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Stem Cell Markers (CD133, CD44, CD24) Ihc Expressions in Colorectal Carcinoma in a Sample of Iraqi Patients

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Abstract

Objective: Colorectal cancer is the second most common cancer among the Iraqi population, according to the latest Iraqi Cancer Registry (2022). For the past 18 years, cancer stem cell markers have been studied and explored in order to identify prognostic markers that could aid in patient management.

Methods: 72 paraffin blocks of colorectal cancer were collected, and multiple sections were taken from each block: one stained with H&E stain, and the others stained by IHC methods for three selected markers (CD133, CD44, and CD24). The scoring of the IHC slides was performed by combining the percentage of positively stained cells with the staining intensity. A score of 4 and above was considered to be positive.

Results: 66.7% of the patients were over 50 years of age, with an equal male-to-female ratio. The majority of tumors were located in the rectum (69.4%), and 88.9% were less than 5 cm in size. Half of the cases were moderately differentiated, and 65.3% were classified as T2 stage. CD133 was expressed in 50% of cases, followed by CD44 (36.1%), while CD24 showed the lowest expression (8.3%). A significant association was found between CD133 expression and tumor site, size, and patient gender. CD44 expression was significantly associated with tumor stage, whereas CD24 expression was significantly associated with both tumor size and stage.

Conclusion: CD133 expression was the most commonly expressed marker in colorectal cancer, whereas CD24 expression was the least common. CD133 and CD24 IHC expression were significantly associated with tumor size, while CD44 and CD24 IHC expression were significantly associated with tumor stage. None of the three markers used in this study showed a significant association with tumor grade.
Keywords: Colorectal carcinoma, stem cell markers, CD133, CD44, CD24, immunohistochemistry (IHC)

Introduction

Colorectal cancer ranks fourth in global incidence, following lung, breast, and prostate cancers, and is the fifth leading cause of cancer-related death, according to the Global Cancer Observatory (2024).[1,2] In Iraq, colorectal cancer is the second most commonly reported malignancy, with 2,871 newly diagnosed cases documented in the 2022 Annual Report of the Iraqi Cancer Registry.[3] Cancer stem cells (CSCs) were first identified in 1997 in cases of acute myeloid leukemia (AML), marking a significant advancement in understanding tumor biology. The recognition of CSC markers in colon cancer in 2007 profoundly reshaped our understanding of tumor initiation, progression, and resistance mechanisms.[4,5] CSCs are characterized by their self-renewal capacity, high metastatic potential, and resistance to radiotherapy and/or chemotherapy.[6] Several surface clusters of differentiation (CD) markers have been explored as solid tumor CSC markers. Among them, CD133, also known as prominin-1 or PROML1, has garnered particular attention. It has been identified as a potential CSC marker in colon, brain, and prostate cancers, with a demonstrated ability to initiate tumor formation.[7] CD133 is currently considered one of the key markers for identifying colon cancer stem cells.[8] Numerous studies have linked CD133 expression with poor clinical outcomes in colorectal cancer, highlighting its potential as a target for advanced therapeutic strategies.[9] CD44, a cell surface glycoprotein expressed on inflammatory cells, has also been recognized as a CSC marker, particularly in head and neck as well as breast cancers.[10] Its functions include cell adhesion, aggregation, angiogenesis, migration, cytokine release, and lymphocyte homing. CD44 is expressed in various tissues, including the pancreas, central nervous system, liver, lungs, and skin.[11] High expression of CD44 has been associated with more aggressive tumor grade and increased metastatic potential in colorectal cancer.[12] CD24 is another highly glycosylated surface protein expressed in a range of normal and malignant cells, including keratinocytes, renal tubules, and pre-B cells.[13] It is significantly overexpressed in colorectal cancer and has been associated with poor prognosis. In this study, we aim to assess the immunohistochemical (IHC) expression of CD133, CD44, and CD24 in colorectal carcinoma tissues obtained from a cohort of Iraqi patients.[14] The goal is to explore the relationship between these markers and various clinicopathological parameters, thereby assessing their potential prognostic significance in colorectal cancer.

Materials and Methods

Patients and Sampling

A cross-sectional study included 72 paraffin-embedded tissue blocks obtained from patients diagnosed with colorectal cancer who provided informed consent. Samples were collected between April 2024 and April 2025 from patients treated either at private hospitals or at Al-Imammain Al-Kadhmain Hospital. Histopathological diagnoses were confirmed by examination of hematoxylin and eosin (H&E) stained slides by two independent pathologists. Tumors were classified according to the American Joint Committee on Cancer (AJCC) 8th edition manual, 2017 (22). Clinicopathologic parameters included in this study were age, gender, tumor site, tumor grade, and tumor stage. Other variables, such as neural and lymphovascular invasion, were excluded due to incomplete or unavailable data.

Hematoxylin and Eosin Staining (H&E)

Several 5-µm sections were cut from each paraffin block using a microtome and placed on adhesive slides. One section from each sample was deparaffinized with xylene, rehydrated through graded ethanol series, stained with hematoxylin and eosin, coverslipped, and examined by two expert pathologists. Remaining sections were reserved for immunohistochemical (IHC) analysis.

Immunohistochemical Staining Procedure

All three markers (CD133, CD44, CD24) were stained using the same protocol. Sections were dewaxed for one hour in an oven at 65°C, followed by two 10-minute immersions in xylene. Rehydration was performed through descending ethanol concentrations from 100% to 70%, each step lasting five minutes, then washed with distilled water. Endogenous peroxidase activity was blocked by incubation in hydrogen peroxide solution for 10 minutes. Sections were washed three times in phosphate-buffered saline (PBS) for five minutes each and then treated with protein block for 10 minutes. After a further three washes in PBS, primary antibodies (polyclonal rabbit anti-CD133, anti-CD44, and anti-CD24, Fine Test, China), diluted 1:100 in PBS, were applied for one hour. Following three PBS washes, secondary antibody was applied for 20 minutes, followed by another three PBS washes. Horseradish peroxidase was added for 20 minutes, then the slides were washed again in PBS. The chromogen 3,3'-diaminobenzidine tetrahydrochloride (DAB) (Abcam, England) was prepared by mixing 49 drops of substrate with one drop of DAB and applied for 10 minutes. Slides were washed with distilled water, counterstained with hematoxylin for 20 seconds, washed again for one minute, dehydrated through graded ethanol (70% to 100%), cleared in xylene for five minutes, and finally mounted with DPX and coverslipped.

Controls

Kidney tissue was used as a positive control for CD133, lymphoid tissue from the tonsil as a positive control for CD24, and the mucosal epithelium of the tonsil as a positive control for CD44.

Evaluation of Immunohistochemistry

Immunostained slides were independently assessed by two pathologists blinded to clinical and pathological data. A semi-quantitative scoring system was used for all markers, combining the percentage of positively stained tumor cells (cytoplasmic or membranous staining) and the staining intensity. The percentage of stained cells was scored on a 0–3 scale: 0 (no staining), 1 (<10%), 2 (10–50%), and 3 (>50%). Staining intensity was also scored on a 0–3 scale, from 0 (no staining) to 3 (strong staining). The total score ranged from 0 to 6, with scores ≥4 considered positive or indicating high expression (23–25). A retrospective power analysis was performed using the observed effect sizes for the primary immunohistochemical markers. The calculated power exceeded 80% for CD133 and CD44, indicating sufficient sensitivity to detect meaningful associations, while the power for CD24 was limited due to its lower expression levels and smaller effect size.

Statistical Analysis

All statistical analyses were processed using statistical software SPSS-22 (Statistical Packages for Social Sciences, Version 26). The data was presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values). Associations between expression levels of CD133, CD44 and CD24 were analyzed by using Chi-square test. $P < 0.05$ was considered statistically significant.

Results

Clinicopathological Characteristics of Colorectal Cancer Patients

The study included 72 colorectal cancer patients with a mean age of 54.61 ± 11.91 years (range 33–70 years). Half were male and half female. Age was divided into two categories: ≤50 years (33.3%) and >50 years (66.7%). The most common tumor location was the rectum (69.4%), followed by the ascending colon (20.8%). Most tumors were ≤5 cm (88.9%). Regarding tumor grade, the majority (50%) were moderately differentiated. Regarding tumor stage, the majority (65.3%) were T2. Immunofluorescence showed positive expression of CD133 in 50% of cases, while CD44 was positive in 36.1% and CD24 in only 8.3% of samples, reflecting the significant variability in the expression of these markers among patients (Table 1).

Association Between Clinicopathological Variables and CD133 Expression in Colorectal Cancer Patients

The results of the immunohistochemical analysis of CD133 expression in colorectal cancer showed a clear variation between the studied groups. Regarding gender, highly significant differences were observed, with males showing a higher percentage of CD133 positivity compared to females. This relationship was statistically significant ($P = 0.001$) with a significantly higher odds ratio (OR = 5.16). Furthermore, a significant association was found between tumor location and CD133 expression, with rectal tumors being more strongly associated with CD133 positivity than other sites ($P = 0.006$, OR = 2.25). Regarding tumor size, tumors larger than 5 cm were strongly associated with CD133 positivity ($P = 0.003$, OR = 8.00). In contrast, differences between age groups ($P = 0.105$), histological grades ($P = 0.613$), or different tumor stages ($P = 0.716$) did not show significant differences in CD133 expression, suggesting that these factors may not play a major role in regulating this marker in colorectal cancer (Table 2 & Figure 1).

Correlation of Clinicopathological Factors with CD44 Expression in Colorectal Cancer Patients

The results of immunohistochemical expression of CD44 in colorectal cancer cases indicate statistically significant relationships with some clinical and demographic characteristics. A significant relationship was found between age and CD44 expression, with the age group ≤50 years showing significantly lower expression compared to the older group, and this relationship was statistically significant ($P = 0.003$, OR = 4.13). A significant difference was also found between males and females, with positive expression being higher in females than

Table 1. **Distribution of demographic, tumor features, and CD133, CD44, CD24 immunohistochemical expression ($n = 72$)**

Variable		**No**	**%**
Age (years) Mean ± SD (Range)		54.61 ± 11.908 (33–70)	
Age groups (years)	≤50	24	33.3
	>50	48	66.7
Sex	Male	36	50
	Female	36	50
Site of tumor	Rectum	50	69.4
	Ascending Colon	15	20.8
	Rectosigmoid	3	4.2
	Sigmoid	4	5.6
Size of tumor (cm)	≤5 cm	64	88.9
	>5 cm	8	11.1
Tumor Grade	Well differentiated	19	26.4
	Moderately differentiated	36	50
	Poorly differentiated	17	23.6
Tumor Stage	T1	19	26.4
	T2	47	65.3
	T3	6	8.3
CD133	Positive	36	50
	Negative	36	50
CD44	Positive	26	36.1
	Negative	46	63.9
CD24	Positive	6	8.3
	Negative	66	91.7

Table 2. **Statistical analysis including *P*-values, odds ratios, and 95% confidence intervals between clinicopathological variables and CD133**

		CD133		***P* value**	**Odds Ratio (OR)**	**95% Confidence Interval (CI)**
		Positive	**Negative**			
Age groups (years)	≤50	15	9	0.105	1.67	0.81 – 3.45
	>50	21	27			
Sex	Male	25	11	0.001	5.16	2.01 – 13.23
	Female	11	25			
Site of tumor	Rectum	30	20	0.006	2.25	1.24 – 4.10
	Ascending Colon	6	9		0.80	0.28 – 2.28
	Rectosigmoid	0	3		0.35	0.01 – 3.33
	Sigmoid	0	4		0.27	0.01 – 2.50
Size of tumor (cm)	≤5 cm	28	36	0.003	0.58	0.25 – 1.33
	>5 cm	8	0		8.00	1.12 – 57.20
Tumor Grade	Well differentiated	11	8	0.613	1.00	0.34 – 2.93
	Moderately differentiated	16	20		0.85	0.32 – 2.23
	Poorly differentiated	9	8		1.10	0.33 – 3.62
Tumor Stage	T1	8	11	0.716	0.85	0.27 – 2.67
	T2	25	22		1.35	0.54 – 3.38
	T3	3	3		1.20	0.21 – 6.77

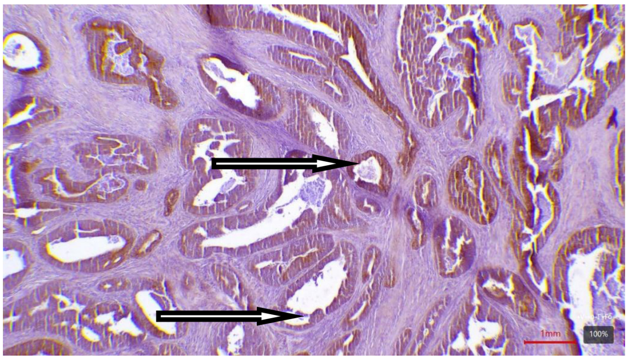

Fig. 1 **CD133 IHC in colorectal cancer power (4x): showing more than 50% of neoplastic glands staining (score 3), the intensity is strong (score3), the combined immunoreactive score in this case is 6.**

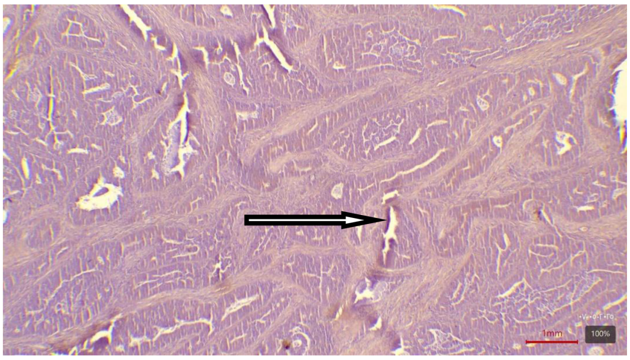

Fig. 2 **CD44 IHC in colorectal cancer Low power view(4x): showing more than 50% of neoplastic glands staining (score 3), the intensity is intermediate (score2), the combined immunoreactive score in this case is 5.**

Table 3. **Statistical evaluation of *P*-values, odds ratios, and 95% confidence intervals clinicopathological factors with CD44 expression**

		CD44		*P* value	Odds Ratio (OR)	95% Confidence Interval (CI)
		Positive	Negative			
Age groups (years)	≤50	3	21	0.003	4.13	1.53 – 11.15
	>50	23	25			
Sex	Male	9	27	0.042	2.44	1.02 – 5.82
	Female	17	19			
Site of tumor	Rectum	20	30	0.082	2.22	0.94 – 5.25
	Ascending Colon	6	9		1.30	0.41 – 4.12
	Rectosigmoid	0	3		0.37	0.01 – 3.47
	Sigmoid	0	4		0.28	0.01 – 2.68
Size of tumor (cm)	≤5 cm	23	41	0.608	0.82	0.26 – 2.61
	>5 cm	3	5		1.20	0.25 – 5.66
Tumor Grade	Well differentiated	5	14	0.520	0.58	0.17 – 1.91
	Moderately differentiated	15	21		0.80	0.29 – 2.19
	Poorly differentiated	6	11		0.93	0.27 – 3.18
Tumor Stage	T1	2	17	0.015	0.20	0.04 – 0.95
	T2	21	26		1.37	0.54 – 3.45
	T3	3	3		1.70	0.27 – 10.61

in males ($P = 0.042$, OR = 2.44). Regarding tumor stage, a significant difference was observed in T1, which was associated with lower CD44 expression ($P = 0.015$, OR = 0.20), suggesting that the expression of this factor may be associated with tumor progression. In contrast, there were no significant differences in tumor location ($P = 0.082$), tumor size ($P = 0.608$), or tumor grade ($P = 0.520$), suggesting that these factors may not influence CD44 expression in colorectal cancer (Figure 2 & Table 3).

Association Between Clinicopathological Characteristics and CD24 Expression in Colorectal Cancer Patients

Immunohistochemical results for CD24 expression in colorectal cancer showed a general decline in positive expression rates, with no significant differences between age groups ($P = 0.315$) or gender ($P = 0.663$), with expression rates being equal between males and females. Furthermore, different tumor sites, including the rectum, did not show statistically significant differences in their relationship to CD24 expression ($P = 0.203$). In contrast, a strong and statistically significant association was found between tumor size and CD24 expression; tumors larger than 5 cm were associated with very high positive expression ($P = 0.000$, OR = 0.00), compared to tumors smaller than 5 cm, which showed no positive expression. Furthermore, there was a clear statistical significance between CD24 expression and tumor stage, with T1 being associated with significantly low expression ($P = 0.005$, OR = 0.05), while T3 had the highest expression. As for the degree of tumor differentiation, the results showed a trend towards a relationship without significant significance ($P = 0.090$), indicating the possibility of a weak association that warrants further study (Table 4 & Figure 3).

Discussion

The global number of colorectal cancer patients is anticipated to reach 3.2 million in 2040, based on the projection of population growth and aging. This increase in incidence is mainly accredit to the raised exposure to environmental risk factors resulting from changing the lifestyle and the western diet.[15,16] The colorectum is affected by multiple types of malignancy but the most common type is mucin secreting adenocarcinoma, other less common malignancy include: gastrointestinal stromal tumors, carcinoid tumors, lymphoma and sarcoma.[17,18] Colonic cancer stem cells are pluripotent neoplastic cells that have the ability to differentiate and commence the carcinogenesis process.[19] Identification of cancer stem cells in different digestive and extra-digestive malignant tumors has been a topic of considerable interest in the literature of current years and was routinely done using cluster of differentiation (CD) markers.[20]

The expression of stem cell markers CD133, CD44, and CD24 in colorectal carcinoma may reflect the presence of cancer stem cells (CSCs), which play a crucial role in tumor initiation, progression, and resistance to therapy.[21] These markers have been implicated in maintaining tumor stemness and promoting epithelial–mesenchymal transition (EMT), a process that facilitates tumor invasion and metastasis.[22]

For example, CD44 is known to regulate EMT through various signaling pathways, enhancing cell motility and invasiveness. Similarly, CD133-positive cells exhibit increased tumorigenic potential and are associated with poor prognosis. Understanding these mechanistic links reinforces the clinical significance of these markers as potential prognostic indicators and therapeutic targets in colorectal cancer.[23] In colorectal cancer, many biomarkers have been recognized at the surface of colonic cancer stem cells, and their function in colon cancer is currently being tested such as CD133, CD24, CD44, EpCAM, ALDH1A1, and ALDH1B1. In this study there was significant association between CD133 IHC expression and tumor size, same findings seen by other studies.[24,25]

Our findings regarding the expression patterns of CD133, CD44, and CD24 in colorectal carcinoma show both consistencies and discrepancies with recent international studies. For instance, the 50% positivity rate of CD133 in our cohort aligns with findings reported by Kunihiro et al. and Reuvekamp et al.,[26,27] who also observed significant associations between CD133 expression and tumor size, stage, and site. Conversely,

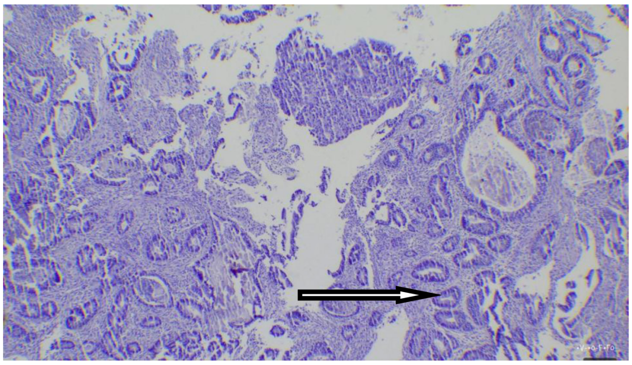

Fig. 3 **CD24 IHC in colorectal cancer Low power view (4x): showing negative staining in the neoplastic glands (score 0).**

Table 4. **Analysis of *P*-values, odds ratios, and 95% confidence intervals between clinicopathological characteristics and CD24 expression**

		CD24		*P* value	Odds Ratio (OR)	95% Confidence Interval (CI)
		Positive	Negative			
Age groups (years)	≤50	3	21	0.315	1.07	0.22 – 5.28
	>50	3	45			
Sex	Male	3	33	0.663	1.00	0.20 – 5.01
	Female	3	33			
Site of tumor	Rectum	6	44	0.203	2.09	0.69 – 6.34
	Ascending Colon	0	15		0.22	0.01 – 3.78
	Rectosigmoid	0	3		0.37	0.01 – 8.94
	Sigmoid	0	4		0.29	0.01 – 7.47
Size of tumor (cm)	≤5 cm	0	64	0.000	0.02	0.001 – 0.30
	>5 cm	6	2		60.00	7.59 – 474.43
Tumor Grade	Well differentiated	0	19	0.090	0.13	0.003 – 1.37
	Moderately differentiated	3	33		0.37	0.07 – 1.88
	Poorly differentiated	3	14		1.02	0.17 – 6.01
Tumor Stage	T1	0	19	0.005	0.05	0.002 – 0.70
	T2	3	44		0.38	0.07 – 1.84
	T3	3	3		11.00	1.13 – 107.04

some studies, such as Miana Gabriela Pop et al., reported no significant clinical correlations with CD133 expression, highlighting variability that may arise from differences in population genetics, sample size, or methodological approaches.[28,29] Regarding CD44, our observation of its association mainly with tumor stage concurs with findings from Egyptian and Japanese cohorts emphasizing its role in tumor progression and poor prognosis.[30] The low expression of CD24 in our study contrasts with higher frequencies reported internationally, suggesting possible ethnic or technical differences.[31]

These comparisons underscore the need for larger, multicenter studies to validate these markers' prognostic value across diverse populations. We did not identify a significant association between CD133 IHC expression and the grade of the tumor unlike a study done by Kazama S et al.,[32,33] that had found that CD133 IHC expression was significantly associated with poor grade of differentiation (grade 3), while Pitule P et al. had found CD133 IHC expression to be more frequent in moderately and well differentiated tumors (grade 2 and grade 1) An updated meta-analysis of 37 studies done by Huang R et al. found that the association with the tumor stage and CD133 IHC expression in colorectal cancer to be significant in contrast with our findings.[34]

Another study had found that high expression of CD133 was positively associated with tumor size, clinical stage and lymphatic metastasis.[35] A study done by (Miana Gabriela Pop et al). revealed non significant association between CD133 IHC expression and any clinical or pathological features of the tumor.[36] Another Iranian study done at 2023,[37] found that There was a statistically significant association between CD133 IHC expression and the patient gender similar to our findings but they also found significant association with tumor stage unlike our findings.[37]

An association with tumor site (higher CD133 IHC expression in rectum than in proximal large intestine) was found in a study done by Suman et al.,[38] that findings in our study. Regarding CD44 in our study the only significant difference found was with the stage of the tumor, while an Egyptian study done at 2023,[38] had found a significant association between CD44 IHC expression and tumor size, grade and stage.

A study done by Rachmita et al.,[39] had found that CD44 is an important CSC marker in colorectal cancer patients. And was linked to poor prognosis focusing on CD44 variant 2.[39] A our knowledge no other studies had analyzed the IHC expression of CD44 with clinicopathological parameters.[40] CD24 IHC expression in our study was seen in 6 cases (8.3%) while it was found to be expressed in 50 to 68% of cases in other studies Gholamzad et al.,[41] We had found no correlation between CD24IHC expression and the tumor grade, similar to another two studies.[42]

Our study showed a significant association between CD24 IHC expression and tumor size and stage this was supported by findings recognized by Zou et al. and Sihombing et al.,[43,44] who had found that CD24 IHC expression is associated with higher tumor grade and stage.[44] Those findings were in contrast to what had been found by Yaghjyan et al.,[45] who had examined CD24 IHC expression in both adenoma and colorectal carcinoma tissue samples and concluded that CD24 expression is considered a favorable prognostic marker in colorectal cancer.[46]

Conclusion

Our results show that CD133 expression is the most common marker expressed in colorectal cancer and CD24 expression is the least common. And regarding the clinical and pathological parameters, CD133, CD24 IHC expression is significantly associated with tumor size while CD44 and CD24 IHC expression is associated significantly with tumor stage, none of the three markers used in this study showed a significant association with tumor grade.

Limitations of the Study

One of the limitations of this study is the relatively small sample size (n = 72), which may affect the statistical power and limit the generalizability of the findings. Additionally, the absence of multivariate analysis to adjust for potential confounders is another limitation, primarily due to the limited sample size and the low frequency of marker expression. Therefore, future studies with larger sample sizes are recommended to validate and expand upon these results using logistic regression or other multivariate methods to provide more robust conclusions.

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None.

Conflict of Interest

All authors have no conflicts of interests to declare.

Author Contributions

Qahtan adnan and Bashar abbas were responsible for the data collection and study design, Noora Kareem was responsible for the scoring of the IHC and HE slides and draft writing. All authors approved the final version of the manuscript draft.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and written informed consent was obtained from all patients.

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