

The Investigation of Lysosomal Membrane-Associated Glycoprotein 3 (LAMP3) on Stromal Cells in Iraqi Stomach Cancer Patients

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Abstract

Background: Lysosomal Membrane-Associated Glycoprotein 3 (LAMP3) also known as cluster of differentiation CD63 is a member of tetraspanin, and a kind of membrane protein (III) is modified by N-glycosylation. It is found in lysosomes and is preferred in different types of cancer. Tumor stromal cells in the primary stage can induce tumorigenesis in numerous types of cancers. Also, stimulates metastatic growth by supplying the pre-metastatic niche. 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. Objective of this study is to appreciate the expression of – LAMP3 in stromal cancer cells in patients with stomach cancer and detect the linkage between the expression of this protein and clinicopathological parameters, it is the first study in Iraq.

Methods: The total formalin-fixed paraffin-embedded blocks number of stomach tissue samples obtained was sixty. These blocks were divided into forty-five blocks as the patients' group and fifteen blocks as the control group. The blocks were cut into histological sections and then discordant into two parts to stain by common histological hematoxylin and eosin and immunohistochemistry technique by using the LAMP3 marker kit.

Results: High score intensity of this marker was recorded in advanced stages (III and IV) in about 29 (64.44%) at score +4 in about 21 (46.6%) respectively. Also, concerning the age it was positively expressed in 11 (24.44%) of patients less or equal to 55 years. Conversely, to patients more than 55 years in about 30 (66.66%) as positive. The diffuse subtype was the highest positive to the marker in about 20 (44.44%). A significant association was seen in the grade of tumor as a positive expression to marker. Invasion depth was highly positively expressed in pT3 and pT4 about 75.55%, and 8.88%. Involving lymph nodes was a low expression of this marker at N0 which was recorded at 8.88%, whereas N1,2 and 3 positively expressed at about 91.11%. The advanced stage (TNM) high was recorded in about 64.44% at III and IV.

Conclusion: This marker might be a good marker for early diagnosis of stomach cancer patients in Iraq.

Keywords: LAMP3 • Exosome • Stromal cell • Stomach cancer • Lysosome

Abbreviations: LAMP3: Lysosomal Membrane-Associated Glycoprotein 3; CD63: Cluster of Differentiation; RNA: Ribonucleic Acid; DNA: Deoxyribonucleic Acid; NBD: N-Terminal Nucleotide-Binding Domain; ATP: Adenosine Triphosphate; CD81: Cluster of Differentiation 81; CD82: Cluster of Differentiation 82; CD9: Cluster of Differentiation 9; HsP60: Heat Shock Proteins 60; HsP70: Heat Shock Proteins 70; HsP90: Heat Shock Proteins 90; EPCAM: Epithelial Cell Adhesion Molecule; PD-L1: Programmed Death-Ligand 1; PDGF: Platelet-Derived Growth Factor;

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MUC1: Mucin 1; AFP: Alpha-Fetoprotein; CD109: Cluster of Differentiation 109; PSA: Prostate-Specific Antigen; GPC-1: Glypican-1; PDZ PSD-95/Dlg/ZO-1: Postsynaptic Density Protein-Drosophila Disc Large Tumor Suppressor/And Zonula Occludens-1 Protein; TMN: Tumor Microenvironment; IHC: Immunohistochemistry; IgG: Immunoglobulin G; SPSS: Statistical package for social science; VitA: Vitamin A; N0: Lymph nodes do not contain cancer; N1: Means there are cancer cells in 1 nearby lymph node; HCC: Hepatocellular Carcinoma

Introduction

The most procure 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 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]. 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 reaches the advanced stage [4]. 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 [5].

The exosome is a vesicle with extremely diversified membrane-boundary phospholipid liberated by all kinds of cells [6]. It is emised its content from the surface of the cell to the extracellular medium as body fluids (cerebrospinal fluid, ascites, blood urine, saliva, tears, and milk) [7]. It is considered a superficies membrane that holds very important proteins: The proteins of the transmembrane, cytoskeleton, antigen-presenting, signal transduction, the transporters membrane, and molecules of adhesion [8]. 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) [9]. It contributes to abundant of processes physiologically and pathologically as: (Immunity, angiogenesis, programmed cell death, the migration of cells, and inflammation), because its proteins which are bind to the receptors of the cell surface and fuse with the cell membrane to transmit its components.

Exosomes also can coordinate different pathways of intracellular by signaling. It is can used as a biomarker for many types of diseases such as (neurodegenerative, tumors, cardiovascular, immunity, and fetal abnormality). 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.

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. Also, ubiquitous proteins, which are existent in all exosomes and participate in the structural physique and effective proteins that demonstrate particular functions and features. the tetraspanin superfamily proteins (CD63, CD81, CD82, CD9), membrane transport and fusion proteins (Annexins and Rabs), heat shock proteins (Hsp60, Hsp70, and Hsp90), cytoskeletal proteins one of the structural proteins. It can be used as an important biomarker for cancer, for instance (Epithelial Cell Adhesion Molecule (EpCAM)/Programmed Death-Ligand 1 (PD-L1)/Epidermal Growth Factor Receptor (HER2, EGFR)/Platelet-Derived Growth Factor (PDGF)/Mucin 1 (MUC1)/Alpha-Fetoprotein (AFP)/Cluster of Differentiation 109 (CD109)/Prostate-Specific Antigen (PSA)/ and Glypican-1 (GPC-1)).

Lysosomal Membrane-Associated Glycoprotein 3 (LAMP3) a member of the superfamily of tetraspanin, and a kind of membrane protein (III) is modified by N-glycosylation. It is tied up with lysosomes and can be preferred in different types of cancer. 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). 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. Tumor ambience is very complicated. It is influenced by many factors as stromal cells and immunity, which frustrate or promote the impacts of genetic epithelial modulation. 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). These cells can declare as an important role in estimating cancer (diagnostic and prognostic). 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. In the primary stage of tumor stromal cells can induce tumorigenesis in numerous types of cancers. Also, these stromal cells stimulate metastatic growth by supplying the pre-metastatic niche. 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. However, this study objective is designed to appreciate the expression of LAMP3 in stromal cancer cells in stomach cancer patients in Iraq.

Materials and Methods

The collection of samples

This research is a retrospective study from February 2019 to November 2021. The total number of samples obtained was sixty. Forty-five blocks were taken randomly from the Gastroenterology and Hepatology Teaching Hospital and private laboratories from patients with stomach cancer, while fifteen control blocks were collected from private laboratories.

Tissue sections staining

All blocks were cut by microtome in 4 μ m. Histological sections were placed on positively charged slides. Routine staining by using Hematoxylin and Eosin (H and E), and Immunohistochemistry (IHC) technique by using Recombinant Human LAMP3 protein (Catalog# 11271-H08H) LAMP3-antibody (mouse monoclonal antibody) (Dilution 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°C. Biotinylated goat anti-rabbit Immunoglobulin G (IgG) was added and incubated for 15 min. Streptavidin-peroxidase reagent also was 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, B).

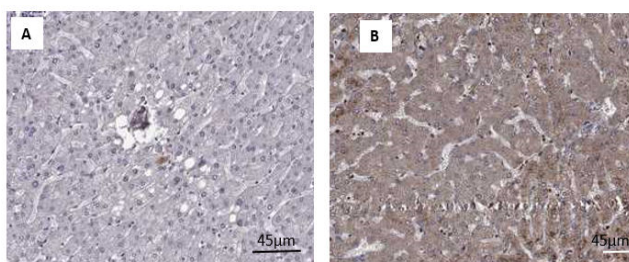


Figure 1. Negative and positive control of cancer cells in human liver (A and B), scale bar 45 μ m, 40X.

The statistical analysis

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

Results

Different clinicopathological parameters are studied in this research, which includes the total number of females in the control group 9 (60%), nevertheless, males 6 (40%). Patients' females' total numbers are recorded as 28 (62.22%), while the total males' numbers are registered as 17 (37.77%). In control and patients' cases, age is divided into: Equal or less than 55 years, and more than 55 years. the total number of control and patients' cases are registered at 4 (26.66%), and 14 (31.11%) equal or less than 55 years respectively, whilst more than 55 years are recorded at 11 (73.33%), 31 (68.88%) respectively. There is a different distribution in histopathological subtypes among patients as follow: 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 is registered as 41 (91.11%), while patients without lymph node involvement are 4 (8.88%). patients' cases are divided into advanced stages (III and IV), and early stages (II) depending on Tumor, Node, and Metastasis (TNM). The most cases are advanced stages (III and IV) in about 29 (64.44%), while early stage (II) was 16 (35.55%) (Table 1).

Clinico-pathological parameters	Findings		Frequency (%)
Age	≤ 55	Control	4 (26.66%)
		Patients	14 (31.11%)
	>55	Control	11 (73.33%)
		Patients	31 (68.88%)
Gender	Female	Control	9 (60%)
		Patients	28 (62.22%)
	Male	Control	6 (40%)

		Patients	
Histopathological types	Patients	Diffuse	22 (48.88%)
		Intestinal	19 (42.22%)
		Mix	4 (8.88%)
Grade of tumor	Patients	Primary	3 (6.66%)
		Moderately	19 (42.22%)
		Poorly	23 (51.11%)
Invasion depth of tumor	Patients	pT2	11 (24.44%)
		pT3 and pT4	34 (75.55%)
Involvement of lymph node	Patients	N0	4 (8.88%)
		N1,2 and 3	41 (91.11%)
Stage of GC (TNM)	Patients	II	16 (35.55%)
		III and IV	29 (64.44%)

Table 1. The distribution of specimens depends on clinicopathological parameters.

The expression of LAMP3 on stromal cancer cell

The statistical analysis showed that high score intensity of this marker in patients at score +4 in about 21 (46.6%), whereas positive scores found at score (+1, +2, +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 score (+2, +3, +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 association between two groups in the expression of the studied marker at stromal cancer cell at $P \leq 0.01$, $P = 0.001$ as seen in Table 2 and Figures 2-6.

Expression of LAMP3		Patients with gastric cancer	Control	P-value
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%)	

Note: *Chi-square P-value is significant ($P \leq 0.01$)

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

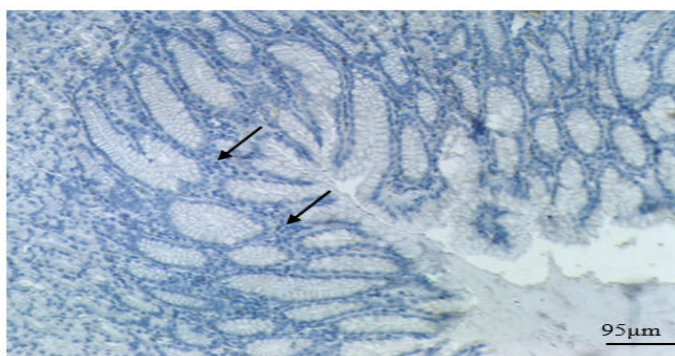


Figure 2. A cross-section in stomach tissue shows the intensity of the staining LAMP3 marker and the negative expression of (LAMP3) at score 0, none of the stromal cancer cells stained with a brown color black arrow, IHC. scale bar 45 μm, 40X.

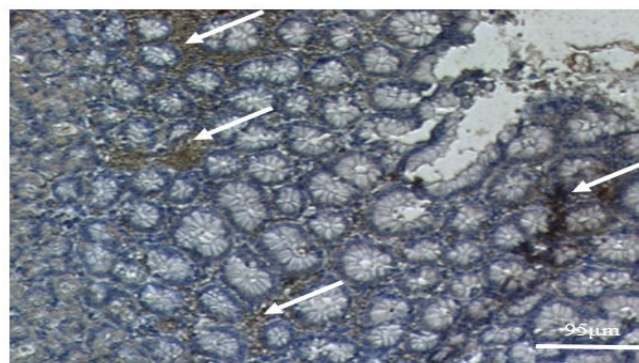


Figure 3. A cross-section in stomach tissue shows the intensity of the staining LAMP3 marker the positive expression of (LAMP3) at score +1, stromal cancer cell stained with brown color white arrow, IHC. scale bar 45 μm, 40X.

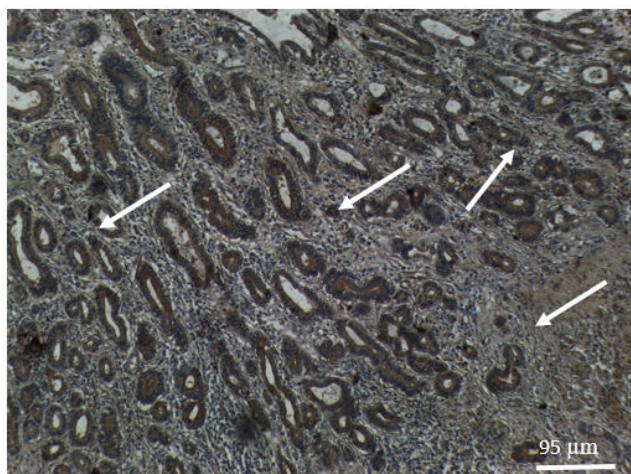


Figure 4. A cross-section in stomach tissue shows the intensity of the staining LAMP3 marker the positive expression of (LAMP3) at score +2, stromal cancer cell stained with brown color white arrow, IHC. scale bar 45 μm, 40X.

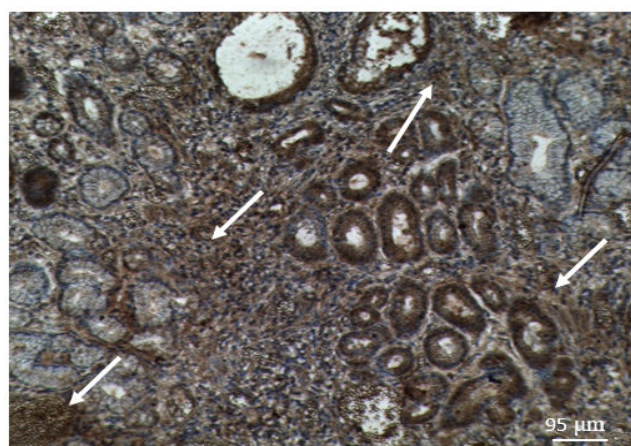


Figure 5. A cross-section in stomach tissue shows the intensity of the staining LAMP3 marker the positive expression of (LAMP3) at score +3, stromal cancer cell stained with brown color white arrow, IHC. scale bar 45 μm, 40X.

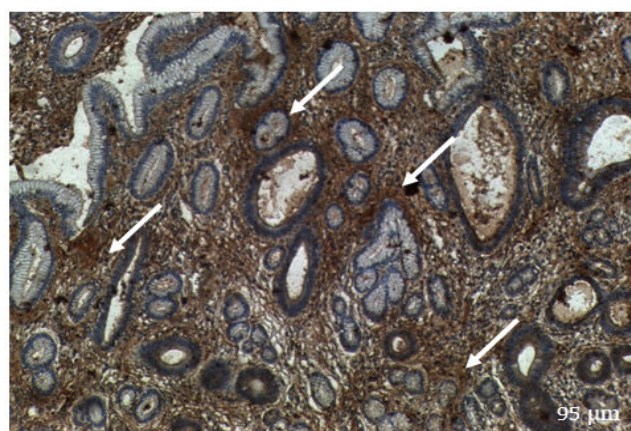


Figure 6. A cross-section in stomach tissue shows the intensity of the staining LAMP3 marker the positive expression of (LAMP3) at score +4, stromal cancer cell stained with brown color white arrow, IHC. scale bar 45μm, 40X.

This study studied the relationship between the marker expressed with clinic-pathological parameters. Concerning the age-positive expressed in 11 (24.44%) of patients less or equal to 55 years were recorded and 3 (6.66%) as negative. Conversely, to patients more than 55 years about 30 (66.66%) as positive but 1 (2.22%). P-value=0.493 larger than 0.01 so there was not a significant association between age and the expression of this 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 positive expressed but 3 (6.66%) were recorded as negative expressed. This indicated that there wasn't a significant association between gender and the expression of marker, P-values were larger than 0.01 in about 0.286.

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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. Depending on BCRG data in the years (2005-2008), stomach cancer mattress the tenth in the whole population in males and ninth in females and remains the ninth most common type of cancer in 2022 [1,2]. The study matches the result of this study, which found that a high incidence was recorded in females compared with males as 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. This corresponds with the results that found patients aged more than 55 years are high recording about 31 (68.88%) of all cases as 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. A deficiency in Vitamin A (VitA) is one of the important factors, which could impact the medical evolution and analysis of breast cancer patients. Natural bioactive compounds are the most powerful and active in health. These compounds could inhibit many types of cancer (with no side effects seen).

The exosome is a very small vesicle of about (30-150 nm) diameter, which excrete many biological substances. It contributes to transmitting intracellular signals. It is found in body fluids and secreted by all types of cells. It has a major role in many biological processes in normal and cancerous cells. It transports signals between cancer cells to induce (the growth of tumors, metastasis, invasion, angiogenesis, innervation of tumors, and resistance to chemotherapeutic drugs). These studies corresponded with this study's results, which indicated a significant association between the Histopathological subtype and the expression of the marker. 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 positive expressed in pT3 and pT4. Involving lymph nodes was a low expression of this marker at N0 whereas N1,2 and 3 positively expressed in about 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 which found that there was a positive expression of LAMP3 in tumor cells correlated with clinic-pathological parameters in (subtype, grade, TNM stages, involvements of lymph nodes) and declared that this marker can be a prospective marker.

Clinicopathological parameters		Expression of LAMP3		P-value
		Negative number (ratio)	Positive number (ratio)	
Age	≤ 55	3 (6.66%)	11 (24.44%)	0.493
	>50	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 and 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%)	
Stage of GC (TNM)	II	0 (0%)	16 (35.55%)	0.0049*
	III and IV	0 (0%)	29 (64.44%)	

Note: *P-value is significant ($P \leq 0.01$) as *Chi-square*

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

Exosome marker Lysosomal Membrane-Associated Glycoprotein 3 (LAMP3) also known as a Cluster of Differentiation 63 (CD63) is a tetraspanins members that include numerous superfamily proteins of the cell surface. It contributed to different processes in different types of cells (differentiation, activation of cells, adhesion, invasion of tumor). It was highly expressed in many types of cancers (breast, colon, melanoma, lung, and ovary). The study concluded that there is a prospective role of this marker 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).

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.

Ethics Approval and Consent to Participate

The experimental protocol was established according to the ethical guidelines of the Declaration of Helsinki and was approved by the Medicine Ethics Committee of the Hospital.

Consent for Publication

Not applicable.

Availability of Data and Material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

RK scrutinized, analyzed, and interpreted the data and was a major contributor to write the manuscript, review, and editing (supporting); SN analyzed data and edited some points; SK conceptualized and contributed to the manuscript writing. AS, AK and EG reread and correct errors. All authors read and approved the final manuscript.

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Conflict of Interest

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

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