e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(6); 2070-2078

Original Research Article

Expression and Clinicopathological Correlation of Cyclin D1 and CD44 Stem Cell Marker in Gastric Carcinoma

Priyanka P.[1], Asha Rani P.S.[2], Swathi M.[3], Eswari V.[4]

[1,2]Assistant Professor, Department of pathology, Anna Gowri Medical College and Hospital, Puttur, Andhra Pradesh, India.

[3]Assistant Professor, Department of pathology, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research, Enathur, Kanchipuram -631552, Tamil Nadu, India.

[4]Professor and Head, Department of pathology, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research, Enathur, Kanchipuram -631552, Tamil Nadu, India.

Received: 27-04-2026 / Revised: 26-05-2026 / Accepted: 28-06-2026

Corresponding Author: Dr. Priyanka P

Conflict of interest: Nil

Abstract:

Aim and Background: The present study aimed to investigate the immunohistochemical expression of CD44 and Cyclin D1 in gastric carcinomas and to assess their correlation with clinicopathological parameters. Gastric cancer (GC) is the fifth most common cancer worldwide and the fourth most leading factor in cancer -related deaths, with an expected million new incidences and 769,000 fatalities in the year 2020.

Materials and Methods: This is a prospective and retrospective study of gastric adenocarcinoma. Study of 20 resected (subtotal, total, radical and palliative gastrectomy) and 10 endoscopic biopsy specimens were collected from the Department of Surgery and Surgical Gastroenterology in the period between June 2019-June 2022 in the Department of pathology, Meenakshi Medical College Hospital and Research Institute. All the patient demographics, clinical presentation, site, size, type of growth and lymph nodes were noted and Immunohistochemical studies for CD 44 and Cyclin DI were done.

Results: CD44 and Cyclin DI expression is noted only in well to moderately differentiated tumors and of intestinal subtype while there is no expression seen in diffuse type and poorly differentiated gastric adenocarcinoma.

Conclusion: In the present study we concluded that expression of CD44 and Cyclin D1 were significantly associated with intestinal type and histopathological grade of tumor hence these can be used as a marker for differentiation of type of gastric cancer.

Keywords: Gastric Cancer, CD44, Cyclin DI, Immunohistochemical Expression.

DOI: 10.25258/ijcpr.18.6.331

Introduction

Gastric cancer (GC) is incredibly uncommon below 30 years. Most frequently, stomach cancer occurs in adults between 6th and 8th decade of life. In India, the age range for stomach cancer is 45 to 55years in the North and 35 to 55years in South. Men have a higher incidence of GC than women [1]. More incidences of GC have been reported in South India than in North Eastern regions [2]. Ninety- five percent of the gastric malignancies are gastric adenocarcinomas. The multistep carcinogenesis of human GC is influenced by many genetic and epigenetic alterations that involve oncogenes, tumor suppressor genes, cell cycle regulators, and cell adhesion molecules. Though numerous pathohistological classifications have been used for Gastric carcinomas, the two most commonly used classification systems are WHO and Lauren's classification. Lauren classified gastric carcinoma into intestinal and diffuse types. WHO classification included not only adenocarcinoma but other rare types also. The method of treatment is determined by the anatomical site of the tumor, size of the tumor and the possibility of obtaining tumor free surgical margin. Surgery is the preferred form of therapy for any respectable stomach cancer. Despite treatment, progression, metastasis, therapy resistance and recurrences are common [3].

Researchers now focus on identifying Cancer Stem Cells (CSC) and targeting them for treatment. Tumor comprises heterogeneous populations of cells which are explained by clonal evolution hypothesis and the stem cell hypothesis. Only a small subset of solid tumor cells is thought to have

stem cell like properties. These cancer stem cells (CSCs), as opposed to non -malignant stem cells, have a higher potential for self - renewal, rapid proliferation, and resistance to chemotherapy or radiation [4].

Cancer stem cells (CSCs) were first identified in acute myeloid leukemia and later found in various solid tumors from brain, breast, colon, prostate, liver, pancreas, and skin. Gastric cancer stem cells (GCSCs) express distinct cell surface markers which include CD44, EpCAM, ALDH, CD-133 and SOX 2. Over expression or under expression of these markers is related to lymph vascular invasion, size of the tumor and response to treatment.

Cell adhesion molecules tightly control the interact ion of cells with one another as well as with the extracellular matrix. Any change in this feature of cell adhesion molecules paves the way for the spread and growth of tumors.

The cluster of differentiation 44 (CD44), the main hyaluronate receptor, encoded by the short arm of chromosome 11 in humans, is an important cell adhesion molecule. The extracellular domain, transmembrane domain, and intracellular domain are the three distinct domains that make up CD44. Its extracellular component interacts with the ligand hyaluronan (HA), and this interact ion creates favorable condition for CSCs to rapidly proliferate and differentiate [5].

CD44 promotes gastric stem cell proliferation by boosting cyclin D1 expression. This is accomplished by recruiting active form of signal transducer and activator of transcription 3 (STAT3) that has been involved in the emergence of carcinogenic consequences. Cyclin D1 proto-oncogene is a cell cycle regulatory protein, involved in the progression of cell cycle from the G1 phase to the S phase. Cyclin D1 forms active complexes with its binding partners, cyclin -dependent kinases 4 and 6 (CDK4 and CDK6), which accelerates cell cycle advancement by phosphorylating and inactivating the retinoblastoma protein. The cyclin D1 protein has a very short half -life (less than 24 minutes). 18 A high level of cyclin D1 activity in a cell causes it to undergo the G1–S transit ion too early, which results in the propagation of DNA damage that has not been repaired and the accumulation of genetic mistakes, which produces a permissive environment for the growth of abnormal cells [6].

Over expression or under expression of CD44 and Cyclin D1 is thought to be significant factor in the development of tumors by influencing various aspects of tumor cell behavior, including proliferation, invasion, metastasis, and the immunological escape response. The purpose of this present study is to evaluate the expression of CD44 and Cyclin D1 in gastric carcinoma and correlate them with clinicopathological features.

Materials and Methods

Our study was a prospective and retrospective of gastric adenocarcinoma carried out at the department of Pathology, MMCH&RI, Kanchipuram for a period of 13 months from June 2021 to June 2022. 30 primary gastric carcinoma patients who underwent gastric resection or endoscopic resection. All resected as well as biopsy specimens irrespective of age and gender were included in the study. Retrieval of tissue blocks from the resected specimens and histopathological slides of the corresponding numbers were collected. New slides were made from the corresponding blocks. The blocks were sectioned into 4 micron thick sections and stained with Hematoxylin - Eosin and IHC stains CD44 and Cyclin D1. Complete basic clinical information of patients was collected from medical records. All the 30 cases were assessed for CD44 and Cyclin D1 expression through immunohistochemical assay. Immunohistochemical stained slides were grouped into positive and negative according to the percentage of cells stained and intensity of stain. Positive control for CD44 and Cyclin D1- Sections from a tonsillar tissue and mantle cell lymphoma case were used as a positive control for CD44 and Cyclin D1 respectively. Negative controls were obtained by replacing the primary antibody with a non-immunized rabbit or mouse serum.

Scoring criteria for CD44: For the interpretation of CD44 expression, both the staining intensity and percentage of cells stained were considered.

1. Intensity of staining was scored as follows:

(0) = No staining

(1+) = Weak staining

(2+) = Moderate staining

(3+) = Strong staining

The Composite score was obtained by multiplying both the intensity of staining as well as the percentage of staining. The composite score ranges from 1 to 9. Composite scores of 1 -3 we r e labeled as ‘low CD4 4 expression ’whereas scores of 4- 9 we relabeled as “high C D4 4 expression”. A tumor with any of the score was considered as positive expression, while those with no staining only was considered as negative expression.

Scoring Criteria for Cyclin D1: The intensity of nuclear staining was graded from 0 to 3 as follows:

Grade 0 – absence of staining

Grade 1 – faint nuclear staining

Grade 2 – moderate nuclear staining

Grade 3 – intense nuclear staining.

The distribution of positive cells in tumors were graded based on the score present in Negative, 1+, 2+ and 3+ indicates no staining, 10% tumor cells, 11-50% tumor cells and more than 50% tumor cells respectively.

Statistical Analysis: All the data's were collected and the association between categorical explanatory variables was assessed by the chi -square test. P value < 0.05 considered as association between outcome variable and explanatory variable. Independent T test was used to assess statistical significance between categorical outcome variable and explanatory continuous variable. P value < 0.05 was considered statistically significant by using IBM SPSS software version 22.

Results

Age and sex wise distribution: Table.1 showed that the age of the patients ranged from 30 -80 years, the mean age was 60.6 ± 10.65. Among them, the most commonly affected age group (33%) was between 61-70 years. In our study, we had an equal gender distribution, 50% of them were male and 50% of them were female.

Table 1: Age and sex wise distribution

Distribution of patients	31-40 years	41-50years	51-60years	61-70years	71 and above
Age wise	1(3.3%)	5(16.7%)	9(30.0%)	10(33.3%)	5(16.7%)
Sex wise	1 male	2 males 3 females	4 males 5 females	5 males 5 females	3 males 2 females

Distribution of CD44 Expression based on pattern of staining: Table.2 showed that our study CD 44 expression was further categorized as low expression and high expression based on the scoring pat tern. Cases with low expression had an equal distribution of cytoplasmic (18.75%) and membranous (18.75%) positivity. Cases with high expression had predominantly membranous positivity (43.75%), (12.5%) had cytoplasmic positivity and (6.25%) had both cytoplasmic as well as membranous positivity.

Table 2: Distribution of CD44 Expression based on pattern of staining

CD 44 Positive Cases	Cytoplasmic	Membranous	Both
Low CD44 Expression	3 (18.75%)	3 (18.75%)	0
High CD44 Expression (10)	2(12.5%)	7(43.75%)	1 (6.25%)

Correlation of Expression of CD44 with tumor location: Table.3 indicated that the tumors in the antropyloric region predominantly showed no staining while more than half of the tumors in cardia, fundus and body showed CD44 expression. This correlation did not show any statistical significance.

Table 3: Correlation of Expression of CD44 with tumor location

Location	Score of CD 44			Chi Square	P Value
	High	Low	Negative		
Cardia, Fundus and Body (N=10)	5 (50%)	2(20%)	3(30%)	2.143	0.343
Antrum and Pylorus (N=20)	5 (25%)	4(20 %)	11 (55%)		

Correlation of expression of CD44 with histologic type: Table 4 mentioned that all the diffuse types of tumor showed no staining for CD44, whereas in the intestinal type of tumor, 10 showed high CD44 expressions, 6 showed low CD44 expression and only 4 of them had no staining. So statistically significant correlation exists between CD44 expression and histologic type of Gastric carcinoma.

Table 4: Correlation of expression of CD44 with histologic type

Histological Type	Score of CD 44			Chi Square	P Value
	High	Low	Negative		
Diffuse (N=10)	0	0	10 (100%)	16.619	<0.001
Intestinal (N=20)	10(50%)	6(30%)	4(20%)		

Correlation of expression of CD44 with histologic grade: Table.5 indicated that the statistical significance exists between CD44 expression and histologic grade because in our study CD44

expression was in proportion with grade of the tumor and well differentiated tumor showed higher expression compared to moderately differentiated tumor and there was no staining in poorly differentiated carcinoma.

Table 5: Correlation of expression of CD44 with histologic grade

Histologic Grade	Score of CD44			Chi square	P Value
	High	Low	Negative		
Well Differentiated (N=10)	6(60%)	2(20%)	2(20%)	18.743	<0.001
Moderately Differentiated (N=10)	4(40%)	4(40%)	2(20%)		
Poorly differentiated (N=10)	0(0%)	0(0%)	10 (100%)		

Correlation of expression of CD44 with tumor stage (pT of TNM): Table.6 indicates among the study population, 2(100%) of pT1 stage had high CD44 score, in 2 of pT2 stage 1 showed high CD44 expression and 1 had no staining, in 2 of pT3 stage 1 showed low CD44 expression and 1 had no staining and among 14 of pT4 stage 7 showed CD44 expression and 7 did not express CD44 maker. The difference in proportion of CD44 score between pT of TNM stage was not statistically significant. (p value 0.586).

Table. 6. Correlation of expression of CD44 with tumor stage (pT of TNM)

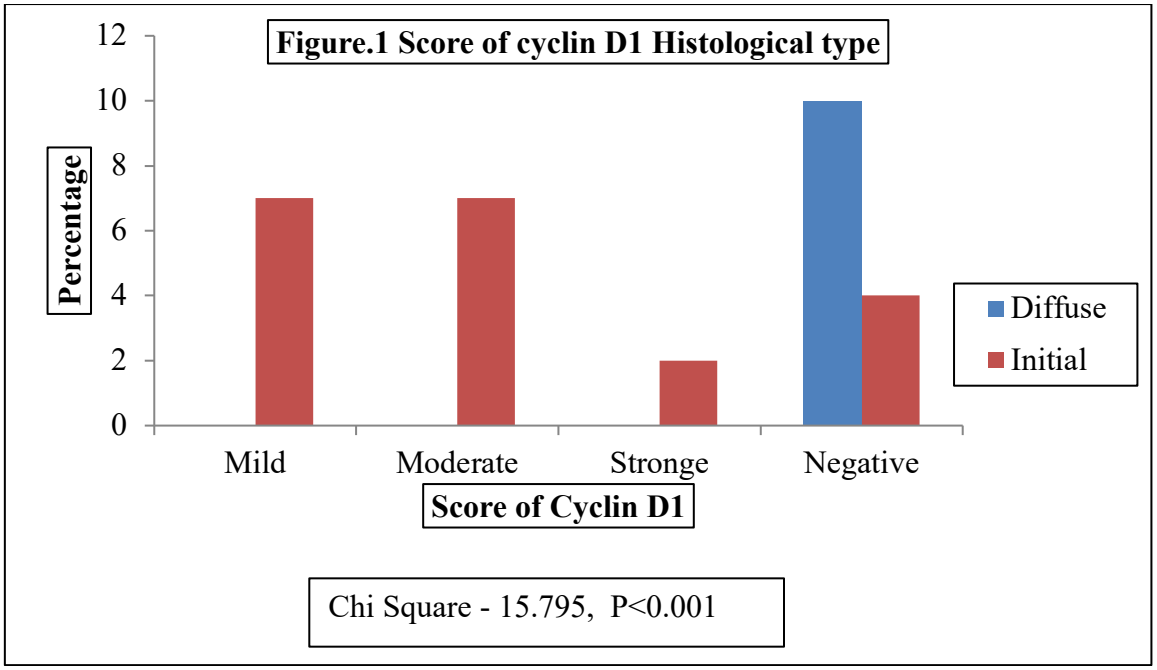
pT of TNM Stage	Score ofCD44			Chi-square	P-value
	High	Low	Negative		
Biopsy(N=10)	2(20%)	3(30%)	5(50%)		
pT1(N=2)	2(100%)	0(0%)	0(0%)		
pT2(N=2)	1(50%)	0(0%)	1(50%)		
pT3(N=2)	0(0%)	1(50%)	1(50%)		
pT4(N=14)	5(35.7%)	2(14.3%)	7(50%)	**6.697**	**0.586**

Distribution based on Cyclin D1 expression: Table 7 showed that among the study population, cases which expressed cyclin D1 were further categorized based on scoring pat tern. All of them showed only nuclear staining and there was no cytoplasmic staining of Cyclin D1 in our study. Among Cyclin D1 expression there was an equal distribution of mi ld (23.33%) and moderate cases (23.33%) and only 6.67% had strong staining. 46.67% of them showed no expression.

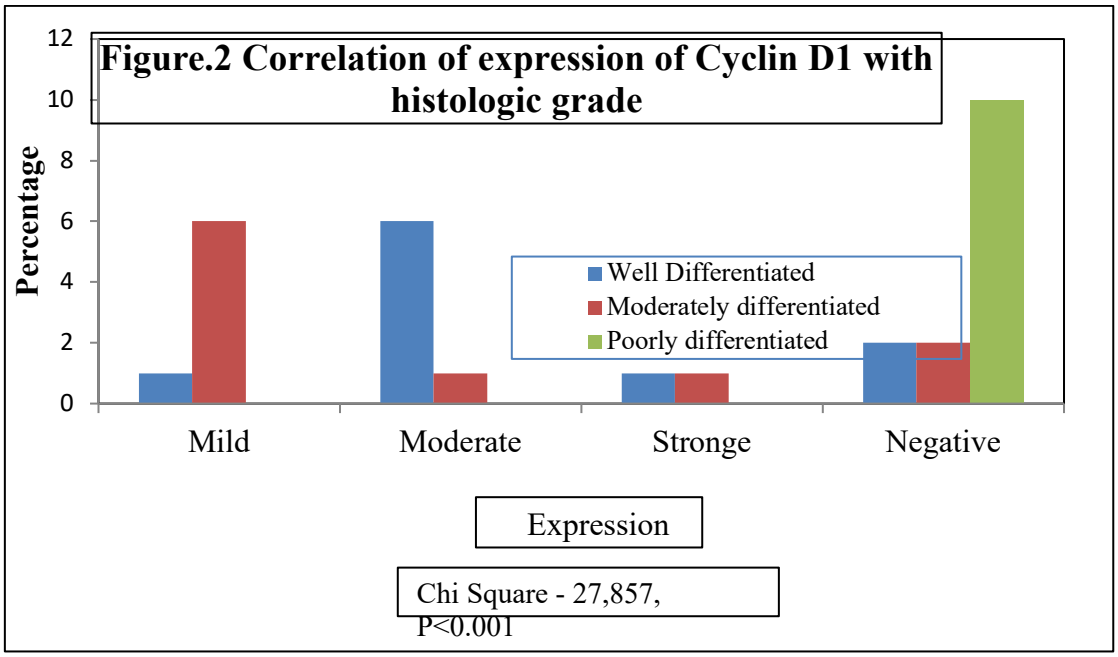
Table 7: Distribution based on Cyclin D1 expression

Score of Cyclin D1	No of Cases	Percentages
Mild	7	23.33%
Moderate	7	23.33%
Strong	2	6.67%
Negative	14	46.67%

Correlation of expression of Cyclin D1 with histologic type: Figure.1. represents that all the dif fuse types of tumor showed no staining for Cyclin D1, whereas in the intestinal type of tumor, mi ld and moderate expression of Cyclin D1 was in equal number, 2 showed strong expression and 4 showed absent staining. This showed a statistically significant relation between CD44 expression and histologic type of Gastric carcinoma.



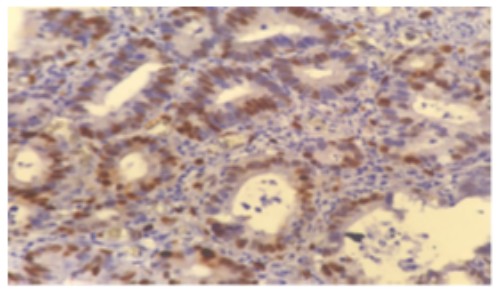
Correlation of expression of Cyclin D1 with histologic grade: Figure.2. Statistical significance exist between Cyclin D1 expression and histologic grade because in our study Cyclin D1expression was in proportion with grades of the tumor that is well differentiated tumor showed more moderate expression, compared to moderately differentiated tumor and there was lack of staining in poorly differentiated carcinoma.



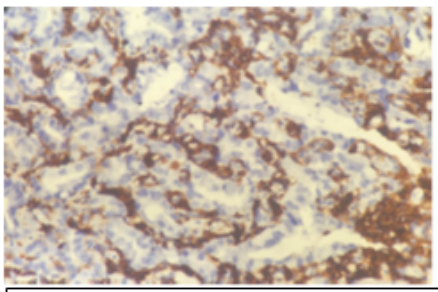
Comparison between Score of CD44 and CYCLIN D1: Table.8 indicates that among the study population, cases with high CD 44(10) expression have predominantly moderate (6) CyclinD1 expression, cases with low CD 44 expression also showed either mild (4) Cyclin D1 expression or no expression. Cases with no CD 44 expression (14) als o had predominantly (10) Cyclin D1 negative staining, 2 of them showed mi ld Cyclin D1 expression, 1 had moderate expression and the remaining 1 had strong Cyclin D1 expression. (p value 0.004).

Table 8: Comparison between Score of CD44 and CYCLIN D1

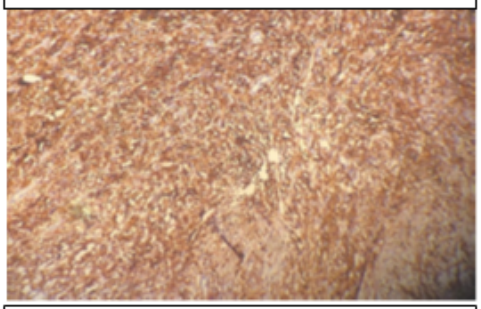
Score Of CD44	Score of Cyclin D1				Chi-square	P-value
	Mild	Moderate	Strong	Negative		
High (N=10)	1(10%)	6(60%)	1(10%)	2(20%)	18.980	0.004
Low (N=6)	4(66.67%)	0(0%)	0(0%)	2(33.33%)		
Negative (N=14)	2(14.29%)	1(7.14%)	1(7.14%)	10(71.43%)		



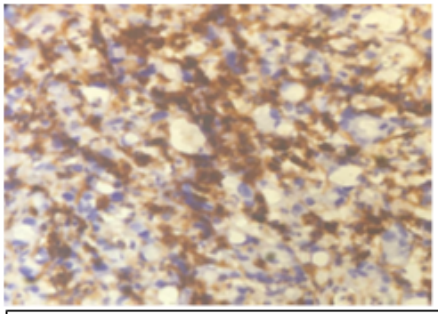
Strong cyclin D1 nuclear positive expression in the tumor cells of well differentiated adeno carcinoma



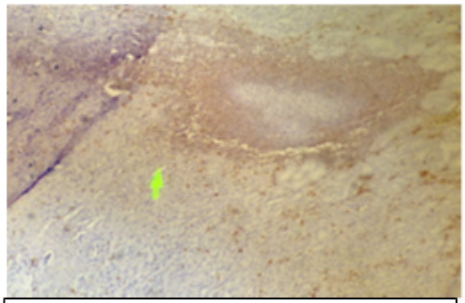
Strong membranous and cytoplasmic positive expression of CD44 in the tumor cells of well differentiated adeno carcinoma



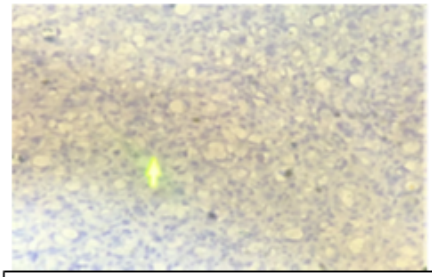
Strong CD44 membranous expression in the tumor cells of moderatelv differentiated adenocarcinoma



Strong cyclin D1 nuclear expression in tumor cells of moderately differentiated adenocarcinoma



CD44 positivity in the lymph node adjacent to the tumor, to differentiate CD44 negative expression in poorly differentiated tumor



Cyclin D1 negative expression in poorly differentiated adenocarcinoma

Immuno Histochemical Images

Discussion

Gastric carcinoma occurs in patients throughout the world, although the incidence varies geographically. GC is the fourth leading cause of mortality. A tiny subset of tumor cells known as CSCs that resemble stem cells play a role in the development, metastasis, and therapy resistance of GC. CD44 has been identified as a CSC marker and as a key actor in controlling the characteristics of CSCs in various tumors, including GC. The present targeted therapeutic approaches in GC primarily aim to destroy non - CSCs; nonetheless, the surviving CSCs in GC are implicated in tumor metastasis and recurrence.

The unchecked cell proliferation by cyclin D1 and increased cell migration signifies its oncogenic activity. Various putative molecular mechanisms under lie the cell migration by the interact ion of cyclin D1 - CDK4/6 complexes, p27kip1 and ROCKII (Rho/ROCK signaling).

These have functions related to cytoskeleton remodeling that contribute cell migration.

Consequently, understanding about pathogenesis of CD44 and Cyclin D1 expression is war ranted for the development of therapy targeting CSCs and cell cycle regulators respectively for effective treatment of GC.

This study at tempts to analyze the expression of cyclinD1 and CD44 and correlate its expression with various clinicopathological parameters. This study was undertaken in 30 gastric carcinoma patients. Patients age ranged from 35 to 76 years. The mean age of the patients recruited in the study was 60.6 years. Takano et al conducted studies in 455 gastric carcinoma patients and found that the median age at diagnosis was 60.6 (range 28-87 yrs) which was similar to our study

In our study, we had an equal gender distribution of 15 (50%) were male patients and 15 (50%) were female patients. Majority of the patients (90%) presented with weight loss, (86.6%) followed by pain abdomen, early satiety (60%), vomiting (43.3%), dysphagia (20%) and malena (13.3%) which was similar to the study done by Barad et al [7].

When we look upon the histologic grade of the tumor 33.3% were diagnosed with well - differentiated adenocarcinoma, 33.3% were moderately differentiated adenocarcinoma, and 33.3% of poorly differentiated adenocarcinoma in this study. However, it was contrary to the study by Emmanuel le Leteurtre et al [8] who observed that poorly differentiated adenocarcinoma constituted the most common type, followed by moderately differentiated and well -differentiated adenocarcinomas.

When lymph node status were studied, our study showed 80% positivity in lymph node metastasis and 20 % negativity in resected specimens, which showed 75% lymph node positivity and 25% lymph node negativity. We had more advanced cases (80%) than early cases (20%) in resected specimen, which was similar to the study done by Takano et al [9]. in 455 cases of gastric carcinoma.

CD44 EXPRESSION IN GASTRIC CARCINOMA: In our study we categorized CD44 positive cases based on staining intensity and percentage of cells stained into low and high expression. Most tumors that expressed CD44 showed high expression (33.33%) and 20% had low expression of CD44. Non-expressors (46.67%) showed complete absence of cytoplasmic as well as membranous staining within the entire tumor. This was similar to the study done by Priyadharisini J et al [10]. Out of 30% cases CD44 positive cases were 53.33%. Our investigation exhibited a strong statistical relationship with the histological subtype. CD 44 expression was largely seen in the intestinal subtype and was absent in the diffuse type. Similarly, in a study by Kamran Ghaf farzadehgan et al [11] stomach cancer was found in 100 patients, and of those, 65% had CD44 positive cases, frequently expressed in intestinal subtype (p=0.002). In a study by T. wang et al[12] 116 cases of stomach cancer cases, CD44 positivity was present in 77% of the patients, which demonstrated strong statistical connect ion with histological stage and tumour grade (p=0.002).

This study showed CD44 expression in well and moderately differentiated histopathological grade but poorly differentiated grade showed no expression, which was consistent with Yamaguchi et al 131 results that differentiated adenocarcinomas expressed CD44 at a much greater level than diffuse-type carcinomas (p=0.014). Review by Wang et al [12]. which contrasted with our results, found that CD4 4 expression was substantially more common in GC with poor/undifferentiated compared with well /moderate differentiation (P=0.027) and in GC with dif fuse type compared with intestinal type histology (P=0.016). Primary tumor stage classification (T of pTNM) demonstrated no statistical significance with CD44 expression in our study, which was in agreement with Cao et al 136 study but at odds with Chen et al 's [13] study, which found that CD44 expression was positively correlated with advanced stage and had been l inked to the emergence of lymph node metastases. Statistically significant relationship was not established between clinicopathological factors like gender, depth of invasion and lymph node status. This finding was consistent with Kamran Ghaf farzadehgan et al [11]. and T. wang et al [12] who also found a statistically significant relationship only for histological type and tumour grade. We had mostly membranous positivity compared to cytoplasmic staining similar to the study by Priyadharisini J [10] in 50 gastric carcinoma cases.

CYCLIN D1 Expression in Gastric Carcinoma: In our study we categorized Cyclin D1 positive cases based on staining intensity and percentage of cells stained into mild, moderate and strong. Most tumors that expressed cyclin D1 showed mi ld (23.33%) to moderate (23.33%) nuclear staining and only 6.67% of cases showed intense nuclear staining. Non-expressors (46.67%) generally showed complete absence of nuclear staining within the entire tumor. So, the summation of all Cyc l in D1 positive cases were 53.33%, similar to the findings by Begnami et al [14]. Our study showed more than 50% of positive cases for cyclin D1 and all of them were of intestinal type, similar to W. Muller et al [15] studies which showed Cycl in D1 immuno expression in approximately 50% of gastric cancers, more commonly in the intestinal type than in the diffuse type whereas in a study done by M. D. Begnami et al [14] the same frequency of cyclin D1–positive cases (50%) was found with no statistical

significance to histologic subtype. Similar results were demonstrated in colorectal carcinomas by Dr Elli Ioachim [16]. However, in a study by W. Muller et al [15] in tumour cell differentiation, differences in cyclin D1 expression did not reach statistical significance.

Cyclin D1 immuno expression in the nucleus was considered as positive, whereas expression in the cytoplasm was regarded as aberrant. Our study had only nuclear positivity. Takano et al [9] investigation's showed that immunohistochemistry positive was limited to nuclei, with the 5% of cases that had high cytoplasmic staining being regarded as negative.

According to Baldin et al [17] in human tumour cell lines, cyclin D1 is confined to the nucleus but vanishes as cells enter the S phase. In agreement, Gillet et al [18] observed that in 5% of breast tumours, there was high cytoplasmic staining without any nuclear reaction. It has been proposed that such tumours should be viewed as negative because the cause of this unusual distribution is unknown. Arber et al [18] pointed out that the presence of cyclin D1 outside the nucleus in colonic neoplasm suggests an additional but as of yet undefinable physiological purpose.

Comparison between score of CD44 and Score of Cyclin D1: In our study, intestinal subtypes and grades with well to moderate differentiation expressed both Cyclin D1 and CD 44. Cases with high CD44 expression also had moderate to strong Cyclin D1 expression whereas in cases with low CD44 expression, Cyclin D1 was either absent or weakly expressed.

Cases lacking CD4 expression were predominant ly lacking in Cyclin D1 expression also. The difference in proportion of CD44 and cyclin D1 Score was statistically significant. (p value 0.004) which was similar to the study done by Ibrahim et al [12] and chang et al [19] studied CD44 expression in Chronic Myeloid Leukemia, showed down regulation of CD44 resulted in down regulation of Cyclin D1 also. This is because CD 44 cancer stem cells regulate and promote Cyclin D1 cell cycle regulator. In thyroid carcinoma, De Falco et al [20]. has demonstrated that CD44 - ICD up regulates Cyclin D1 expression by recruiting CREB transcript ion factor.

Conclusion

Our research revealed a significant association of Cyclin D1 and CD 44 with histological type and histopathological grade as well as between the markers. A substantial association between Cyclin D1 and Tumor stage is also present. These findings suggest that certain marker profile's

may play a crucial role in therapeutic care of patients with gastric cancer in the future. The results of our study showed that Cyclin D1, a cell cycle regulator is enhanced by CD 44 cancer stem cells. Cyclin D1 is crucial for the G1 checkpoint of the cell cycle. Therefore, over expression of Cyclin D1 causes an early G1-S phase transition that propagates unrepaired DNA and leads to abnormal cell proliferation. This present study gives a better understanding of the fundamental basis of how Cyclin D1 and CD44 expressions were regulated, Which will be helpful to understand the mechanism underlying the pathogenesis of GC and developing targeted therapy in GC.

References

1. Yeole BB. Trends in cancer incidence in esophagus, stomach, colon, rectum and liver in males in India. Asian Pac J Cancer Prev. 2008 Mar;9(1):97-100.
2. Sharma A, Radhakrishnan V. Gastric cancer in India. Indian Journal of Medical and Paediatr ic Oncology. 2011 Jan;32(01) :12 -6.
3. Jothy S. CD44 and its partners in metastasis. Clinical & experimental metastasis. 2003 May;20(3):195-201.
4. Shibue T, Weinberg RA. EMT, CSCs, and drug resistance: the mechanistic link and clinical implications. Nature reviews Clinical oncology. 2017 Oct ;14(10):611-29.
5. Naor D, Sionov RV, Ish-Shalom D. CD44: structure, function and association with the malignant process. Advances in cancer research. 1997 Jan 1;71:241-319.
6. Hall M, Peters G. Genetic alterations of cyclins, cyclin –dependent kinases, and Cdk inhibitors in human cancer. Advances in cancer research. 1996 Jan 1;68:67-108.
7. Barad AK, Mandal SK, Harsha HS, Sharma BM, Singh TS. Gastric Cancer a clinicopathological study in a tertiary care centre of North - eastern India. Journal of Gastrointestinal Oncology. 2014 Apr;5(2):142.
8. Leteurt re E, Zerimech F, Piessen G, Wacrenier A, Leroy X, Copin MC, Mariet te C, Aubert JP, Porchet N, Buisine MP. Relat ionships between mucinous gast ric carcinoma, MUC2 expression and survival. World journal of gastroenterology: WJG. 2006 Jun 6;12(21):3324.
9. Takano Y, Kato Y, Masuda M, Ohshima Y, Okayasu I. Cyclin D2, but not cyclin D1, overexpression closely correlates with gastric cancer progression and prognosis. The Journal of pathology. 1999 Oct ;189(2):194-200.
10. Priyadharisini J. Cd44 (Cell Adhesion Molecule) Expression in Gastric Adenocarcinoma-Prognostic Importance. A Study of 50 Cases (Doctoral dissertation, Stanley Medical College, Chennai) .
11. Ghaf farzadehgan K, Jafarzadeh M, Raziee HR, Sima HR, Esmaili - Shandiz E, Hosseinnezhad

H, Taghizadeh -Kermani A, Moaven O, Bahrani M. Expression of cell adhesion molecule CD44 in gastric adenocarcinoma and its prognostic importance. World journal of gastroenterology: WJG. 2008 Nov 11;14(41):6376.
12. Wang T, Ong CW, Shi J, Srivastava S, Yan B, Cheng CL, Yong WP, Chan SL, Yeoh KG, Iacopetta B, Sal to-Tellez M. Sequential expression of putative stem cell markers in gastric carcinogenesis. British journal of cancer. 2011 Aug;105(5):658 -65.
13. Chen Y, Fu Z, Xu S, Xu Y, Xu P. The prognostic value of the CD44 expression in gastric cancer: a meta-analysis. Biomed Pharmacother. 2014;68:693–7.
14. Begnami MD, Fregnani JH, Nonogaki S, Soares FA. Evaluat ion of cell cycle protein expression in gastric cancer: cyclin B1 expression and its prognostic implication. Human pathology. 2010 Aug 1;41(8):1120-7.
15. Müller W, Noguchi T, Wi rtz HC, Hommel G, Gabbert HE. Expression of cell cycle regulatory proteins cyclin D1, cyclin E, and their inhibitor p21 WAF1/CIP1 in gastric cancer. The Journal of pathology. 1999 Oct ;189(2):186-93.
16. Ioachim E. Expression patterns ofcyclins D1, E and cyclin dependent kinase inhibitors p21waf1/cip1, p27kip1 in colorectal carcinoma: Correlation with other cell cycle regulators (pRb , p 53 and Ki - 67 and PCNA) and clinico pathological features. International journal of clinical practice. 2008 Nov;62(11):1736 -43.
17. Baldin V, Lukas J, Marcote MJ, Pagano M, Draet ta G. Cyclin D1 is a nuclear protein required for cell cycle progression in G1. Genes & development . 1993 May 1;7(5):812-21.
18. Arber NA, Hibshoosh HA, Moss SF, Sut ter TH, Zhang Y, Begg ME, Wang SH, Weinstein IB, Holt PR. Increased expression of cyclin D1 is an early event in multistage colorectal carcinogenesis. Gastroenterology. 1996 Mar 1;110(3):669 -74.
19. Chang G, Zhang H, Wang J, Zhang Y, Xu H, Wang C, et al . CD44 targets Wnt/β -catenin pathway to mediate the proliferation of K562 cells. Cancer Cell Int . 2013;13:117.
20. De Falco V, Tamburr ino A, Ventre S, Castel lone MD, Malek M, Manié SN, et al . CD44 proteolysis increases CREB phosphorylation and sustains proliferation of thyroid cancer cells. Canc er Res.2012;72:1449–58.