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Expression of CD44 in Gastric carcinoma and its correlation with Cadherin-11 expression and clinicopathological parameters—A Pilot study on the promising Immunohistochemical markers.

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ABSTRACT:

Gastric cancer is a significant concern with many unanswered questions, particularly cancer stem cells, the tumour environment, and specific gene expressions. The prognosis for advanced gastric cancer remains poor. Identifying predictive markers for cancer progression and prognosis would help assess clinical outcomes and potential treatment stratification for gastric cancer patients. This study aims to analyse the role of CD44 and CDH-11 in gastric cancer. The study will include 30 gastrectomy specimen reports, and the clinicopathological parameters will be noted. The expressions of CD44 and CDH-11 will be examined in the tumour tissues. The statistical analysis will be performed. Our study found that most gastric carcinoma patients were men aged 61-70. Tumors were mostly poorly differentiated, with intestinal-type adenocarcinoma being the most common. CD44 expression was observed in 80% of patients and was associated with tumour grade and extent. The study found a significant association between CD44 expression and tumour grade ($p=0.005$). Our study found that 80.0% of CD44-positive cases also showed positive Cadherin 11 expression. Statistical analysis suggested a potential link between the two markers, with a trend towards correlation that requires further investigation. Hence, CD44 could serve as a prognostic indicator for gastric cancer.

Keywords: Gastric Carcinoma, CD44, CDH-11, Epithelial-mesenchymal transition.

INTRODUCTION:

Gastric cancer ranks as the sixth most common cancer globally and is the third leading cause of cancer mortality [1]. Despite recent progress in cancer therapy and increased knowledge of tumour biology, many areas in gastric cancer remain unexplored, especially the epithelial-mesenchymal transition part [2]. Cancer stem cells are a subset of the tumour population that can initiate tumours and reconstitute the cellular heterogeneity typical of their tumours of origin [3]. Several reports have suggested that cancer stem cells can initiate cancer progression by inducing cancer metastasis and therapeutic resistance in gastric cancer, resulting in poor survival [4]. The tumour environment is the cellular environment in which the tumour exists, including the extracellular matrix, mesenchymal stem cells, endothelial cells and signalling molecules such as growth factors and cytokines. Cancer and the surrounding tumour microenvironment are constantly interacting with each other [5].

CD44 is a family of transmembrane glycoprotein receptors encoded by the highly conserved CD44 gene on chromosome 11 in humans [6]. The CD44 gene comprises 20 exons and 19 introns. It binds to hyaluronic acid, and the resultant intracellular signalling is linked to diverse cellular functions, including cell adhesion, migration, and invasion. Thus, CD-44 has been implicated in tumorigenesis and metastasis [7].

Tumour budding, defined as single cells or small clusters of tumour cells at the invasive front of the tumour, is thought to be a histological representation of epithelial-mesenchymal transition [EMT] [8]. The invasive front of tumours (ITF) is believed to be of significant prognostic value due to several key characteristics. These include the lack of cohesiveness among the cells at the ITF, leading to invasive behaviour; the secretion of proteolytic enzymes by these cells, which can facilitate the degradation of surrounding tissues and contribute to tumour progression; the reorganisation of the extracellular matrix, a crucial component of the tumour microenvironment, which can promote tumour invasion and metastasis; and the increased cell proliferation observed at the ITF, indicating rapid tumour growth and potential aggressiveness. These combined features make the ITF a critical area for understanding tumour behaviour and predicting clinical outcomes [9,10].

CDH-11 (Cadherin-11) is a type-2 classical cadherin in the integral membrane protein family that facilitates calcium-dependent cell-cell adhesion. It is located on human chromosome 16q22.1.6. Abnormal regulation of CDH-11 plays a role in numerous pathological processes, such as inflammation, fibrosis, cellular migration, invasion, epithelial-mesenchymal transition (EMT), and cancer development [11]. Hence, more knowledge about the role of EMT

in metastasis and its control is essential. The role of CDH11 in GC progression remains unclear. CDH-11 expression, if proven, can be an excellent predictive tool for metastases and can be used in treating patients with gastric cancer.

Limited research has been undertaken regarding the interaction between Invasive front of tumours (ITF) and the expression of CD44. Our study aims to address this gap by analysing the expression of CD44 in gastric tumour tissues and ITF. Furthermore, we seek to examine the potential correlation between CD44 expression and its correlation with CDH-11 expression and various clinicopathological parameters.

MATERIALS AND METHODS:

The Institutional Ethics Committee, SRIHER, approved this Pilot study. Thirty gastrectomy specimen reports were retrieved from the Department of Pathology, SRIHER, Chennai, Tamil Nadu, India and the clinicopathological parameters were noted.

Inclusion criteria: Cases with histopathologic diagnosis of Gastric Carcinoma were included in the study.

Exclusion Criteria: Cases with histopathologic diagnosis of biopsy specimen, Benign tumour and all other neoplasms were excluded.

Formalin-fixed and paraffin-embedded tissue blocks of the resected gastric cancer specimens were cut into 3-micrometre thick sections, deparaffinised and rehydrated. Each section was stained with a CD44 polyclonal antibody (IgG, Unconjugated, E-AB-63249, Elabscience,1:100 dilution) and CDH11 polyclonal antibody (IgG, Unconjugated, GTX109792, GeneTex, 1:100 dilution). After this, it was incubated with a secondary antibody for 30 minutes at room temperature. Positive control for CD44 – Human Tonsil and positive control for CDH-11: Human Placenta. Strong CD-44 and CDH-11 membranous immunostaining in more than 10 % of the epithelial tumour cells was considered positive.

Two pathologists independently blinded to the clinicopathological parameters performed the immunostaining examination. When a discrepancy occurred, a final decision was established by reassessment using a penta-headed microscope.

Statistical analysis was performed using SPSS v.26 software. Numerical variables were expressed as the mean and standard deviation (SD). The Chi-square test was used, and statistical associations between clinicopathological parameters were assessed with the $\chi 2$ test and p values were also determined.

RESULTS:

Table 1: Demographic and Clinicopathological Characteristics of Gastric Carcinoma Patients

VARIABLES		**FREQUENCY (n=30)**	**PERCENTAGE (%)**
Age (years)	<30	1	3.3
	31-40	3	10.0
	41-50	5	16.7
	51-60	7	23.3
	61-70	9	30.0
	>70	5	16.7
	Mean ±SD	57.13 ± 13.72	
	Range	29-77	
GENDER	Male	23	76.7
	Female	7	23.3
Histological grade	well differentiated	1	3.3
	Moderately differentiated	13	43.3
	Poorly differentiated	16	53.3
Histological type	Adenocarcinoma - Intestinal type	21	70.0
	Adenocarcinoma with focal signet ring cells and mucinous features	1	3.3
	Adenocarcinoma with focal signet ringcells.	3	10.0
	Adenocarcinoma with focal signet ring cells (5%).	1	3.3
	Adenocarcinoma with neuroendocrine differentiation	1	3.3

	Mucinous carcinoma with signet cells	1	3.3
	Papillary Adenocarcinoma	1	3.3
	Signet ring cell carcinoma	1	3.3
TUMOR EXTENT	Invades muscularis mucosa	1	3.3
	Invades muscularis propria	8	26.7
	Invades serosa	6	20.0
	Invades submucosa	1	3.3
	Invades visceral peritoneum	1	3.3
	Penetrates subserosal connective tissue.	13	43.3
LYMPH NODE INVASION	Present	18	60.0
	Absent	12	40.0
PERINEURAL INVASION	Present	9	30.0
	Absent	21	70.0
CD44	Positive	24	80.0
	Negative	6	20.0
CADHERIN 11	Positive	12	40.0
	Negative	13	43.3
	Cytoplasmic positive	5	16.7

Table 2: Expression of CD44 in Gastric Carcinoma and Its Association with Clinicopathological Parameters

Clinicopathological Parameters		**CD 44**		**P value**
		POSITIVE (n=24)	NEGATIVE (n= 6)	
AGE GROUP	<44	4(16.7%	1(16.7%)	0.458
	45-70	17(70.8%)	3(50.0%	
	>71	3(12.5%)	2(33.3%)	
GENDER	Male	5(83.3%)	18(75.0%)	1.000
	Female	1(16.7%)	6(25.0%)	
HISTOLOGICAL GRADE	Well differentiated	0(0%)	1(16.7%)	0.005*
	Moderately differentiated	8(33.3%)	5(83.3%)	
	Poorly differentiated	16(66.7%)	0(0%)	
TUMOR EXTENT	Invades muscularis mucosa	1(4.2%)	0(0%)	0.287
	Invades muscularis propria	6(25.0%)	2(33.3%)	
	Invades serosa	6(25.0%)	0(0%)	
	Invades submucosa	0(0%)	1(16.7%)	
	Invades visceral peritoneum	1(4.2%)	0(0%)	
	Penetrates subserosal connective tissue.	10(41.7%)	3(50.0%)	
LYMPH NODE INVASION	Present	16(66.7%)	2(33.3%)	0.184
	Absent	8(33.3%)	4(66.7%)	
PERINEURAL INVASION	Present	8 (33.3%)	1 (16.7%)	0.637
	Absent	16(66.7%)	5 (83.3%)	

Table 3: Association between CD44 and Cadherin 11 Expression

CD44	CADHERIN 11			TOTAL	P value
	POSITIVE	NEGATIVE	CYTOPLASMIC POSITIVE		
POSITIVE	12(100.0)%	8(61.5%)	4(80%)	24(80.0%)	χ^2=5.769, p=0.056
NEGATIVE	0(0%)	5(38.5%)	1(20.0%)	6(20.0%)	
TOTAL	12(100%)	13(100%)	5(100%)	30(100%)	

DISCUSSION:

Our study revealed that the highest proportion of patients were 61 to 70 years old, with a greater representation of men. These results align with a similar study conducted by Selcukbiricik F et al.[12]. The demographic breakdown of patients reveals that 57.1% are male and 42.9% are female. Among the male patients, most are under 50 years old, with only 14.3% being over 70. In contrast, female patients are more likely to fall within the 50-70 years age group, indicating a delayed onset of gastric carcinoma. Both male and female patients show a lower percentage of those over 70 years old, underscoring a noteworthy gender disparity in the age distribution of gastric carcinoma patients.

Most of the tumours observed in the study were poorly differentiated, followed by moderately differentiated. Among these, intestinal-type adenocarcinoma was identified as the most prevalent. These findings agreed with the results reported in separate studies conducted by Zheng H et al. and Isik M et al. [13,14]. Tumour extent analysis indicated that 43.3% of tumours had invaded the subserosal connective tissue, and lymph node invasion was present in 60% of cases. This finding aligned with the study conducted by Yasuda K et al. and Morgagni P et al. studies [15,16].

Cluster of differentiation 44 (CD44) serves as a cell surface receptor for hyaluronic acid, a vital constituent of extracellular matrices. Situated on chromosome 11p13, the CD44 gene comprises 20 exons, with ten exons active in the standard form known as CD44s [17]. CD44, cell surface glycoprotein, has been reported to mediate cell adhesion to extracellular matrices, promote cell motility, facilitate matrix degradation, regulate cell proliferation, and enhance cell survival. In addition, it is known to be of particular importance in the invasion and metastasis of tumours [18].

Previous studies have shown that elevated expression of CD44 is commonly observed in gastrointestinal tumours and is closely associated with tumour invasion, lymph node metastasis, and patient overall survival [19].

Our study showed that 80% of the patients had an expression of CD44, which is consistent with the research findings of Marrelli D et al. [20]. The distribution of CD44 expression in various age groups showed no significant correlation. However, most patients with positive CD44 expression belonged to the 45-70 age group (p=0.458), similar to the study conducted by Ryu MS et al. [21]. The gender distribution analysis revealed that 83.3% of male participants and 16.7% of female participants showed positivity for CD44, which was in correlation with the study by Senol S et al. [22]. The statistical analysis indicated no significant difference in the distribution of CD44 positivity between males and females, with a p-value of 1.000.

In the study, a statistically significant association was observed between the expression of CD44 and the histological grade of the tumours (p=0.005). Interestingly, the analysis revealed that poorly differentiated tumours exhibited a higher CD44 positivity rate (66.7%) than moderately and well-differentiated. This finding suggests a potential correlation between CD44 expression and the degree of tumour differentiation, which is statistically significant. This finding is consistent with the study by Jang BI et al. [23].

The statistical analysis revealed a correlation between the expression of CD44 and the extent of the tumour, with a calculated p-value of 0.287. Interestingly, a significant percentage (66.7%) of patients with tumours infiltrating the subserosal connective tissue and the serosa exhibited CD44 expression. This suggests that as the depth of tumour invasion increased, the expression of CD44 became more pronounced. These findings are consistent with a study conducted by Hong RL [24]. There was no statistically significant correlation between the size of the tumour, the invasion of lymph nodes, and perineural invasion and the expression of CD44. However, it is interesting that approximately 66.7% of patients with lymph node invasion exhibited CD44 positivity, similar to the Chen Y et al. study [25].

Understanding and assessing the invasive front is of paramount importance across different types of gastric malignancies. The invasive front of a tumour consists of detached groups of tumour cells located at the advancing edge of the tumour. This area is significant as it contains valuable prognostic information to help determine the disease's progression and potential outcomes [26]. Our study found that the tumours expressing CD44 also displayed

expression at the invasive tumour front. This correlation suggests a possible association between CD44 expression and tumour invasiveness.

CDH11, a type 2 Cadherin family member, is known for its capacity for homophilic binding, which relies on Ca++. During developmental stages, CDH11 plays a crucial role in facilitating the movement of neural crest cells. CDH11 is primarily expressed in adult tissues in osteoblasts, which maintain and regulate bone health and metabolism [27]. It is hypothesised that the endogenous expression of CDH11 in osteoblasts, along with its ability to bind with homophilic CDH11 physically, may contribute to the stabilisation of metastasised tumour cells in bone stromal niches, thus enabling bone metastasis. This potential role of CDH11 in tumour cell behaviour and its consequences for bone metastasis warrants further investigation to understand the underlying mechanisms better [28].

The study examining the relationship between CD44 and Cadherin 11 expression in patients with gastric carcinoma found that 80.0% of CD44 positive cases also showed positive Cadherin 11 expression in 100.0% of those cases. The analysis showed a potential link between the expression of CD44 and Cadherin 11. The statistical test approached significance, with a chi-square value of 5.769 and a p-value of 0.056. This suggests a trend towards correlation, indicating that there may be an association between the two markers. Further investigation is needed to explore this potential relationship.

Thus, it is indicated that CD44 is significantly upregulated in gastric cancer and acts as an independent prognostic indicator. These findings suggest that CD44 holds substantial promise as a predictive marker for evaluating the prognosis of gastric cancer.

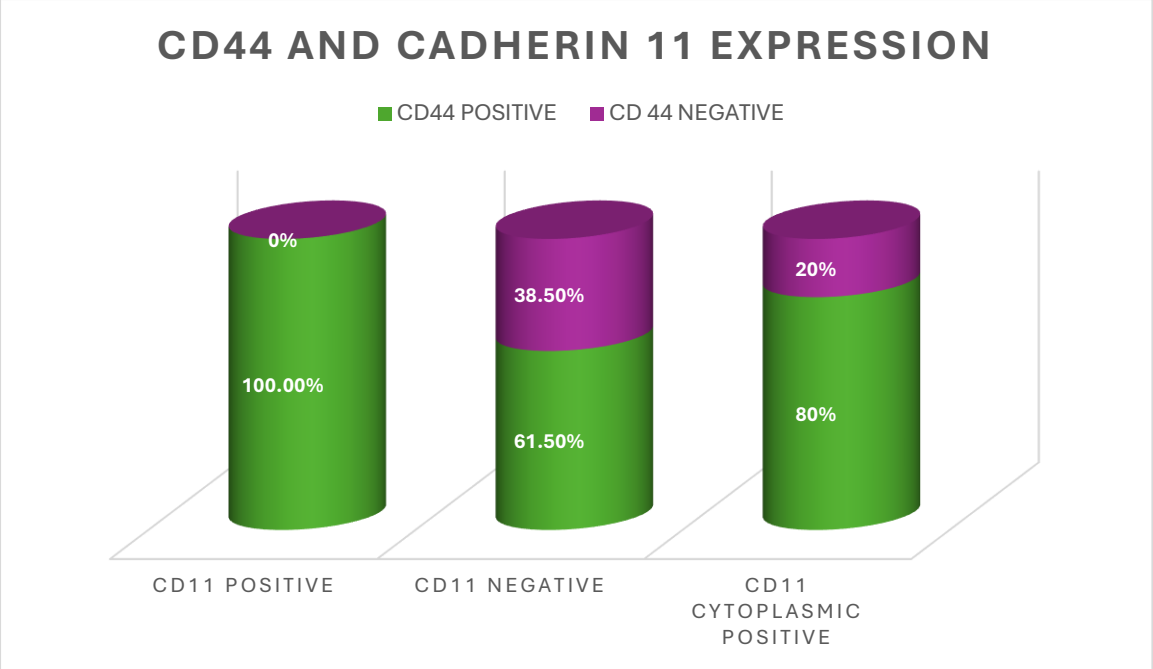

Fig 1: *The bar plot displays the CD44 and Cadherin 11 expression frequency among the patients. CD44 positivity was observed in most cases, while Cadherin 11 expression showed a varied distribution among positive, negative, and cytoplasmic positive cases.*

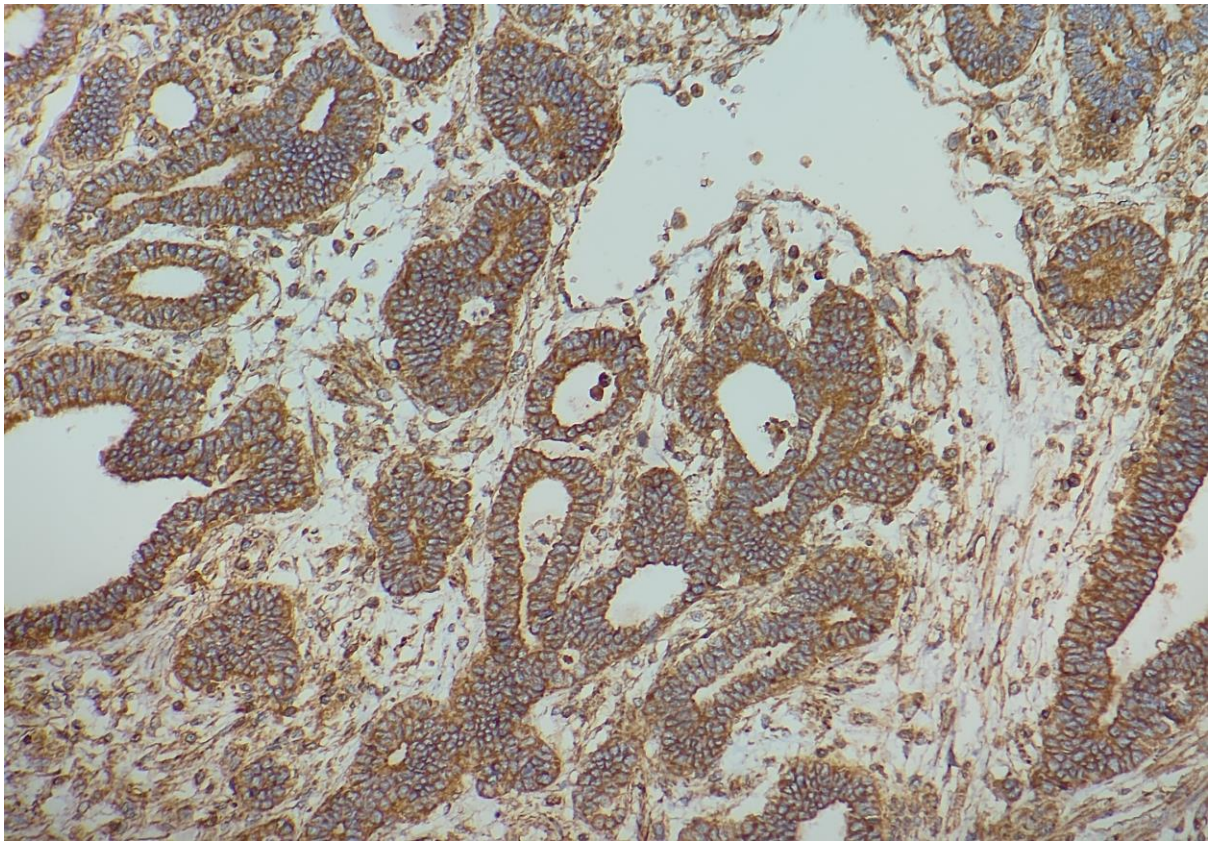

Fig 2: *CD44 expression in tumor cells [20x magnification]*

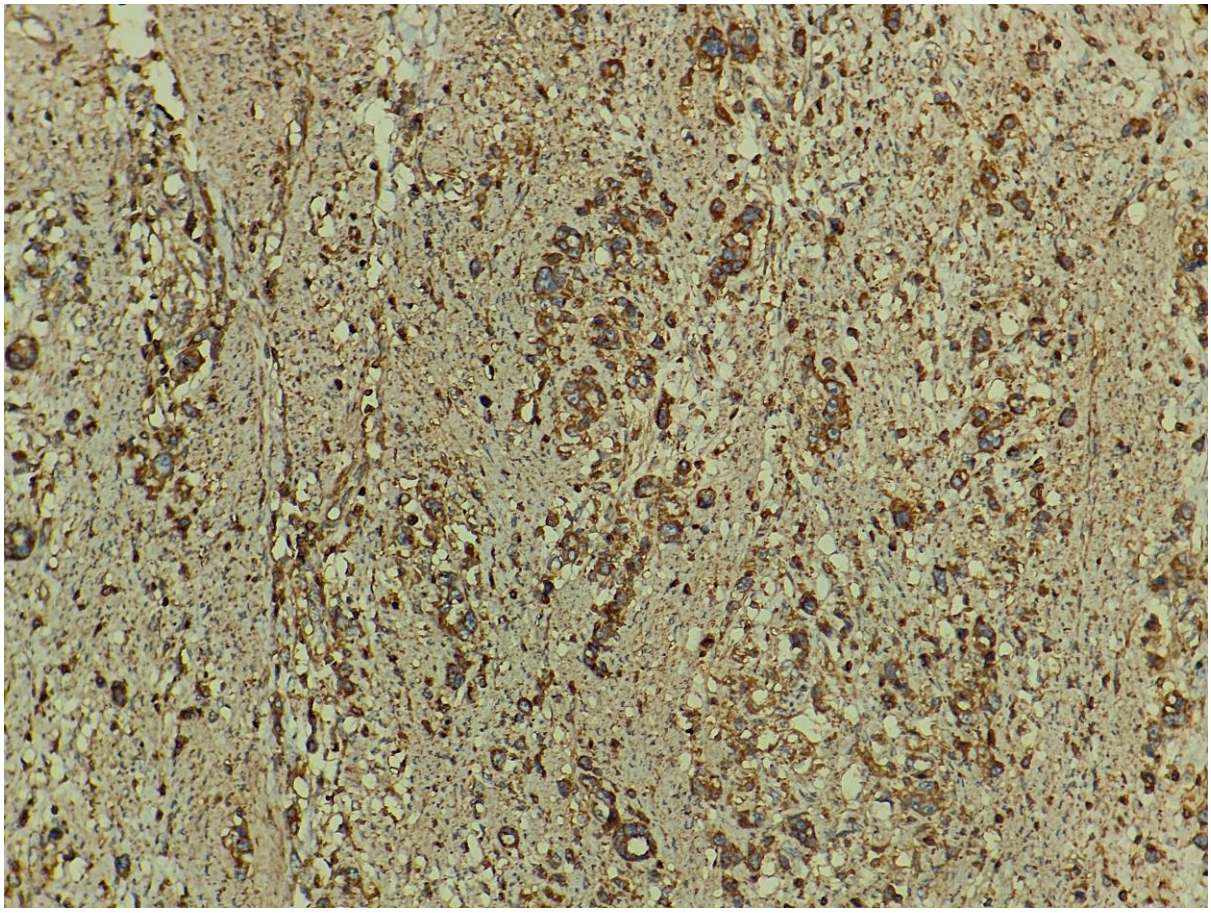

Fig 3*: CD44 expression in diffusely infiltrating tumour cells [20x magnification]*

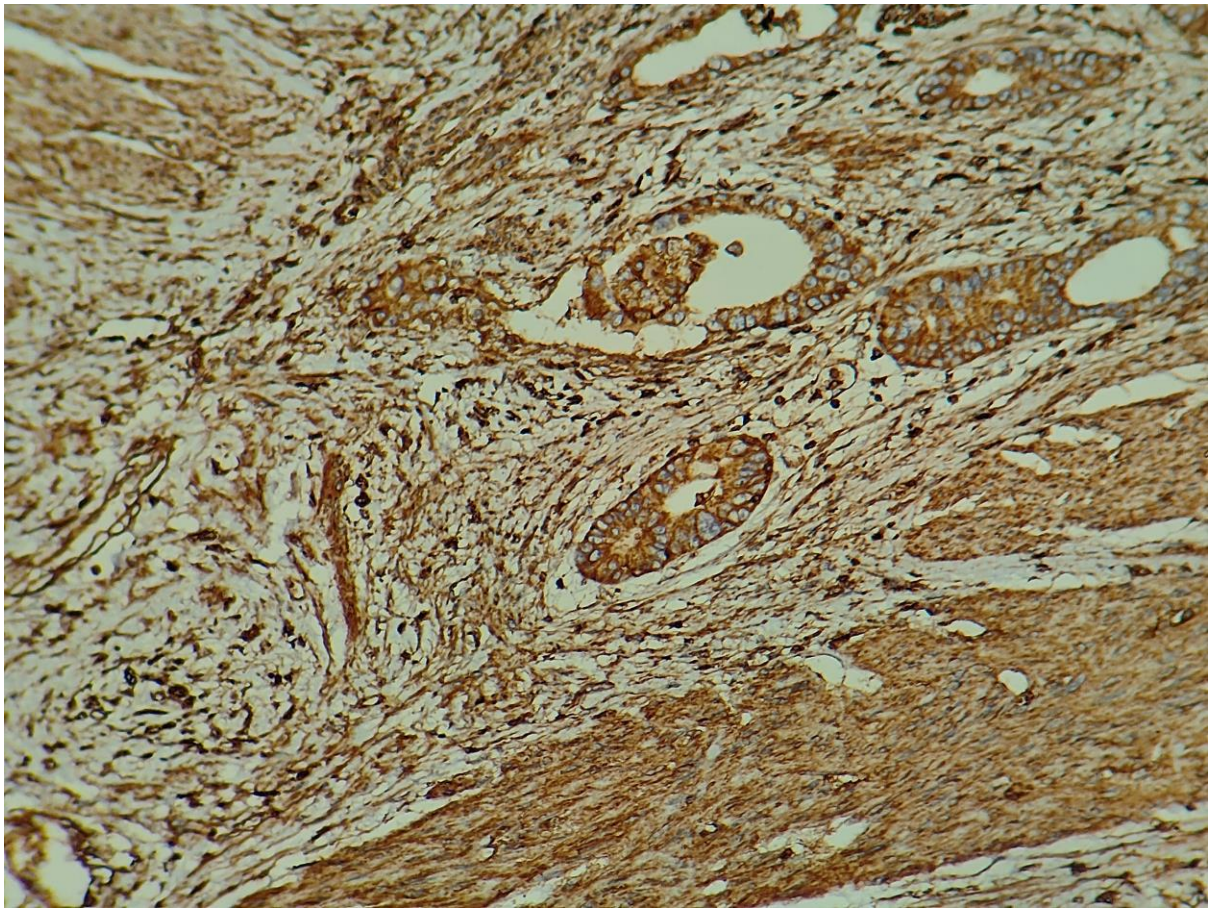

Fig 4: CD44 expression in the Invasive Tumor Front [40x magnification]

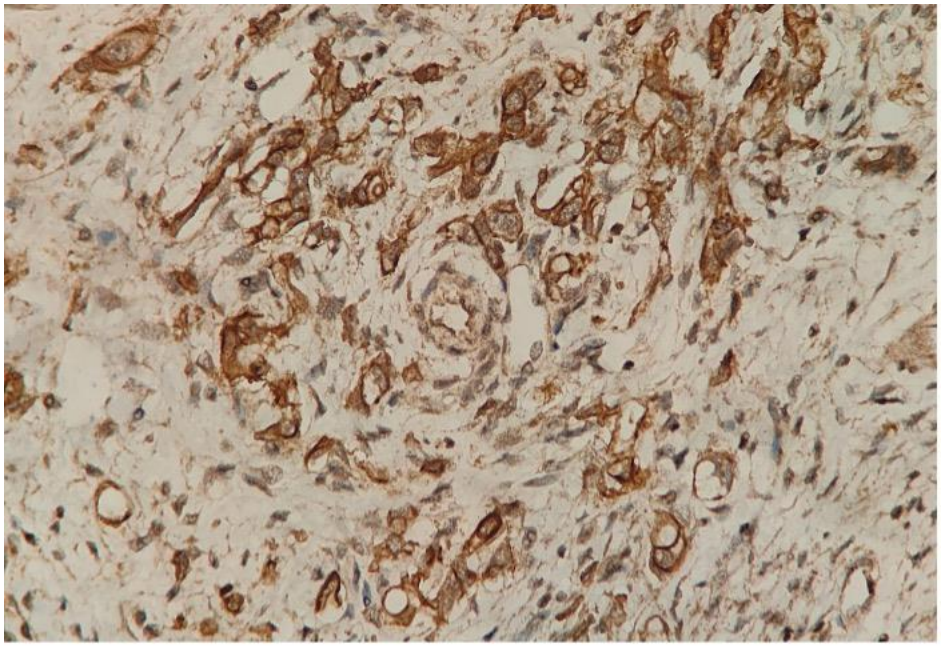

Fig 5: CDH-11 expression tumor cells [40x magnification]

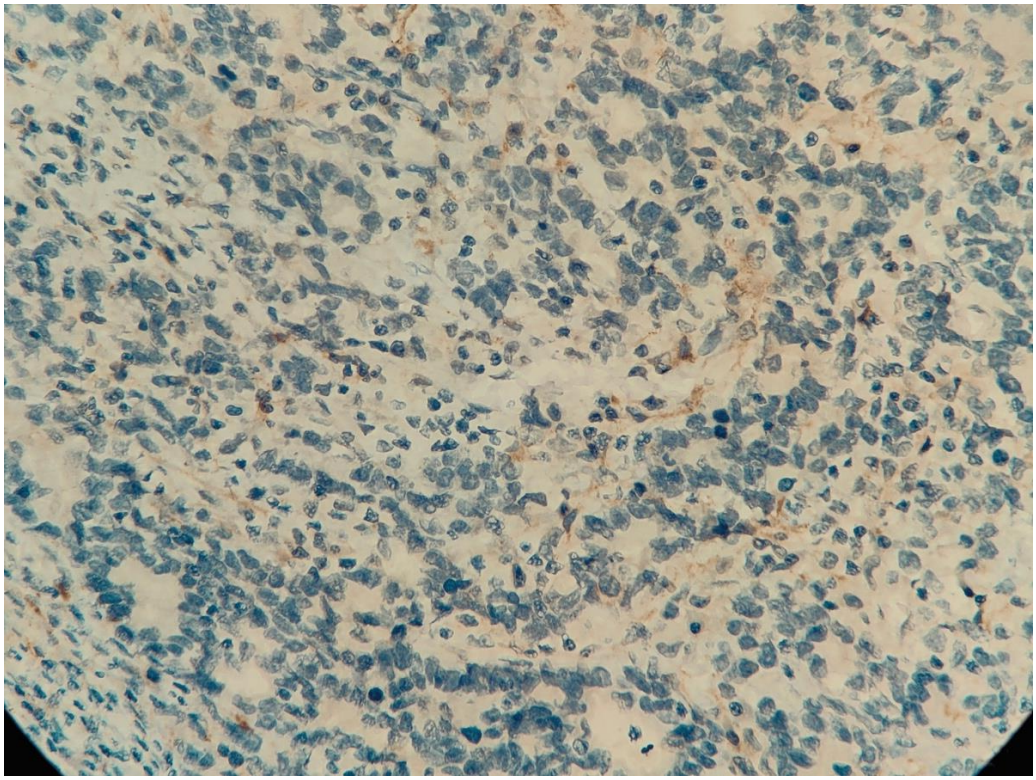

Fig 6: CD44 Negative expression [40x magnification]

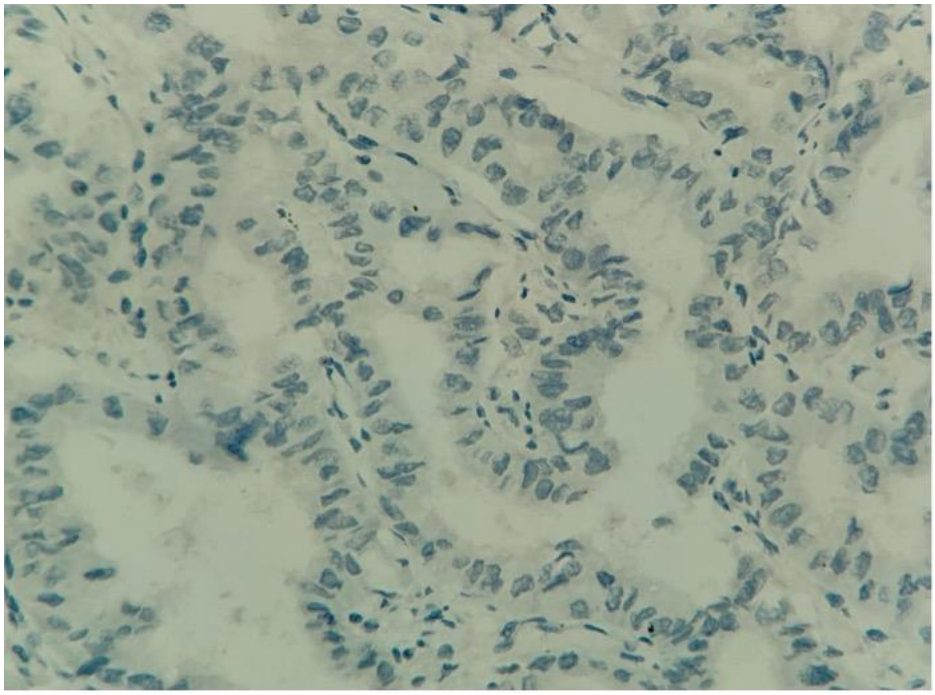

Fig 7: CDH-11 Negative expression [40x magnification]

CONCLUSION:

Our study revealed that a significant proportion of gastric carcinoma cases were observed in male patients aged 61-70, with poorly differentiated tumours being the predominant type. Notably, our study found a correlation between the expression of CD44 and higher tumour grade and deeper tumour extent. Furthermore, the presence of CD44 was detected in tumours with lymph node invasion, suggesting its potential utility as a prognostic indicator for gastric cancer. These findings require further in-depth research to investigate the intricate relationship between CD44 and Cadherin 11 expression and their possible implications for gastric carcinoma prognosis. In the future, it is essential to prioritise research efforts towards comprehensively investigating the intricate molecular pathways associated with promoting tumour progression by CD44 and CDH11. A detailed understanding of these mechanisms is paramount for developing targeted therapies to effectively address the specific molecular processes driving the progression of these tumours.

REFERENCES:

1. Wang W, Dong LP, Zhang N, Zhao CH. Role of cancer stem cell marker CD44 in gastric cancer: a meta-analysis. International journal of clinical and experimental medicine. 2014;7(12):5059.
2. Yan Y, Zuo X, Wei D. Concise review: the emerging role of CD44 in cancer stem cells: a promising biomarker and therapeutic target. Stem cells translational medicine. 2015 Sep 1;4(9):1033-43. 10.5966/sctm.2015-0048
3. Kodama H, Murata S, Ishida M, Yamamoto H, Yamaguchi T, Kaida S, Miyake T, Takebayashi K, Kushima R, Tani M. Prognostic impact of CD44-positive cancer stem-like cells at the invasive front of gastric cancer. British Journal of Cancer. 2017 Jan;116(2):186-94. 10.1038/bjc.2016.401.
4. Klonisch T, Wiechec E, Hombach-Klonisch S, Ande SR, Wesselborg S, Schulze-Osthoff K, Los M. Cancer stem cell markers in common cancers–therapeutic implications. Trends in molecular medicine. 2008 Oct 1;14(10):450-60. 10.1016/j.molmed.2008.08.003
5. Ishigami S, Ueno S, Arigami T, Uchikado Y, Setoyama T, Arima H, Kita Y, Kurahara H, Okumura H, Matsumoto M, Kijima Y. Prognostic impact of CD133 expression in gastric carcinoma. Anticancer research. 2010 Jun 1;30(6):2453-7.
6. Jackson DC. Multiple variants of the human lymphocyte homing receptor CD44 are generated by insertions at a signal site in the extracellular domain. J Biol Chem. 1992;23:527-77.
7. Sneath RJ, Mangham DC. The normal structure and function of CD44 and its role in neoplasia. Molecular pathology. 1998 Aug;51(4):191.
8. Rowe RG, Weiss SJ. Navigating ECM barriers at the invasive front: the cancer cell–stroma interface. Annual Review of Cell and Developmental. 2009 Nov 10;25(1):567-95. 10.1136/mp.51.4.191
9. Sharma M, Sah P, Sharma SS, Radhakrishnan R. Molecular changes in the invasive front of oral cancer. Journal of Oral and Maxillofacial Pathology. 2013 May 1;17(2):240-7. 10.4103/0973-029X.119740
10. Pun C, Luu S, Swallow C, Kirsch R, Conner JR. Prognostic Significance of Tumour Budding and Desmoplastic Reaction in Intestinal-Type Gastric Adenocarcinoma. Int J Surg Pathol. 2023 Sep;31(6):957-966. doi: 10.1177/10668969221105617. Epub 2022 Jun 20. PMID: 35726174; PMCID: PMC10492422. 10.1177/10668969221105617

11. Row S., Liu Y., Alimperti S., et al.: Cadherin-11 is a novel regulator of extracellular matrix synthesis and tissue mechanics. Journal of Cell Science. 2016, 129:2950-2961. 10.1242/jcs.183772.
12. Selcukbiricik F, Buyukunal E, Tural D, Ozguroglu M, Demirelli F, Serdengecti S. Clinicopathological features and outcomes of patients with gastric cancer: a single-centre experience. World J Gastroenterol. 2013;19(14):2154-61. doi: 10.3748/wjg.v19.i14.2154. PMID: 23599641; PMCID: PMC3627879. 10.3748/wjg.v19.i14.2154.
13. Zheng H, Takahashi H, Murai Y, Cui Z, Nomoto K, Miwa S, Tsuneyama K, Takano Y. Pathobiological characteristics of intestinal and diffuse-type gastric carcinoma in Japan: an immunostaining study on the tissue microarray. Journal of Clinical Pathology. 2007 Mar 1;60(3):273-7.
14. Isik M, Caner S, Metin Seker M, Civelek B, Odabas H, Ozdemir N. Gastric adenocarcinoma under 40; more metastatic, less differentiated. J BUON. 2011 Apr 1;16(2):253-6.
15. Yasuda K, Adachi Y, Shiraishi N, Inomata M, Takeuchi H, Kitano S. Prognostic effect of lymph node micrometastasis in patients with histologically node-negative gastric cancer. Ann Surg Oncol. 2002;**9**:771–774. 10.1007/BF02574499.
16. Morgagni P, Saragoni L, Scarpi E, Zattini PS, Zaccaroni A, Morgagni D, Bazzocchi F. Lymph node micrometastases in early gastric cancer and their impact on prognosis. World J Surg. 2003;**27**:558–561. 10.1007/s00268-003-6797-y

17. Aruffo A, Stamenkovic I, Melnick M, Underhill CB, Seed B. CD44 is the principal cell surface receptor for hyaluronate. *Cell.* 1990;61:1303–13. 10.1016/0092-8674(90)90694-A.
18. Köbel M, Weichert W, Crüwell K, Schmitt WD, Lautenschläger C, Hauptmann S. Epithelial hyaluronic acid and CD44v6 are mutually involved in the invasion of colorectal adenocarcinomas and linked to patient prognosis. *Virchows Arch.* 2004;445:456–464. 10.1007/s00428-004-1095-0.
19. da Cunha CB, Oliveira C, Wen X, Gomes B, Sousa S, Suriano G, Grellier M, Huntsman DG, Carneiro F, Granja PL, Seruca R. De novo expression of CD44 variants in sporadic and hereditary gastric cancer. *Lab Invest.* 2010;90:1604–14. 10.1038/labinvest.2010.155.

20. Marrelli D, Marano L, Ambrosio MR, Carbone L, Spagnoli L, Petrioli R, Ongaro A, Piccioni S, Fusario D, Roviello F. Immunohistochemical markers of the epithelial-to-mesenchymal transition (EMT) are related to extensive lymph nodal spread, peritoneal dissemination, and poor prognosis in the microsatellite-stable diffuse histotype of gastric cancer. Cancers. 2022 Dec 7;14(24):6023.
21. Ryu MS, Park HJ, Moon CM, Kim SE, Jung HK, Shim KN, Jung SA, Cho MS. Expression of CD44 according to clinicopathologic characteristics of gastric cancer. The Ewha Medical Journal. 2018 Jul 1;41(3):63-74. 10.12771/emj.2018.41.3.63
22. Senol S, Aydin A, Kösemetin D, Ece D, Akalin I, Abuoglu H, Duran EA, Aydin D, Erkol B. Gastric adenocarcinoma biomarker expression profiles and their predictive value. Journal of Environmental Pathology, Toxicology and Oncology. 2016;35(3). 10.1615/JEnvironPatholToxicolOncol.2016016099
23. Jang BI, Li Y, Graham DY, Cen P. The Role of CD44 in the Pathogenesis, Diagnosis, and Therapy of Gastric Cancer. Gut Liver. 2011 Dec;5(4):397-405. doi: 10.5009/gnl.2011.5.4.397. Epub 2011 Nov 21. PMID: 22195236; PMCID: PMC3240781. 10.5009/gnl.2011.5.4.397.
24. Hong RL, Lee WJ, Shun CT, Chu JS, Chen YC. Expression of CD44 and Its Clinical Implication in Diffuse–Type and Intestinal–Type Gastric Adenocarcinomas. Oncology. 1995 Jun 30;52(4):334-9. 10.1159/000227485.
25. Chen Y, Fu Z, Xu S, Xu Y, Xu P. The predictive value of CD44 expression in gastric cancer: a meta-analysis. Biomedicine & Pharmacotherapy. 2014 Jul 1;68(6):693-7. 10.1016/j.biopha.2014.08.001.
26. Saigusa, S., Tanaka, K., Mohri, Y. *et al.* Clinical significance of RacGAP1 expression at the invasive front of gastric cancer. *Gastric Cancer* **18**, 84–92 (2015). https://doi.org/10.1007/s10120-014-0355-1
27. Van Roy F. Beyond E-cadherin: roles of other cadherin superfamily members in cancer. Nature Reviews Cancer. 2014 Feb;14(2):121-34. 10.1038/nrc3647
28. Feng Z, Li X, Ren Z, Feng J, He X, You C. Prognostic and predictive value of cadherin 11 for patients with gastric cancer and its correlation with tumor microenvironment: results from microarray analysis. BioMed Research International. 2020;2020(1):8107478. 10.1155/2020/8107478