lymph node metastasis and poorly differentiated in Oral squamous cell carcinoma (OSCC) cases, indicating that this marker has a potential function in OSCC carcinogenesis and has a vital function in cell transformation oncogenic, suggesting that LAMP3 may be poor prognosis good predictive marker for in this type of cancer [37,38]. Extracellular vesicles as exosomes are abundantly known as remarkable intercellular communication mediators. It has important functions in many physiological and pathological paths. It displays a major pledge as a modern approach biomarker of disease, as a curative factor, and as a medicine delivery vehicle [39,40].

6. Conclusion

LAMP3 is positively expressed in stromal cancer cells, especially in advanced-stage stomach cancer It may be a good prognostic marker for stomach cancer.

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Ethical responsibilities of authors

The ethical guidelines of the Declaration of Helsinki were approved by the Medicine Ethics Committee of the Hospital. (No.62 dated 1/2/2024)

Conflict of interest

The authors declare that they do not have any disclaimers or conflicts of interest.

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