Evaluation of Stromal CD10 Expression in Gastric Adenocarcinoma

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Abstract

Background: Gastric cancer is the fifth most common cancer in the world. The stroma assumes a noteworthy part in the growth and progression of gastric carcinoma regardless of its epithelial nature. Accumulating data indicate that CD10 expression by stromal cells is involved in carcinogenesis. This study aimed to assess the immunohistochemical expression of CD10 in stromal cells of gastric adenocarcinoma and its association with some clinicopathological parameters.

Materials and methods: This cross-sectional study was carried out at the Department of Pathology, Chittagong Medical College, from March 2021 to December 2022. A total of 50 cases of gastric adenocarcinoma, represented by formalin-fixed paraffin-embedded tissue blocks, were included in the study. Hematoxylin and Eosin (H&E)-stained slides from each case were examined to assess the tumour grade, depth of invasion and nodal metastasis. Additionally, an immunohistochemical analysis was conducted to evaluate CD10 expression in the stromal cells of the tumour samples.

Results: CD10 expression in stromal cells was detected in 64% of the cases. Furthermore, stromal CD10 expression showed a significant association with the depth of tumor invasion (p = 0.014). However, stromal CD10 expression had no significant association with age (p=0.434) sex (p=0.147) tumor type (p=0.375) histological grade (p=0.518) and nodal metastasis (p=0.092).

Conclusion: Present study and previous studies support that stromal CD10 expression may be regarded as a negative prognostic indicator for gastric adenocarcinoma.

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Introduction

Gastric cancer remains one of the leading causes of cancer-related deaths worldwide, with gastric adenocarcinoma accounting for approximately 90% of cases.[1,2] In Bangladesh, gastric cancer ranks as the sixth most common cancer, with a prevalence rate of 6.21%. According to the latest World Health Organization (WHO) data published in 2020 gastric cancer deaths in Bangladesh reached 6,799 or 0.95% of total deaths.[3]

The Tumor Microenvironment (TME) is essential in cancer progression and CD10, a cell surface metalloprotease, has been associated with modulating the TME in various cancers.[4] CD10 plays a role in breaking down biologically active Extracellular Matrix (ECM) peptides, which are involved in key processes such as tissue remodeling, embryonic development and angiogenesis. As a metalloprotease, CD10 contributes to ECM degradation, thereby promoting tumor invasion and metastasis.[4,5] This is particularly mediated by Cancer-Associated Fibroblasts (CAFs) in the stroma, promoting a pro-invasive microenvironment.[6] CD10 processes peptides like endothelin-1 and may cleave chemokines or cytokines, which may enhance angiogenesis, cancer cell proliferation and aiding tumor immune evasion.[4,5] Initially recognized as the common acute lymphoblastic leukemia antigen, CD10 was later identified on early B-cell precursors in the bone marrow. In addition to its presence in lymphoblastic leukemia and B-cell non-Hodgkin lymphoma, CD10 expression has also been detected in cancers affecting the head and neck, lungs, breast, prostate, testis, and colorectum.[4,5,7-12]

However, association between CD10-positive stromal cells and invasion and metastasis in gastric carcinoma have been studied less frequently and the findings were not in line. While

CD10 expression in stromal cell is generally associated with aggressive tumor behavior and poor prognosis in gastric adenocarcinoma, there is controversy due to inconsistent findings across studies.[13-16]

Considering the prevailing controversy and shortage of study, especially in Bangladesh this study aimed to examine the expression of stromal CD10 in gastric adenocarcinoma and explore its correlation with various clinicopathological factors such as patient age, gender, tumour type, tumour grade, depth of invasion and lymph node status. The aim is to investigate how stromal CD10 expression may relate to these clinical and pathological characteristics in gastric adenocarcinoma, present study could contribute valuable knowledge that may lead to improved prognostic and therapeutic strategies for this challenging disease.

Materials and methods
This analytical cross-sectional study was conducted in the Pathology Department, Chittagong Medical College, Chattogram, Bangladesh, from March 2021 to December 2022. Fifty conveniently selected patients who were histopathologically diagnosed with gastric adenocarcinoma were included in this study. Patients with recurrent cases of gastric adenocarcinoma and those who had received chemo or radiotherapy for gastric adenocarcinoma were excluded.

Demographic and histopathological information were collected using a structured case record form. Tumors were graded into well-differentiated, moderately differentiated and poorly differentiated adenocarcinoma. The gastric specimens after total or partial gastrectomy were received at reception fixed in 10% formalin and then sent for routine histopathological processing. Tissue processing was done following standard protocol. All the slides were stained with Hematoxylin and Eosin (H&E). Histopathological Examination was done for tumour sub-typing and grading. After evaluating histopathological diagnosis of the lesion, the paraffin embedded block of the samples which met the criteria of inclusion were collected to perform Immunohistochemical (IHC) staining.

IHC Examination: The most representative tumor tissue was chosen from each case and 3-5 m sections of formalin fixed paraffin embedded tissues were taken to poly-L-lysine coated slides. Then deparaffinization was done at hot air oven & xylene and rehydration with graded concentration of alcohol. Antigen retrieval was done by microwave and then the sections were stained with primary antibody against CD10 (monoclonal antibody, dilution 1:50, Dako, Denmark) for 30 min. This method was carried out manually following the DAKO EnVisionTMstaining method and deparaffinized and hydrated. Membranous and cytoplasmic CD10 expression in stromal cells was evaluated. Cases with more than 10% positivityin stromal cells were classified as positive (Figure 1) while those with less than 10% positivity were considered negative (Figure 2).
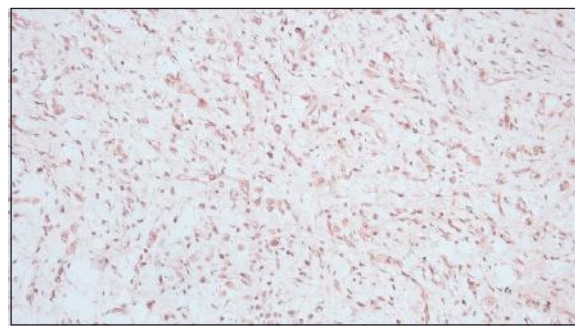
Figure 1 Photomicrograph showing Intestinal type GA, Grade III (×20) CD10 expression: Positive (+)

Figure 2 Photomicrographshowing Intestinal type GA, Grade I (×20) CD10 expression: Negative (-)

Data were fed into SPSS Windows version 23.0 for processing and analysis. Qualitative variables were expressed as frequency (Percentage) and compared between groups by Chi-square test. p value less that 0.05 was considered statistically significant.

The study was approved by the Ethical Review Board of Chittagong Medical College (Memo No. CMC/PG/2022/824, Date: 16/04/2022). Informed written consent was obtained from the patient.

Results

The age ranged between 30 and 75 years in the present study. Out of a total of 50 cases, most of the cases 34(68%) belonged to the age group of >50 years, with a mean age of 56.98 ± 9.55 years, and 39 (78%) patients were male (Table I). About three quarter (74%) of the tumour were intestinal type and 40% tumors were poorly differentiated (Grade III) tumors. Out of 50 tumour, 10 (20%) tumor invades the muscularis propria, 34 (68%) tumor penetrates the sub serosal connective tissue without invasion of the visceral peritoneum or adjacent structures and rest of the 6 (12%) tumors invades the serosa or adjacent structures. There were 20 (40%) cases showing metastasesin lymph nodes and 30 (60%) cases without metastases in lymph nodes (N0 stage). Among 50 tumors studied, 32 (64%) showed a positive CD10 expression in stromal cells (Table I).

Table I Tumor characteristics of the 50 cases of gastric adenocarcinoma

Chracteristics	Count	Percent (%)
Age groups		
≤50 years	16	32.0
>50 years	34	68.0
Sex		
Male	39	78.0
Female	11	22.0
Histological type		
Intestinal	37	74.0
Diffuse	13	26.0
Tumor grade		
Well- differentiated	3	6.0
Moderately differentiated	12	24.0
Poorly differentiated	20	40.0
Depth of invasion		
Muscularis propria	10	20.0
Subserosa	34	68.0
Serosa	6	12.0
Nodal metastases		
Present	20	40.0
Absent	30	60.0
CD10 expression		
Positive	32	64.0
Negative	18	36.0

Age group and sex of the patients had no significant association with CD10 expression in stromal cells. Among the intestinal type, 25 (67.6%) were positive for CD10, whereas, among diffuse types 7 (53.8%) were positive for CD10 immunoreactivity. However, the association between tumour type and stromal CD10 immunoreactivity failed to reach significance (Table II). The association between tumor grade and stromal C10 immunoreactivity did not show any significant result (p=0.518). There were three Grade I tumors, of which 2 (66.7%) were CD 10 positive and 1 (33.3%) were CD10 negative. In the 27 Grade II tumors, 9 (33.3%) showed CD 10 positivity and 18 (66.7%) were CD10 negative. Out of the 20 Grade III tumors, 7 (35%) were CD10 positive and 13 (65%) were CD10 negative. Depth of invasion was significantly associated with stromal CD10 expression. Out of 10 tumour which invaded up to muscularis propria, only 3 (30%) were CD10 positive and 7 (70%) were CD10 negative. Out of 34 tumour which invaded up to subserosa, 23 (67.6%) were CD10 positive and 11 (32.4%) were CD10 negative. Out of 6 tumour which invaded up to serosa, all of them (100%) were CD10 positive. Proportion of the patients with nodal metastasis with stromal CD10 positive immunoreactivity was higher than the patients without nodal metastasis (73.3% versus 50%). However, the difference failed to reach statistical significance (p=0.092).

Table II Association amongstromal CD10 immunoreactivity and clinicopathological factors (n=50)

Variables	CD10 immunoreactivity		
	Negative	Positive	p value*
Age groups			
≤50 years (n=16)	7 (43.8)	9 (56.3)	0.434
>50 years (n=34)	11 (32.4)	23 (67.6)	
Sex			
Male (n=39)	12 (30.8)	27 (69.2)	0.147
Female (n=11)	6 (54.5)	5 (45.5)	
Tumour type			
Intestinal (n=37)	12 (32.4)	25 (67.6)	0.375
Diffuse (n=13)	6 (46.2)	7 (53.8)	
Tumour grade			
Grade I (n=3)	2 (66.7)	1 (33.3)	0.518
Grade II (n=27)	9 (33.3)	18 (66.7)	
Grade III (n=20)	7 (35.0)	13 (65.0)	

Variables	CD10 immunoreactivity		
	Negative	Positive	p value*
Depth of invasion			
Muscularis Propria (n=10)	7 (70.0)	3 (30.0)	0.014
Subserosa (n=34)	11 (32.4)	23 (67.6)	
Serosa (n=6)	0 (0)	6 (100.0)	
Nodal metastasis			
Absent (n=20)	10 (50.0)	10 (50.0)	0.092
Present (n=30)	8 (26.7)	22 (73.3)	

Data were expresses as frequency (Percentage),
*Chi-square test.
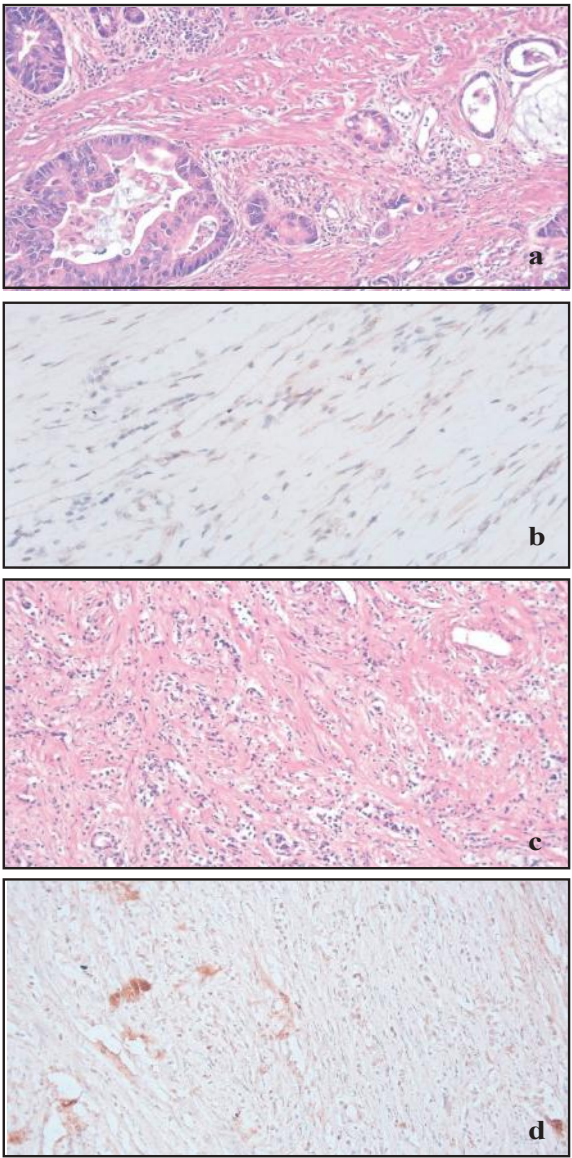
Figure 3 Photomicrograph showing **a.** Intestinal type GA, Grade II, Invasion: Serosa, H&E (×20) **b.** Positive CD10 expression(x40) **c.** Diffuse type GA, Grade III, Invasion: Subserosa, H&E (×20) **d.** Positive CD10 expression (x20)

Discussion

CD10 is a well-known metalloproteinase expressed by various cell types.[17] Their release from stromal myofibroblasts in malignant tumors enhances the growth of cancer cells.[18] In the present study, out of 50 tumors studied, 64% showed a positive CD10 expression in stromal cells and remaining 36% cases were negative for CD10 immunoreactivity. This result was similar to that found by Mohan et al. where 62.5% cases showed a positive CD10 expression in stromal cells.[19] In contrast, other studies observed comparatively lower positivity rate (15%-46%).[13,14,16]

Mean age of the patients was 52.3 years (SD ± 9.2 years) and most of the patients (68%) were in more than 50 years age group. The age distribution agreed to the previous hospital-based study conducted in Bangladesh.[20,21] Gastric cancer is more likely to be found in males, who account for approximately 60% of all gastric cancer diagnoses. It is also a cancer that is generally diagnosed more frequently with increasing age. The average age at diagnosis is 68.[22] In the present study male outnumber female with a male to female ratio 3.5:1, which was also agreed with the local studies.[20,21] Similar to the study of Aziz et al. CD10 expression was not associated with age and sex of the patients in the present study.[16]

The present study demonstrated higher immunoreactivity of stromal CD10 in intestinal type than the diffuse types of gastric adenocarcinoma (67.6% versus 53.8%) without any statistical significance. Previous study by Aziz et al. found that among CD10 positive cases, 91.6% were intestinal type, and 8.3% was a diffuse type, whereas, among negative cases, 54.4% were intestinal type and 45.6% were diffuse type.[16] Huang et al. found a statistically significant association between such immunoreactivity and tumor type, as he observed that most stromal CD10 positive tumors were of intestinal type.[14] Intestinal-type gastric adenocarcinoma arises from Helicobacter pylori-associated chronic gastritis that induces intestinal metaplasia. It undergoes dysplasia followed by carcinoma in situ and invasive carcinoma and chronic inflammation recruits bone marrow-derived myofibroblasts positive for CD10.[23] In agreement with previous studies, the association between tumor grade and

stromal C10 immunoreactivity did not show any significant result in the current study.[16,19,24] The positivity rate was 66.7%, 33.3% and 35%, respectively in Grade I, II, and III tumors.

In the present study, depth of invasion was significantly associated with stromal CD10 expression, which was similar to the study of Mohan and Krishnan, where a statistically significant correlation was observed between the depth of invasion in gastric adenocarcinoma and CD10 expression.[19] In a similar study conducted by Jafarian et al. a significant association was found between tumor invasion and CD10 expression.[13] This indicates that CD10 expression in stromal cells may play a crucial role in the development of gastric cancer. Additionally, the proliferation of CD10-positive stromal cells appears to contribute to the invasion mechanism in gastric cancer. Research by Huang et al. has also demonstrated that stromal cells expressing CD10 may be involved in gastric carcinogenesis, suggesting that CD10 expression facilitates invasion and metastasis in differentiated gastric carcinoma.[14] Proportion of the patients with nodal metastasis with stromal CD10 positive immunoreactivity was higher than the patients without nodal metastasis (73.3% versus 50%) in the present study. However, the difference failed to reach statistical significance. Similar to present study, although a majority (About 92%) of stromal CD10 positive samples had positive lymph nodes, this was not significant statistically because 85% of stromal CD10 negative cases had lymph nodes, in the study of Aziz et al. Sravan et al. demonstrated a significant correlation between stromal CD10 expression and lymph nodal metastasis.[16,24] Compatible results about such association with lymphovascular invasion and lymph node status were found by Jafarian et al. Unlike the findings of this study, Huang et al. reported a significant correlation between stromal CD10 positivity and both lymphovascular invasion and nodal metastasis.[13,14] Furthermore, another study analyzing 78 cases of gastric lesions identified a strong association between CD10 expression and lymph node metastasis.[25] The differences between the results of this research and previous studies may be attributed to various factors, such as sample size, fixation duration, antigen retrieval techniques, antibody type and

scoring criteria.This study revealed a significant link between stromal CD10 expression and the depth of invasion in gastric adenocarcinoma. This finding highlights the role of CD10 in tumor invasion and metastasis, indicating a more aggressive biological behavior.Previously, Pan et al. demonstrated that peptide prodrugs enhanced the effectiveness of cytotoxic drugs.[26] However, these prodrugs were susceptible to cleavage by peptidases, including CD10 found in the tumor microenvironment. Their findings suggested that inhibiting CD10 could improve the therapeutic index of these drugs. New cancer therapy to enhance the effect of already present cytotoxic drugs and medications to prevent gastric cancer in high-risk patients can be invented depending on the present research and future studies on the molecular basis of stromal–cancer interaction. High expressions of post-CD10 and pre-CD10 were related to worse tumor regression grade in neoadjuvant chemotherapy in gastric carcinoma. CD10 expression has been associated with chemoresistance and overall survival, serving as a predictive biomarker for tumor regression and prognosis in patients with locally advanced gastric cancer.[27] Therefore, the present study findings might add to the growing body of evidence, which could be applied to a new cancer therapy that blocks the induction of CD10-positive stromal cells in gastric cancer tissue. This approach may reduce the activities of the CD10-positive stromal cells, which accelerate tumor aggressiveness. Further studies on the molecular basis of CD10 expression in stromal–cancer interaction will be required to pursue such new therapeutic strategies.

Limitations
Due to financial and time constraints study sample was taken from a single institute and sample size was relatively small which may not reflect the exact scenario of whole country.Information regarding distal metastasis could not be included due to lack of logistic support like PET scan, which could give more conclusive decision regarding prognostic significance of CD10. Stromal CD10 expression in other types of gastric tumours could not be assessed.

Conclusion
Stromal CD10 immunoreactivity was identified in 64% of gastric adenocarcinoma cases, which was

significantly correlated with the tumor depth of invasion. Stromal CD10 expression may serve as a promising target for evaluating the depth of invasion in gastric adenocarcinoma.

Recommendations

Due to the aggressive nature of gastric carcinoma, there is a necessity for a comprehensive study that can shed light on the role of CD10 expression in the advancement of gastric cancer. This large-scale investigation could potentially provide valuable insights into the disease's progression.

Contributions of authors

RAM-Design, acquisition of data, data analysis, drafting and final approval.

ZS-Data analysis, critical revision and final approval.

JR-Interpretation of data, drafting and final approval.

MFA-Acquisition of data, drafting and final approval.

PB-Conception, critical revision and final approval.

Disclosure

All the authors declared that there is no conflict of interest.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2021;71(3):209-249.
[https://doi.org/10.3322/caac.21660.

2. Mukaisho KI, Nakayama T, Hagiwara T, Hattori T, Sugihara H. Two distinct etiologies of gastric cardia adenocarcinoma: Interactions among pH, Helicobacter pylori and bile acids. Frontiers in Microbiology. 2015;6:412-419.
[https://doi.org/10.3389/fmicb.2015.00412.

3. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A et al. Cancer statistics for the year 2020: An overview. International journal of cancer. 2021;149(4):778-789.
https://doi.org/10.1002/ijc.33588.

4. Wang S, Xiao Y, An X, Luo L, Gong K, Yu D. A comprehensive review of the literature on CD10: its function, clinical application, and prospects. Frontiers in Pharmacology. 2024;15:1336310.
https://doi.org/10.3389/fphar.2024.1336310.

5. Mishra D, Singh S, Narayan G. Role of B cell development marker CD10 in cancer progression and prognosis. Molecular Biology International. 2016;2016(1):4328697.
https://doi.org/10.1155/2016/4328697.

6. Oya Y, Hayakawa Y, Koike K. Tumor microenvironment in gastric cancers. Cancer science. 2020;111(8):2696-707.
https://doi.org/10.1111/cas.14521.

7. Fukusumi T, Ishii H, Konno M, Yasui T, Nakahara S, Takenaka Y et al. CD10 as a novel marker of therapeutic resistance and cancer stem cells in head and neck squamous cell carcinoma. British Journal of Cancer. 2014;111(3):506-514.
https://doi.org/10.1038/bjc.2014.289.

8. Gürel D, Karg A, Karaman I, Önen A, Ünlü M. CD10 expression in epithelial and stromal cells of non-small cell lung carcinoma (NSCLC): A clinic and pathologic correlation. Pathology & Oncology Research. 2012;18:153-160.
https://doi.org/10.1007/s12253-011-9421-8.

9. Jana SH, Jha BM, Patel C, Jana D, Agarwal A. CD10-a new prognostic stromal marker in breast carcinoma, its utility, limitations and role in breast cancer pathogenesis. Indian Journal of Pathology and Microbiology. 2014;57(4):530-536.
https://doi:10.4103/0377-4929.142639.

10. Dall'Era MA, True LD, Siegel AF, Porter MP, Sherertz TM, Liu AY. Differential expression of CD10 in prostate cancer and its clinical implication. BMC Urology. 2007;7(3):1-11.
https://doi.org/10.1186/1471-2490-7-3.

11. Fankhauser CD, Sulser T, Zhong Q, Barghorn A, Moch H, Bode PK. CD10 expression in 325 testicular germ cell tumours. Journal of Clinical Pathology. 2015;68(5):400-403.
https://doi.org/10.1136/jclinpath-2014-202806.

12. Ogawa H, Iwaya K, Izumi M, Kuroda M, Serizawa H, Koyanagi Y et al. Expression of CD10 by stromal cells during colorectal tumor development. Human Pathology. 2002 ;33(8):806-811.
https://doi.org/10.1053/hupa.2002.125773.

13. Jafarian AH, Kooshki Forooshani M, Takallou L, Mohamadian Roshan N. CD10 expression in gastric carcinoma is correlated with tumor grade and survival. Univ Med. 2019;38(1):41-47.
https://univmed.org/ejurnal/index.php/medicina/article/view/792.

14. Huang WB, Zhou XJ, Chen JY, Zhang LH, Meng K, Ma HH et al. CD10-positive stromal cells in gastric carcinoma: correlation with invasion and metastasis. Japanese Journal of Clinical Oncology. 2005;35(5):245-250.
https://doi.org/10.1093/jjco/hyi076.

15. Sato Y, Itoh F, Hinoda Y, Ohe Y, Nakagawa N, Ueda R et al. Expression of CD10/neutral endopeptidase in normal and malignant tissues of the human stomach and colon. Journal of Gastroenterology. 1996;31:12-17. https://doi.org/10.1007/BF01211181.

16. Aziz SJ, Jalal JA, Hamadameen KS. Stromal CD10 expression in gastric adenocarcinoma. Journal of Medicine and Life. 2022;15(5):679-684. https://doi: 10.25122/jml-2021-0244.

17. Maguer-Satta V, Besançon R, Bachelard-Cascales E. Concise review: Neutral endopeptidase (CD10): A multifaceted environment actor in stem cells, physiological mechanisms, and cancer. Stem Cells. 2011;29(3):389-396. https://doi.org/10.1002/stem.592.

18. Hassona Y, Cirillo N, Heesom K, Parkinson EK, Prime SS. Senescent cancer-associated fibroblasts secrete active MMP-2 that promotes keratinocyte dis-cohesion and invasion. British journal of cancer. 2014;111(6):1230-1237. https://doi.org/10.1038/bjc.2014.438.

19. Mohan BP, Krishnan SK. CD10 expression in gastric adenocarcinoma and its correlation with histopathological features and lymph node metastasis. Asian Journal of Medical Sciences. 2021;12(10):75-80. https://doi.org/10.3126/ajms.v12i10.38754.

20. Nahar MJ, Matubber MM, Rahman MM, Rahman MM, Billah SMB, Sayed M et al. Evaluation of pre-operative clinical finding and per-operative assessment of carcinoma stomach in tertiary settings of Bangladesh. J. Surg. Sci. 2020;22(1):43-46. https://banglajol.info/index.php/JSS/article/view/44023.

21. Shahi A, Koyyala VP, Rathaur ES, Biddut MA, Hossain A, Hasan MK et al. Association between gastric Cancer with behavioral and dietary factors: a Hospital Based Case-Control Study in South Asia. Asian Journal of Oncology. 2021. https://doi.org/ 10.1055/s-0041-1740106.

22. Hartgrink HH, Jansen EP, van Grieken NC, van de Velde CJ. Gastric cancer. The Lancet. 2009;374(9688):477-490. https://doi: 10.1016/S0140-6736(09)60617-6.

23. Quante M, Tu SP, Tomita H, Gonda T, Wang SS, Takashi S et al. Bone marrow-derived myofibroblasts contribute to the mesenchymal stem cell niche and promote tumor growth. Cancer Cell. 2011;19(2):257-272. https://doi.org/10.1016/j.ccr.2011.01.020.

24. Sravan C, Kanna S, Kuma KM. Expression of CD10 Marker in Stromal Cells of Gastric Carcinoma: A Prospective Study. Scholars Academic Journal of Biosciences. 2017;5(3):192-199. https://doi:10.36347/sajb.2017.v05i03.011.

25. Bassyoni OY, Nasif SN. Tissue expression of CD10 and CD15 proteins in gastric lesions: Correlation with clinicopathological features. Egyptian Journal of Pathology. 2017;37(2):321-327. https://doi:10.1097/01.XEJ.0000526553.77396.

26. Pan C, Cardarelli PM, Nieder MH, Pickford LB, Gangwar S, King DJ et al. CD10 is a key enzyme involved in the activation of tumor-activated peptide prodrug CPI-0004Na and novel analogues: implications for the design of novel peptide prodrugs for the therapy of CD10+ tumors. Cancer research. 2003;63(17):5526-5531. http://cancerres.aacrjournals.org/content/63/17/5526.

27. Tong Y, Zhao Z, Zhang J, Wang W, Zhu Y. High expressions of CD10, FAP and GPR77 in CAFs are associated with chemoresistance and worse prognosis in gastric cancer. Frontiers in Oncology. 2022;12:984817. https://doi.org/10.3389/fonc.2022.984817.