RESEARCH ARTICLE

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Immunohistochemical Expression of CD90, CD133, and TPM1 in Relation to Gastric Cancer and *H. pylori* Association

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Abstract

Background: Gastric cancer (GC) is the second most common cause of cancer-related death worldwide. Multiple malignancies overexpress CD90, making it a helpful diagnostic and prognostic marker. CD133 is suggested to be related to poor prognosis in GC. Tropomyosin-1 (TPM1) tumor-suppressor gene low expression may predict poor survival in GC. Our study aimed to investigate CD90, CD133, and TPM1 immunohistochemical expression in GC in relation to diagnosis, prognosis, and Helicobacter pylori (*H. pylori*) infection. **Methods:** 144 paraffin blocks containing gastric cancerous (108 cases), and non-cancerous (36 cases) tissue were analyzed histopathologically for the type of lesion, grade, and stage of malignancy and by using an immunohistochemical assay for studying the expression of CD90, CD133, and TPM1. Data analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 20.0. **Results:** The obtained results showed a significantly higher expression of CD90 and CD133 while showing a significantly lower expression of TPM1 in malignant samples compared to benign ones. CD90 was significantly higher in grade-3, stage-3, and N3 ($p<0.05$), with no significant difference concerning positive and negative *H. pylori* samples. CD133 percentage and H-score were significantly higher in grade-2 and stage-4 tumors than in other grades and stages, while being insignificantly higher in N3 and *H. pylori*-positive cases. TPM1 expression levels were significantly downregulated in GC and *H. pylori*-positive cases ($p<0.05$). TPM1 downregulation was associated with grade progression, increased depth of invasion, and tumor node metastasis. **Conclusion:** CD90, CD133, and TPM1 immunohistochemical expression in the gastric biopsy are related firmly to grades and stages of GC as well as *H. pylori* infection, so they could be of prognostic value. Further studies on a larger sample size are recommended.

Keywords: Tissue markers- malignancy- Stomach- target therapy

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Introduction

Gastric cancer (GC) is a highly aggressive cancer with a heterogeneous character that continues to be a worldwide health issue. Gastric carcinoma is the fourth most common type and the second leading cause of cancer-related death worldwide. GC is not common in the young population (under 45 years of age), with only around 10% of individuals seeing disease progression (Machlowska et al., 2020). Gender, age, diet, smoking, alcohol, Epstein-Barr virus (EPV), and Helicobacter pylori (*H. pylori*) are some of the risk factors for GC (Czyzewska, 2013; Karimi et al., 2014; Richa et al., 2022). This life-threatening disease can be diagnosed either by blood chemistry tests and biomarkers, endoscopic tests including upper endoscopy or endoscopic ultrasound, or other imaging tests such as a CT scan or biopsy (Cuzzuol et al., 2020).

Biomarkers are biological substances that are partly or fully engaged in the process of carcinogenesis and may be used in the identification of aberrant alternations in the patient. Cancer biomarkers fall into three broad categories, each of which has a distinct characteristic, such as their therapeutic application, diagnostic, and prognostic properties. Cluster differentiation 90 (CD90) is a cell adhesion molecule and the smallest member of the immunoglobulin superfamily with a molecular weight of 25–37 KDa (Kumar et al., 2016). As a tumor marker, CD90 has been shown to have significantly high expression in esophageal cancer and other digestive cancers. CD90 might be a useful biomarker for pancreatic adenocarcinoma, in which desmoplastic stroma plays a significant role in tumor development and angiogenesis. CD90 was found to be expressed in 95% of clinical gastric tumor samples by immunohistochemical staining (Zhu et al., 2015). CD133 (prominin-1) is utilized to identify and isolate cancer stem cells (CSCs) from brain, colon, pancreatic, prostate, lung, and liver cancers (Glumac & Lebeau, 2018). CD133 was shown to be expressed in

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57.4% of GC samples, and a tight relationship between CD133 and poor prognosis in gastric adenocarcinoma was discovered (Smith et al., 2008). Tropomyosin-1 (TPM1) is recognized to function as an actin-binding cytoskeletal protein in a variety of cells (Wang et al., 2015). A previous study investigated TPM1 mRNA and its protein expression levels in patients with GC and concluded that downregulation of TPM1 was associated with depth of invasion and tumor node metastasis, and the overall survival analysis indicated that low TPM1 expression predicted poor survival (Hu et al., 2020).

In the current study, we aimed to estimate the value of immunohistochemical expression of each of the three categories-markers in relation to the histopathological characterization of GC and accordingly to a predicted prognosis.

Materials and Methods

Materials

The material used in the current study included tissue microarray analysis of 144 paraffin blocks including GC (108 cases: Adeno Ca (84) & Signet Ring Ca (24)) and non-cancerous tissue (36 cases; including 30 cases of chronic gastritis and 6 cases of congestive gastropathy) taken from biopsy specimens received at the pathology department of Theodor Bilharz Research Institute. Specimens were analyzed for routine histopathological and immunohistochemical study. The clinical data related to each case was achieved from the histopathology reports of patients.

Methods

Histopathological study

Hematoxylin and eosin-stained sections were prepared for routine diagnosis, grading, and staging of tumors. Sections were also stained by giemsa stain for detection of *H. pylori* microorganisms (Bae & Kim, 2016).

All sections were assessed and scored according to the WHO system. Sections were examined using light microscope [Scope A1, Axio, Zeiss, Germany]. Photomicrographs were taken using a microscope-camera [AxioCam, MRc5, Zeiss, Germany]. All procedures were done at the pathology department of Theodor Bilharz Research Institute, Giza, Egypt.

Immunohistopathological staining

Immunohistochemistry for CD90 (Cat. Number: YPA2404, Chongqing Biospes, China), CD133 (Cat. Number: YPA2403, Chongqing Biospes, China), and TPM1 (Cat. Number: YPA2403, Chongqing Biospes, China) were performed on tissue sections cut from the paraffin blocks at 4μm onto positively charged slides (Superfrost Plus, Menzel-Glaser, Germany) and stained on an automated platform (Dako Autostainer Link 48) using: 1:100 dilution for all biomarkers. Heat-induced antigen retrieval was used for 30 min at 97°C in the high-PH EnVision™ FLEX Target Retrieval Solution. Then endogenous peroxidase blocking was done by (3% H_2O_2) for 4 minutes at 37°C. Slides were incubated with primary antibody for 40 minutes at 37°C followed by a universal secondary antibody for 20 minutes at 37°C. Slides were incubated in streptavidin-horseradish peroxidase (SA-HRP) D for 15 minutes at 37°C and then the substrate, 3,3′-diaminobenzidine tetrahydrochloride (DAB) was added for 10 minutes followed by counter-staining of tissue sections using Hematoxylin.

Assessment of biomarkers expression

Immunohistochemical (H-score) was based upon the product of the percentage of CD90, CD133, and TMP1'expressing cells multiplied by stain intensity (0 = negative, 1 = weak, 2 = moderate, 3 = strong) for each specimen. The percentage of each marker in the cells (percentage of positive expression; 0=no staining, 1 = <10%, 2 = 10–50%, 3 = 51–80%, 4 = >80%) was assessed by the mean of % of cellular positivity in three different microscopic fields under 200× magnification. When the multiplication product of the percentage of positive cells and stain intensity was ≥5, the specimen was considered positive for biomarkers' expression as modified from Jenkins et al. (2007).

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 20.0 was used for data cleaning, management, and analysis. Categorical variables were presented using number and percent, whereas continuous ones were presented by mean and standard deviation (mean ± SD). Also, Chi square test was applied for comparing the significance between percentage, with p value considered significant if < 0.05.

Results

This study was conducted on 144 tissue microarray processed paraffin blocks of GC (108: 84 adenocarcinomas, 24 signet ring carcinoma) and non-cancerous/gastritis (36) lesions, assessed for CD90, CD133, & TPM1 immunohistochemical expression and results are recorded in Table 1 and Figure 1.

Gastric biopsy specimens were taken from 87 males and 57 females of mean age (54.54 years) for males and (54.59) years for females with no significant difference between both genders ($p > 0.05$). As regards the age distribution in benign and malignant cases included in this study, the mean age for benign cases was (51.50 years), while the mean age for malignant cases was (55.31 years) with no significant difference ($p > 0.05$). Regarding the age distribution of studied lesions, the mean age for gastritis cases was (51.50 years), for adenocarcinoma was (54.16 years) while the mean age for signet ring carcinoma was (59.27 years) with no significant difference ($p > 0.05$).

Malignant samples showed a significantly higher percentage of positive cases & H-Score of CD90 than the benign samples ($p < 0.0001$ & $p < 0.0001$ respectively), with no significant difference between adenocarcinoma & signet ring tumors. The expression of CD90 was lower in grade-1 tumors and increased in higher grades, being significantly the highest in grade-3 ($p = 0.0294$). CD90 percentage in stage-1 cases was the lowest and significantly increased in higher stages, having the highest

Table 1. Relation of Immunohistochemical Expression of Studied Markers to Histopathological Data

Diagnosis (N)	Sex	Age	CD90		CD133		TPM1	
All Cases (144)	M=87	54.54±17.22	Positive	H-Score	Positive	H-Score	Positive	H-Score (M±SD)
	F=57	54.59±14.82	(%)	(M±SD)	(%)	(M±SD)	(%)	
Benign (36)	M=22	50.50±17.47	10 (27.78%)	1.33±0.65	21 (58.33%)	15.42±8.382	25 (69.44%)	7.92±2.69
	F=14	52.09±13.98						
Malignant (108)	M=65	53.31±12.75	75 (69.44%)	7.72±3.58	102 (94.44%)	185.69±100.63	54 (50%)	5.36±3.14
	F=43	55.10±10.36						
Adeno Ca (84)			55 (65.48%)	7.64±3.65	80 (95.24%)	192.68±102.16	43 (51.19%)	5.91±3.08
Signet Ring Ca (24)			20 (83.33%)	8.00±3.54	22 (91.67%)	161.25±97.45	11 (45.83%)	5.16±3.54
Grade								
G1 (6)			2(33.33%)	5.50±4.95	3 (50%)	25.00±21.21	4 (66.67%)	6.00±4.24
G2 (48)			32(66.67%)	8.00±3.48	48 (100%) *	205.00±89.29*	31 (64.58%)	6.00±2.92
G3 (54)			41(75.93%) *	7.72±3.69	51 (94.44%) *	186.39±101.97*	19 (35.19%)	4.06±3.12
Stage								
T1 (6)			2(33.33%)	5.50±4.95	4 (66.7%)	40.00±0.0	4 (66.67%)	7.00±0.0
T2 (12)			6 (50%)	8.25±3.30	10 (83.33%)	217.50±99.45	6 (50%)	5.00±0.00
T3 (42)			37 (88.10%) #	8.64±4.21	40 (95.24%) #	213.93±87.09#	20 (47.62%)	4.57±3.46
T4 (48)			30 (62.50%)	7.06±2.95	48 (100%) #	171.25±104.94#	24 (50%)	4.31±2.80
Lymph Node Metastasis								
N0 (42)			27 (64.29%)	7.14±3.655	39 (92.86%)	183.21±109.64	27 (64.29%)	7.50±3.94
N1 (15)			8 (53.33%)	7.20±3.347	13 (86.67%)	164.00±96.07	8 (53.33%)	4.60±2.19
N2 (30)			20 (66.67%)	8.60±4.006	29 (96.67%)	186.00±90.46	12 (40%)	4.20±2.70
N3 (21)			21 (100%)	8.00±3.464	21 (100%)	205.71±117.17	9 (33.33%)	3.12±2.31
Helicobacter Pylori@								
Positive (17/36)			6 (60%)	3.58±0.54	12 (70.59%)	21.55±7.53	2 (11.67%)	2.00±0.37
Negative (19/36)			4 (40%)	1.06±0.75	9 (47.37%)	18.17±9.04	10 (52.63%)	7.11±0.78

*, Significant difference with G1 group (P < 0.05); #, Significant difference with T1 group (P < 0.05); @, Helicobacter pylori was assessed only in benign gastric cases (36 cases)

percentage in stage-3 (p = 0.0015). Moreover, CD90 expression was significantly higher in N3 than N0 cases (p = 0.0019) while no significant difference was observed in CD90 expression between negative and positive *H. pylori* cases (p > 0.05).

The malignant samples had a significantly higher percentage of positive cases & H-Score of CD133 than the benign samples (p<0.0001 & p < 0.0001, respectively) while the adenocarcinoma group's CD133 percentage & H-score were non-significantly higher than the signet ring group. Grades 2 and 3 had a significantly higher percentage (p < 0.0001 and p = 0.0006, respectively) and H-score (p < 0.0001) of CD133 than grade-1 group while grade-2 group was insignificantly higher than grade-3 group. Furthermore, stage-4 cases had a significantly higher CD133 percentage and H-score compared to stage-1 (p = 0.0001 and p < 0.0001, respectively). On the other hand, N3 cases showed the highest CD133 percentage and H-score with no significant difference between different lymph node metastasis groups. In addition, *H. pylori* Positive cases showed higher CD133 expression than negative *H. pylori* cases, with no significant difference.

TPM1 percentage of positive cases was significantly reduced in malignant cases compared to benign cases (p < 0.05) while adenocarcinoma cases were insignificantly higher than signet ring cases (p > 0.05). TPM1 percentage and H-score were the highest in grade-1 while being the lowest in grade-3 (p > 0.05). However, TPM1 percentage were significantly higher in grade-3 than grade-2 cases. Moreover, TPM1 expression was the highest in stage-1 compared to stage-4, being insignificantly downregulated with tumor progression. The expression of TMP1 was higher in lymph node metastasis, followed by downregulation with tumor metastasis progression, being significantly lower in N3 and N2 cases compared to N0 cases (p = 0.0211 and p = 0.0429, respectively). The same observations were found in TPM1 H-scores. There was a significant decrease in TPM1 percentage and H-score in *H. pylori*-positive compared to *H. pylori*-negative cases (p = 0.0103 and p <0.0001, respectively).

From Table 1, we concluded that CD90 and CD133 showed upregulation from benign to malignant cases and with advanced malignancy and showed higher values in *H. pylori* associated benign cases. In contrast, TPM1 expression showed downregulation in malignancy and in *H. pylori* positive benign gastric cases.

Discussion

GC ranks fourth among cancer-related fatalities

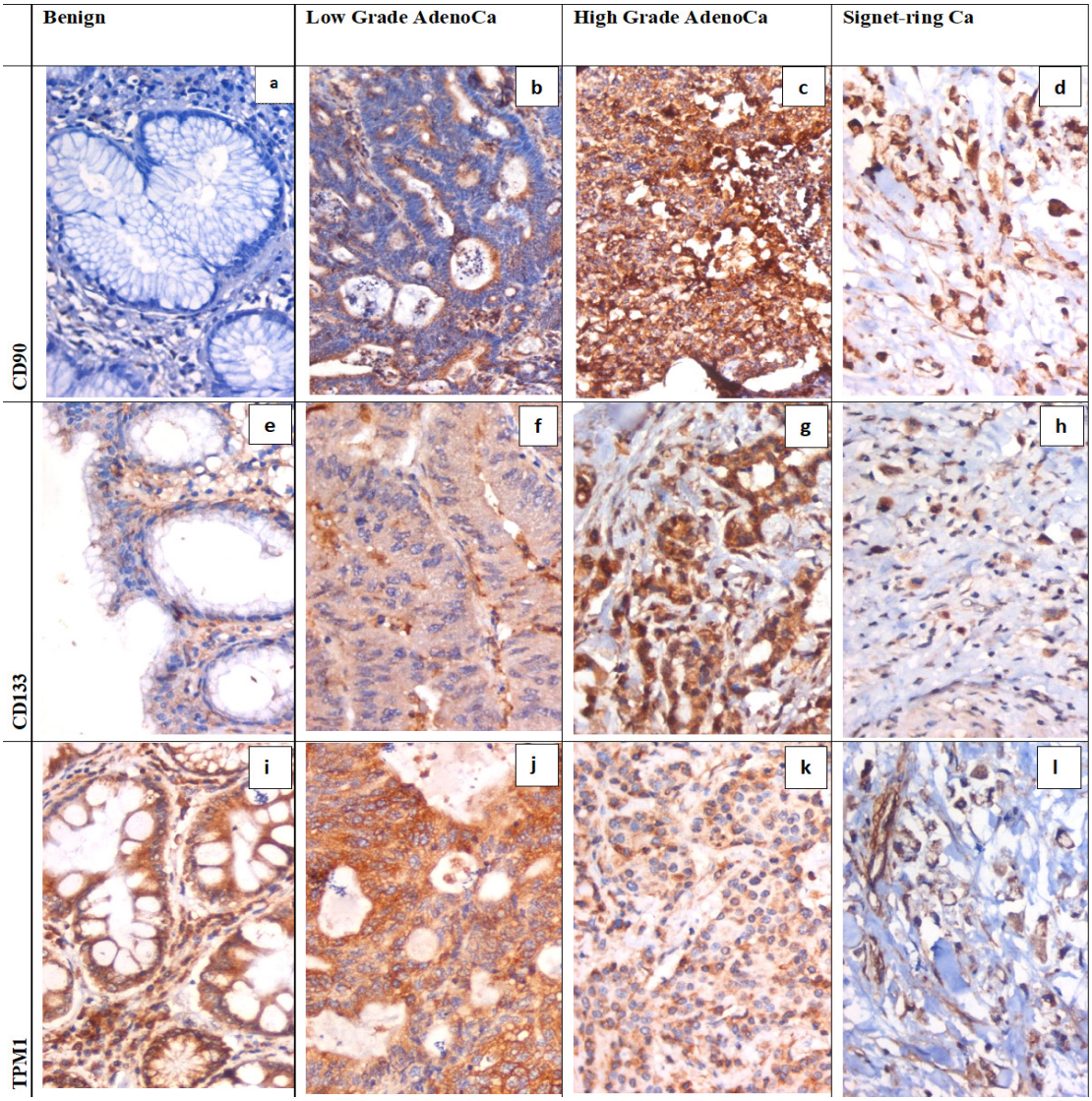

Figure 1. Showed the Tissue Expression of Studied Biomarkers. CD90 & CD133 showed low expression in benign gastric lesions (a & e) with increased expression in low grade gastric adenocarcinoma (b & f) and high expression in high grade gastric adenocarcinoma (c & g) and in signet ring carcinoma (d & h). On the other hand, benign gastritis with intestinal metaplasia showed high expression of TPM1 (i). Low grade adenocarcinoma showed moderate expression of TPM1 (j), while high grade adenocarcinoma (k) and signet-ring carcinoma (l) showed lower expression of TPM1. (IHC, BAB, X400)

globally, with a median survival rate of less than a year for advanced patients. Due to its advanced state upon diagnosis, GC has a high fatality rate (Smyth et al., 2020). The progression of GC is linked to both modifiable and non-modifiable risk factors, such as an infection with *H. pylori*, bad eating and lifestyle habits, advanced age, gender, and having a low socioeconomic position. Elimination of *H. pylori*, reforming of unhealthy behaviors, and usage of screening tools are the three primary components of GC prevention (Rawla & Barsouk, 2019). In the era of microscopic pathology, one of the most important challenges is determining the histological properties of tumor cells and devising a classification system that may indicate the patient's prognosis (Cuzzuol et al., 2020).

Markers of gastric tumors have been used for a variety of purposes, including diagnosis, assessment of treatment responses, screening for recurrence after successful therapy, and identification of the clinical stage of the disease. There are classical biomarkers including CEA and CA 19-9 detected in the last century and used as a prognostic way for GC. Moreover, there are also novel biomarkers that can be used as a prognostic marker for many types of cancers. Cancer biomarkers fall into three broad groups, each of which has a distinct characteristic such as their therapeutic application, diagnostic, and prognostic markers (Lee et al., 2020).

The purpose of our study was the evaluation of CD90, CD133, and TPM1 immunohistochemical expression in GC tissue in relation to benign gastric tissue as regard to diagnosis and prognosis and in relation to the presence or absence of *H. pylori*. According to our results, the mean age for all studied cases was (54.54 years) in males and (54.59 years) in female. Kim et al., (2018) reported that the malignant group's mean age was (61.5 years) while the benign group's mean age was (64.6 years) presenting

no significant differences between both groups. This is concomitant with our results, which showed that the mean age for malignant cases was (55.31 years), while the mean age for benign cases was (51.50 years) with no significant difference. According to what was demonstrated by Martínez-Galindo et al., (2015), the mean age of signet ring carcinoma was higher than the mean age of both adenocarcinoma and gastritis with high significant difference.

As regards the expression of CD90 in different studied gastric lesions included in this study, CD90 positive cases and H-Score showed a significant increase in signet ring cases and adenocarcinoma cases compared to benign cases. This agreed with Zhu et al., (2015) who stated that the expression of CD90 in malignant tissues was higher than that of benign tissue as it was upregulated by 3.46-folds. According to the study of Numakura et al., (2019), the expression of CD90 in signet ring lesions was the highest compared to both gastritis and adenocarcinoma lesions with significant difference. This was in agreement with our study, where we reported a higher level of CD90 expression in signet ring carcinoma cases compared to conventional adenocarcinoma.

We also found a significant increase in CD90 expression in relation to higher grades and stages of tumors. This was also consistent with the study of Numakura et al., (2019). In addition, we found a significant higher expression of CD90 in relation to lymph node metastasis, which agreed with Scognamiglio et al., (2014) and Wang et al., (2013) studies.

Additionally, there was no significant difference in CD90 expression in presence or absence of *H. pylori*, although the CD90 percentage and H-Score were higher in presence of *H. pylori* compared to absence of *H. pylori*. The results of Deka et al., (2021) showed agreement with ours, as they proved that the expression of CD90 in *H. pylori* associated lesions is higher than *H. pylori* non-associated lesions.

CD133 is the most often utilized cell surface antigen to identify and isolate CSCs from a variety of solid tumors such as brain, colon, pancreatic, lung, prostate, and liver tumors. Recently, contradictory information about the accuracy of employing CD133 as a marker for CSCs identification and/or isolation has emerged (Glumac and Lebeau, 2018). Our findings showed that malignant cases had a significantly higher percentage and H-score of CD133 expression than the benign cases, agreeing with the findings of O'Brien et al., (2007) and Noel et al., (2019) which also showed that CD133 expression is lower in benign tissues than malignant tissue.

The current study also revealed a highly significant expression of CD133 in adenocarcinoma and signet ring cases. In addition, grade-2 cases showed the most positive CD133 expression. These results were congruent with the findings of Attia et al., (2019) who found grade-2 adenocarcinoma to have the highest significant expression of CD133. Moreover, Stage-4 and satage-3 cases had significantly higher CD133 expression and H-score compared to stage-1 group, being consistent with the studies of Li et al., (2009) and Kim et al., (2019) which showed a greater proportion of CD133 positive cells in stage IIIB in colon cancer patients, as well as in high-stage and high-grade gastric cancer respectively. N3 cases had the highest percentage of positive CD133 expression and H-score as well. Hashimoto et al., (2014) investigated CD133 expression in 189 gastric cancer patients having undergone a gastrectomy and their findings were consistent with ours, explaining that patients with gastric cancer who had cytoplasmic CD133 expression also showed a higher likelihood of developing lymph node metastases, peritoneal spread, and treatment resistance. Our results revealed that positive *H. pylori* cases had an elevated percentage of CD133-positivity. Howard et al. (2018) observed increase in CD133 expression with a lack of significant difference between positive and negative groups.

TPM1 is a member of the tropomyosin family known to function as an actin-binding cytoskeletal protein in a variety of cells (Wang et al., 2015). Alterations in tropomyosin expression directly influence the development and progression of cancer, whereas mutations in tropomyosin are directly linked to cardiac and skeletal muscle disorders (Wang et al., 2019). TPM1 is also found to be a tumor-suppressor gene (TSG) that is crucial for the development and spread of tumors (Hu et al., 2020). Our study revealed a significant decrease in TPM1 percentage of positive cases expression in malignant studied cases compared to benign ones. Additionally, the reported levels of TPM1 H-score in signet ring carcinoma was lower than the corresponding H-score in benign cases but nearly equal to that of adenocarcinoma cases with no significant difference. These findings were in accordance with a study by Lin et al., (2019) who stated that TPM1 expression was reduced in GC tissues and cell lines compared to nearby gastric epithelium.

Our results also showed that TPM1 expression especially the H-score was downregulated with GC progression in grade, stage, and lymph node metastasis, which is concomitant with the study by Hu et al. (2020) who stated that downregulation of TPM1 was correlated to grade progression, depth of invasion, and lymph node metastasis.

We found that both TPM1 percentage and H-score were significantly lower in *H. pylori*-positive cases while being higher in *H. pylori*-negative cases. Keeping with Libânio et al. (2015) results, stating that *H. pylori* may influence tumor suppressor microRNAs through DNA methylation and epigenetic silencing to impact inflammation-mediated gastric carcinogenesis.

In conclusion, the expression of the CD90 marker as a positive mediator for malignancy and CD133 as a cancer stem cell marker is significantly higher in GC compared to benign cases. Additionally, there is a correlation between their expression and the progression of the tumor in terms of grades and stages, as well as positive lymph node metastasis. Therefore, both markers may have a diagnostic and prognostic value in GC. This should aid in early and personalized treatment, leading to a higher survival rate of gastric adenocarcinoma.

On the contrary, TPM1 expression showed a significant downregulation in malignancy and with tumor progression. So, TPM1 might be a predictive biomarker

for GC diagnosis and prognosis, and a potential significant molecular target for GC therapy. We recommend using follow-up data for patients to confirm the marker's prognostic value.

Author Contribution Statement

TA Suggested the idea of the current work and was responsible for a major part of histopathological diagnosis. SA was responsible for the immunohistochemical study of CD90. NH was responsible for the immunohistochemical study of CD133. NSG was responsible for the immunohistochemical study of TPM1. NSG, TA, SA, and NH contributed to the collection of data, tabulation of results, and manuscript writing. NSG and GS reviewed the manuscript. FH and MM Shared in revising the manuscript and arranging the references. All authors gave their final approval and agreed to be accountable for all aspects of the work..

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Not applicable.

Ethics approval and consent to participate

This research work was approved by the ethical committee of Theodor Bilharz Research Institute, Cairo, Egypt according to the regulations adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 under Federal Wide Assurance No. FWA00010609. Informed consent was taken by all participants and approved by the ethical committee.

Consent for publication

Not applicable.

Availability of data and materials

All data and sources of used materials are available up-on reasonable request.

Competing interests

The authors declare no competing interest.

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