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DETECTION OF CD44 IMMUNOHISTOCHEMICAL EXPRESSION AND CLINICOPATHOLOGICAL CORRELATES IN COLORECTAL CARCINOMA

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ABSTRACT

Background:
Cluster of differentiation 44 (CD44) is a non-kinase cell surface glycoprotein overexpressed in cancer stem cells (CSCs). Cells overexpressing CD44 exhibit several CSC traits, including self-renewal, epithelial–mesenchymal transition (EMT) capability, and resistance to chemo- and radiotherapy. CD44's role in maintaining CSC stemness and promoting tumour progression is primarily mediated through binding with its principal ligand, hyaluronan (HA), activating signalling pathways that drive cell proliferation, adhesion, migration, and invasion. The CD44 gene undergoes extensive alternative splicing generating standard (CD44s) and variant (CD44v) isoforms with distinct functional roles in colorectal carcinogenesis.

Materials and Methods:
The present cross-sectional study evaluated immunohistochemical CD44 expression in 50 surgically resected CRC specimens from SRM Medical College Hospital and Research Centre, Kattankulathur, Tamil Nadu. CD44 expression was scored as low (<10% positive tumour cells), moderate (10–50%), or strong (>50%).

Results:
Low expression was identified in 16% (n=8), moderate in 44% (n=22), and strong in 40% (n=20) of cases. Strong CD44 expression was significantly associated with lymphovascular invasion (LVI, p=0.043), TNM stage (p=0.019), and AJCC stage group (p=0.016). No significant association was observed with histological grade (p=0.756), perineural invasion (p=0.518), tumour budding (p=0.579), or tumour infiltrating lymphocytes (p=0.389). These results establish CD44 as a clinically relevant biomarker of tumour aggressiveness and an objective marker of invasion and staging progression in CRC.

KEYWORDS: colorectal cancer; CD44; cancer stem cells; immunohistochemistry; prognostic marker; lymphovascular invasion; TNM staging; clinicopathological association

INTRODUCTION

Colorectal carcinoma (CRC) ranks third in global cancer incidence and second in cancer-related mortality, accounting for approximately 1.93 million new cases and 940,000 deaths annually worldwide.1 Most cases arise via the adenoma–carcinoma sequence, and standard pathological assessment per College of American Pathologists guidelines provides essential staging and grading data.2 However, conventional histopathological parameters do not fully capture tumour biological heterogeneity, particularly in early-to-intermediate stage disease where the decision to administer adjuvant therapy is most contested.3

CD44 is a transmembrane, non-kinase, single-chain glycoprotein initially identified in lymphocytes and subsequently found expressed in numerous solid tumour cell lines.4 It is a principal target of the Wnt/β-catenin signalling pathway — constitutively active in CRC through APC mutations — and functions as a positive feedback amplifier of Wnt signalling.5 Cells overexpressing CD44 exhibit canonical CSC traits: self-renewal capacity, EMT capability, and resistance to chemotherapy and radiotherapy.6

CD44 and its specific isoforms have been shown to play a central role in CRC carcinogenesis, progression, metastasis, and resistance to therapy.7 The clinicopathological impact of CD44 suggests it could serve as a molecular biomarker for prognostication and potentially as a therapeutic target.8 The present study aims to evaluate the immunohistochemical expression of CD44 in surgically resected CRC specimens and to correlate CD44 expression intensity with comprehensive clinicopathological parameters, with the objective of assessing its utility as a supplementary prognostic marker.

AIMS AND OBJECTIVES

- To study the expression pattern of CD44 in colorectal carcinoma and correlate it with pathological parameters.
- To evaluate the diagnostic utility and prognostic significance of CD44 in colorectal carcinoma.

MATERIALS AND METHODS

Study Design and Setting

A cross-sectional study incorporating both prospective and retrospective CRC resection specimens was conducted between January 2024 and January 2026 at the Department of Pathology, SRM Medical College Hospital and Research Centre, Kattankulathur, Tamil Nadu, India. Institutional Ethics Committee approval was obtained prior to study commencement.

Sample Size

Sample size was calculated using the formula $n \geq z^2p(1-p)/d^2$, with a prevalence estimate of 66%, confidence level of 95% ($z=1.96$), and margin of error of 13.2%, yielding a minimum sample of 50 cases.

Inclusion and Exclusion Criteria

Cases of histopathologically confirmed colorectal adenocarcinoma (all subtypes) on resection specimens — hemicolectomy, total colectomy, low anterior resection, and abdominoperineal resection — were included. Exclusion criteria comprised colonic biopsies, inadequate samples, inflammatory bowel disease, familial adenomatous polyposis, and specimens received post-radiotherapy or chemotherapy.

Histopathological Evaluation

Haematoxylin and eosin (H&E)-stained sections (4–5 μm) were assessed for tumour site, laterality, gross morphology, histological type, grade, depth of invasion, lymphovascular invasion (LVI), perineural invasion (PNI), tumour infiltrating lymphocytes (TILs), tumour budding, and TNM staging per AJCC 8th edition guidelines.

CD44 Immunohistochemical Assessment

Sections of 4 μm were cut onto positively charged hydrophobic slides. The Peroxidase–Anti-Peroxidase (PAP) method was employed using monoclonal anti-CD44 primary antibody and secondary antibody kits (PATHINSITU). Microwave-based antigen retrieval was performed. Sections from tonsil tissue served as positive controls.

CD44 expression was scored based on the percentage of positive tumour cells showing cytoplasmic/membranous staining: low expression (<10% positive tumour cells), moderate expression (10–50%), and strong expression (>50%). Statistical significance was set at $p < 0.05$; analyses were performed using IBM SPSS Statistics Version 22.

RESULTS

Clinicopathological Profile

The study comprised 50 surgically resected CRC specimens with a mean age of 62.14 ± 10.04 years (range 41–78). A male predominance was observed (60% male, 40% female). Left-sided tumours accounted for 54% (n=27) and right-sided for 46% (n=23). The ascending colon was the most common tumour site (24%), followed by rectosigmoid junction (18%) and sigmoid colon (16%). Adenocarcinoma constituted 98% (n=49) of cases; one case (2%) was signet ring cell type. Grade 2 (moderately differentiated) tumours predominated (74%, n=37). LVI was identified in 28% (n=14) and PNI in 12% (n=6). Stage I was the most common AJCC group (48%, n=24).

CD44 Expression Profile

In the study population, moderate CD44 expression was the most common pattern, identified in 44% (n=22) of cases. Strong expression was observed in 40% (n=20) and low expression in 16% (n=8) of cases. Collectively, moderate or strong CD44 expression (positive CD44) was found in 84% of all cases (Table 1).

Table 1: Distribution of CD44 expression in the study population (N=50)

CD44 Expression	Frequency (N=50)	Percentage (%)
Low (<10% positive cells)	8	16.0
Moderate (10–50% positive cells)	22	44.0
Strong (>50% positive cells)	20	40.0
Total	50	100.0

CD44 Expression and Lymphovascular Invasion

A statistically significant stepwise association was identified between CD44 expression intensity and lymphovascular invasion (p=0.043). LVI was absent in all low-expression cases (0/8, 0%), present in 22.7% of moderate-expression cases (5/22), and rose to 45% in strong-expression tumours (9/20). This clear escalation mirrors increasing CD44 surface density and confirms CD44's biological role in facilitating tumour cell intravasation (Table 2).

Table 2: CD44 expression and lymphovascular invasion (N=50)

CD44 Expression	LVI Present	LVI Not Identified	p-value

Low (N=8)	0 (0%)	8 (100%)	0.043
Moderate (N=22)	5 (22.7%)	17 (77.3%)	
Strong (N=20)	9 (45.0%)	11 (55.0%)	

CD44 Expression and Pathological Staging

A statistically significant association was identified between CD44 expression intensity and TNM stage (p=0.019) and AJCC stage grouping (p=0.016). All low-expression tumours were Stage I (100%), with 87.5% confined to pT2N0Mx. In strong-expression tumours, pT3N1Mx was the predominant stage (40%) and 40% of strong-expression cases were AJCC Stage IIIB. This stepwise stage migration with rising CD44 intensity confirms CD44 as a reliable molecular marker of tumour progression (Table 3).

Table 3: CD44 expression and pathological staging (N=50)

TNM/AJCC Stage	Low (N=8)	Moderate (N=22)	Strong (N=20)	p-value
pT1N0Mx	1 (12.5%)	4 (18.2%)	2 (10%)	0.019
pT2N0Mx	7 (87.5%)	7 (31.8%)	3 (15%)	
pT2N1Mx	0 (0%)	2 (9.1%)	3 (15%)	
pT3N0Mx	0 (0%)	6 (27.3%)	4 (20%)	
pT3N1Mx	0 (0%)	3 (13.6%)	8 (40%)	
Stage I	8 (100%)	11 (50%)	5 (25%)	0.016
Stage IIA	0 (0%)	6 (27.3%)	4 (20%)	
Stage IIIA	0 (0%)	2 (9.1%)	3 (15%)	
Stage IIIB	0 (0%)	3 (13.6%)	8 (40%)	

CD44 Expression and Other Parameters

No statistically significant association was observed between CD44 expression and histological grade (p=0.756), perineural invasion (p=0.518), tumour budding (p=0.579), tumour infiltrating lymphocytes (p=0.389), tumour laterality (p=0.167), or gross morphology (p=0.163). A summary of all correlations is presented in Table 4.

Table 4: Summary of CD44 expression correlations with clinicopathological parameters. NS = non-significant; S = significant

Parameter	p-value	Significance
Tumour site	0.084	NS
Tumour laterality (L vs R)	0.167	NS
Gross morphology	0.163	NS
Histological grade	0.756	NS
Lymphovascular invasion (LVI)	0.043	S
Perineural invasion (PNI)	0.518	NS
Tumour infiltrating lymphocytes (TILs)	0.389	NS
Tumour budding	0.579	NS
TNM staging	0.019	S
AJCC stage group	0.016	S

DISCUSSION

i. Comparison of CD44 Expression Among Study Population

In the present study, moderate or strong CD44 expression was identified in 84% of cases (low: 16%, n=8; moderate: 44%, n=22; strong: 40%, n=20). This high positivity rate is in line with the majority of published IHC studies of CD44 in CRC.

Marked heterogeneity in absolute CD44 positivity rates exists across the literature (44–95%), driven by substantial methodological variation in antibody clone selection, scoring systems, positivity thresholds, and tissue processing.9
The highest rate (95%) of CD44 positivity was reported by Elakad et al., reflecting a broad definition of positivity (any detectable staining in ≥10% of cells),10 while the lowest rate (44%) was reported by Sajjadi-Jazi et al., who applied strict quantitative thresholds.11 Kim et al., studying CD44v6 in 187 Stage II/III CRC patients using IHC, reported positivity in 72.2% of cases,12 while Abdou et al., studying cancer stem cell markers in 70 CRC patients, reported CD44 positivity in 80% of cases.13
The large study by Alqahtani et al. (n=1,137) using strict membrane intensity criteria reported 47.7% positivity,14 and the meta-analysis by Huang et al. pooling 48 studies (3,496 patients) confirmed overall CD44 overexpression in approximately 60% of CRC.8 The 40% strong expression in our study is consistent with these stringently defined rates.

ii. Comparison of CD44 Expression With Lymphovascular Invasion

A statistically significant stepwise association was identified between CD44 expression intensity and lymphovascular invasion (p=0.043). LVI was absent in all low-expression cases (0/8, 0%), present in 22.7% of moderate-expression cases (5/22), and rose to 45% in strong-expression tumours (9/20), a clear escalation that mirrors increasing CD44 surface density.
The biological basis for this association is well established: CD44 acts as a co-receptor for hyaluronan and MMP-9, which degrades the extracellular matrix and basement membrane, enabling cancer cell intravasation into blood and lymph vessels.15 This explains the rising LVI rates across CD44 expression levels (0% low, 23% moderate, 45% strong; p=0.043).
This finding is corroborated by multiple independent published series. Kim et al., evaluating CD44v6 in 187 Stage II/III CRC patients, found significant associations between CD44v6 overexpression and angiolymphatic invasion, deeper tumour invasion, and lymph node metastasis.12 El-Guindy et al. similarly demonstrated that CD44 overexpression was significantly associated with lymphovascular invasion in CRC.16 Tang et al., in 56 CRC cases, reported that CD44v3 overexpression correlated with vascular invasion ($p<0.05$) while CD44v4 overexpression correlated with depth of invasion ($p<0.05$), confirming that CD44 isoforms collectively facilitate multiple steps in the invasion–metastasis cascade.17
At the population level, the meta-analysis by Huang et al. pooling 48 studies confirmed a significant association between CD44 overexpression and lymph node metastasis,8 and the CD44v6-specific meta-analysis by Wang et al. across 21 studies (n=3,918) further demonstrated that CD44v6 overexpression was significantly associated with lymph node invasion and advanced disease stage.18
The clinical relevance of this association is most pronounced in the pT2 subgroup, where LVI may represent the only high-risk pathological feature present in an otherwise early-stage tumour. In such cases, strong CD44 expression — reflecting active MMP-mediated matrix degradation and enhanced intravasation capacity — could serve as a complementary IHC marker to identify tumours warranting closer surveillance or adjuvant therapy consideration, even when conventional staging parameters alone would not trigger intervention.3

iii. Comparison of CD44 Expression and Pathological Stage

A statistically significant association was identified between CD44 expression intensity and both TNM stage (p=0.019) and AJCC stage group (p=0.016). All low-expression tumours were Stage I (100%), with 87.5% confined to pT2N0Mx, while strong CD44 expression was concentrated at the opposite end of the staging spectrum, with 40% of strong-expression cases being pT3N1Mx and 40% classified as Stage IIIB. This stepwise stage migration with rising CD44 intensity confirms CD44 as a reliable molecular marker of tumour progression rather than a non-specific marker of malignancy.
The biological basis is rooted in the adenoma–carcinoma sequence itself. As tumours accumulate mutations along the APC→KRAS→SMAD4→TP53 axis, Wnt/β-catenin signalling becomes constitutively active and directly drives CD44 transcription.5 As tumours grow and encounter hypoxia with deeper mural invasion, HIF-1α further amplifies CD44 expression, creating a self-reinforcing loop that equips cancer cells with the molecular tools required for invasion and nodal spread.19
Abdou et al., in 70 CRC cases, found a highly significant relationship between CD44 expression and AJCC stage ($p<0.001$).13 Elakad et al., in 85 cases, demonstrated significant associations between CD44 and T-stage (p=0.009), lymph node metastasis ($p<0.001$), and overall disease stage ($p<0.001$), mirroring the TNM-stratified CD44 gradient observed in our cohort.10 Mahdi et al., in their Iraqi series of 72 cases, confirmed a significant association between CD44 expression and tumour stage ($p<0.05$), further establishing the reproducibility of this relationship across geographically and ethnically diverse populations.20
Ziranu et al., extending this observation into the metastatic setting, found CD44 overexpression significantly correlated with Stage IV disease (p=0.0241) and markedly inferior overall survival (median OS 14.5 versus 30.7 months, p=0.0011), demonstrating that the CD44–stage relationship identified in our early-to-intermediate stage cohort extends and amplifies at the metastatic end of the disease spectrum.21
At the meta-analytic level, Huang et al., pooling 48 studies across 3,496 patients, confirmed that CD44 overexpression was significantly associated with worse overall survival (HR=1.32, 95% CI 1.08–1.61, p=0.007),8 while Dai et al., in a separate meta-analysis of 30 studies, similarly identified CD44 overexpression as an independent poor prognostic factor (HR=1.44, 95% CI 1.13–1.85).22

iv. Comparison of CD44 Expression With Tumour Grade

No significant CD44–grade correlation (p=0.756) was identified, which is the most biologically striking null finding, given CD44's key role in cancer stem cell biology. Yet this disconnect has clear precedent in the literature.

Sajjadi-Jazi et al., in a 102-case Iranian CRC series, found no association between CD44 standard isoform expression and any clinicopathological parameter including histological grade, stage, gender, or tumour location.11 Hassan et al., in 60 Iraqi CRC cases, similarly found no statistically significant correlation between CD44 expression and grade, T stage, N stage, or overall TNM stage grouping.23 Bhangu et al. equally reported no significant CD44–grade association in their Indian surgical series, noting that CD44 expression patterns did not follow the expected gradient of increasing dedifferentiation.24

This dissociation is attributable to histological grade reflecting morphological differentiation — the degree to which tumour glands retain normal architectural organisation — while CD44 expression reflects Wnt/β-catenin-driven activation of cancer stemness programmes that operate independently of morphological differentiation.5 A Grade 2 moderately differentiated tumour can therefore harbour abundant CD44-high cancer stem cells fully capable of lymphovascular invasion and nodal spread, as directly demonstrated by the significant CD44–LVI and CD44–stage associations in our series.

v. Comparison of CD44 Expression With Tumour Budding

The absence of a significant CD44–budding association (p=0.579) in our series is consistent with findings reported by Lugli et al., who observed that tumour budding and CD44 expression, while both reflecting aspects of EMT-associated invasiveness, do not always co-localise or correlate at the individual tumour level.25 Tumour budding reflects EMT at the invasive front while CD44 marks stem cells throughout the tumour. These distinct mechanisms explain their independence in our cohort, supporting combined use for better risk stratification.

vi. Comparison of CD44 Expression With Tumour Infiltrating Lymphocytes

The absence of a significant CD44–TIL association (p=0.389) reflects the biological independence of cancer stemness from immune infiltration in our cohort. CD44-high cancer stem cells have been shown by Iliopoulos et al. to actively contribute to immune evasion through secretion of IL-6, IL-8, and TGF-β, which suppress cytotoxic T lymphocyte activity and promote regulatory T cell expansion — mechanisms that would tend to reduce rather than increase TIL density in CD44-high tumours.26

Yan et al. similarly demonstrated that CD44-high CRC cells downregulated MHC class I surface expression, rendering them less recognisable to CD8+ cytotoxic T cells and further uncoupling CD44 expression from TIL recruitment.27 The null CD44–TIL finding in our series reflects a biologically plausible immunosuppressive consequence of CD44-mediated stemness that warrants further investigation in larger series with additional subtyping.

vii. Comparison of CD44 Expression With Perineural Invasion

The absence of a CD44–PNI association (p=0.518) is consistent with the independence of perineural invasion from CD44-mediated pathways. Perineural invasion is primarily governed by neurotrophic signalling rather than by hyaluronate–CD44 receptor interactions.28 Bakst et al. and Liebl et al. both confirmed that PNI in gastrointestinal malignancies is driven by neurotropism-dependent rather than stemness-dependent molecular programmes, explaining why CD44 — a marker of hyaluronate-mediated invasiveness and vascular intravasation — does not predict perineural spread.29

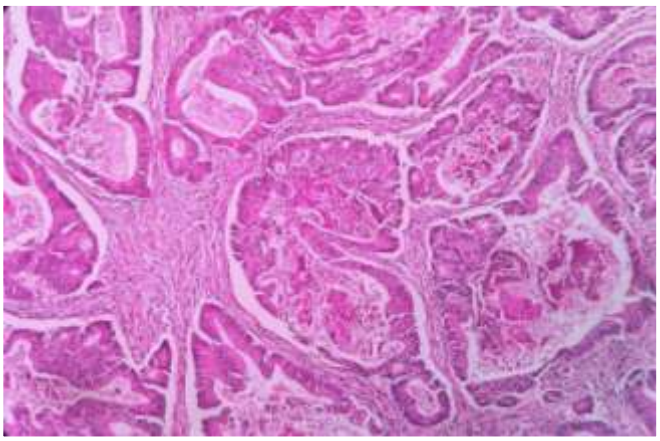

Figure 1: Well differentiated adenocarcinoma colon showing predominantly glandular differentiation, H&E, 100x

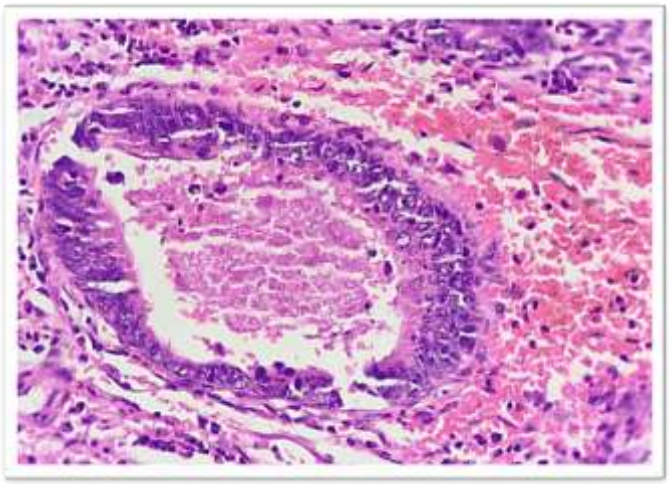

Figure 2: Well differentiated adenocarcinoma colon showing garland necrosis with necrotic debris present in the lumen, H&E400x

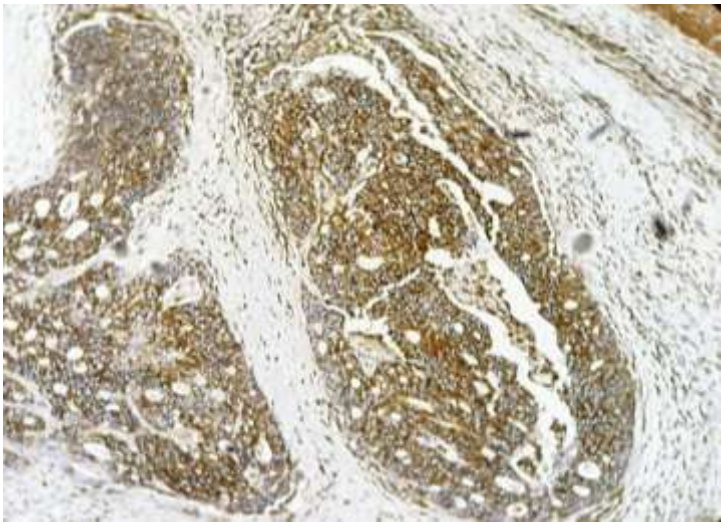

Figure 3: Strong CD44 expression in adenocarcinoma colon, IHC,100x

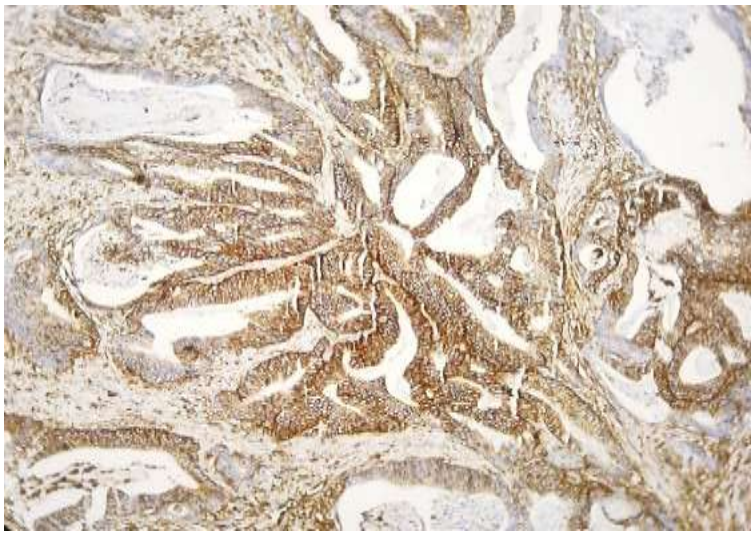

Figure 4: Moderate CD44 expression in adenocarcinoma colon, IHC,100x

CONCLUSION

CD44 overexpression in CRC plays a crucial role in enhancing carcinogenic processes. In the present study of 50 surgically resected CRC specimens, moderate or strong CD44 expression was identified in 84% of cases. CD44 expression intensity was significantly associated with lymphovascular invasion (p=0.043), TNM staging (p=0.019), and AJCC stage grouping (p=0.016), confirming its role as a reliable molecular marker of tumour aggressiveness and progressive invasion in CRC.

Importantly, the dissociation between CD44 expression and histological grade (p=0.756) confirms that CD44 and conventional histopathological parameters measure different and complementary dimensions of tumour biology. A Grade

2 moderately differentiated tumour can harbour strong CD44 expression predicting LVI and advanced stage while appearing entirely conventional under routine assessment. This makes CD44 IHC particularly clinically valuable in early-to-intermediate stage CRC.

CD44 represents a promising supplementary prognostic biomarker for routine CRC pathology reporting. Its inclusion alongside conventional histopathological parameters at the time of surgical resection could objectively identify high-risk Stage I/II patients warranting intensified surveillance or adjuvant therapy consideration a clinical gap that conventional TNM staging alone cannot reliably bridge. Prospective studies on larger multicentre cohorts with long-term follow-up are needed to confirm the independent prognostic and predictive role of CD44 and to define standardised scoring thresholds for clinical application.

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