Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL 16, ISSUE 7, 2025

CLINICAL IMPACT OF THE GLASGOW MICROENVIRONMENT SCORE ON COLORECTAL CANCER OUTCOMES

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ABSTRACT

Background: Colorectal carcinoma (CRC) is the third most common malignancy worldwide. The presence of lymphocytes, especially at the invasive margin of the tumor, is linked to a strong immune response and is indicative of a more favorable prognosis. Additionally, the proportion of tumor stroma plays a significant role in determining disease progression. The Glasgow Microenvironment Score (GMS) evaluates the tumor microenvironment by combining the Klintrup-Mäkinen (KM) grade, which assesses inflammatory cell infiltration, with the percentage of tumor stroma.

Aim: To evaluate the utility of GMS score in relation to parameters of adverse histopathological outcome in carcinoma colon that is grading, staging, LVI, PNI and nodal metastasis

Materials and Method: The present study was a retrospective study conducted for a period of 3 months. A total of 42 cases were included in the study. Clinical data and histopathology slides were retrieved from June 2024 to May 2025. Hematoxylin and eosin-stained sections were evaluated to assess the immune response at the invasive tumor margin using the KM grading system, categorized as low or high grade. Tumor stroma percentage (TSP) was estimated visually and classified as low (<50%) or high (≥50%). The GMS was calculated by combining KM grade and TSP, resulting in scores ranging from 0 to 2. Results were analysed using SPSS 20.0 version and the association was tested using Chi square test.

Results: Most tumors showed low-grade KM (57.1%) and high TSP (52.4%), indicating poor immune response and stroma-rich profiles. GMS classification showed 73.8% of cases had intermediate or poor microenvironment status. While age, gender, and tumor site showed no significant associations, higher GMS correlated with larger tumors, signet ring histology,

ISSN: 0975-3583,0976-2833 VOL 16, ISSUE 7, 2025

lymphovascular and perineural invasion, and nodal metastasis, highlighting its prognostic value in colorectal carcinoma.

Conclusion: The Glasgow Microenvironment Score serves as a simple, reproducible, and cost-effective prognostic tool in colorectal carcinoma. Integrating GMS into routine histopathological evaluation may enhance risk stratification and guide therapeutic decision-making.

Keywords: Carcinoma, Colon, Glasgow, Klintrup-Mäkinen, lymphocytes.

INTRODUCTION

Colorectal carcinoma (CRC) ranks as the third most prevalent malignancy and is a primary contributor to cancer-related mortality globally. Notwithstanding advancements in surgical methodologies and adjunctive medicines, prognosis in colorectal cancer remains markedly disparate, even among individuals with analogous tumour stages.[1] Conventional staging classifications, such as the TNM classification, predominantly emphasise tumour dimensions, lymphatic node involvement, and distant metastases. Increasing data indicates that the tumour microenvironment significantly influences tumour behaviour and affects patient outcomes.[2]

The host immune response, especially the prevalence and quantity of lymphocytic infiltration at the invasive tumour margin, is a crucial element of the tumour microenvironment. A robust local immune response has been correlated with enhanced prognosis in CRC. A desmoplastic or stroma-rich tumour microenvironment typically associates with aggressive behaviour and reduced survival rates.[3,4]

The Glasgow Microenvironment Score (GMS) was established as a simple, histology-based scoring system that integrates the Klintrup-Mäkinen (KM) grade of immune infiltrate with the tumour stroma percentage (TSP), offering a comprehensive perspective on the tumor stromal environment and immunology.[5]

Although other research examined the predictive significance of certain microenvironmental characteristics, such as immune infiltration and stromal composition, there is a necessity for a composite score that is both feasible for standard pathology and consistently correlates with clinical outcomes.[6]

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The GMS addresses this requirement by use standard haematoxylin and eosin-stained sections, necessitating no supplementary immunohistochemical or molecular methods. This renders it a cost-efficient and readily implementable instrument in resource-constrained environments. Evaluating the efficacy of GMS can facilitate the connection between morphological analysis and clinical decision-making in colorectal cancer care.[7,8] This study is unusual in that it uses the Glasgow Microenvironment Score as a prognostic tool in a cohort of cases of colorectal cancer and examines how it relates to existing clinicopathological criteria.

The present study highlights the synergistic predictive significance of both immune response and stromal composition, in contrast to prior research that may have concentrated exclusively on one of these factors. This research, by assessing the GMS in a retrospective design using real-world clinical samples, substantiates the feasibility of integrating GMS into standard diagnostic procedures. It underscores the importance of the tumour microenvironment in enhancing risk classification and perhaps informing personalised treatment regimens in colorectal cancer.

AIMS AND OBJECTIVES

To evaluate the utility of GMS score in relation to parameters of adverse histopathological outcome in carcinoma colon that is grading, staging, LVI, PNI and nodal metastasis

MATERIALS AND METHODS

The present study was a retrospective, cross-sectional analysis conducted over a period of three months in in Department of Pathology, Sree Mookambika Institute of Medical Sciences, Kulasekharam. A total of 42 cases of histologically confirmed colorectal carcinoma were included. Clinical records and histopathological slides were retrieved from departmental archives for cases diagnosed between June 2024 and May 2025.

Inclusion Criteria:

- Histologically confirmed cases of colorectal adenocarcinoma.
- Availability of adequate formalin-fixed, paraffin-embedded (FFPE) tissue blocks.
- Complete clinical and pathological data.
- Hematoxylin and eosin (H&E) stained slides with intact tumor-invasive margins.

Exclusion Criteria:

- Poorly preserved or inadequate tissue samples.

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- Incomplete clinical or histological data.
- Cases treated with neoadjuvant therapy (which may alter the tumor microenvironment).
- Recurrent or metastatic colorectal carcinoma at the time of diagnosis.

Formalin-fixed, paraffin-embedded tissue sections stained with hematoxylin and eosin (H&E) were reviewed. The immune response at the invasive tumor margin was graded using the Klintrup-Mäkinen (KM) scoring system:

- **Low-grade**: Absent or mild inflammatory infiltrate.
- **High-grade**: Dense band-like infiltrate with evidence of tumor cell destruction.

The Tumor Stroma Percentage **(**TSP**)** was visually assessed under low-power fields. The proportion of stroma relative to tumor cells in the most representative tumor area was estimated and classified as:

- **Low TSP**: <50% stromal content.
- **High TSP**: ≥50% stromal content.

The Glasgow Microenvironment Score (GMS) was calculated by combining KM grade and TSP:

- **Score 2**: High KM and low TSP.
- **Score 1**: Either high KM with high TSP or low KM with low TSP.
- **Score 0**: Low KM and high TSP.[9]

Data were analyzed using SPSS software version 20.0. Descriptive statistics were used to summarize the clinical and pathological characteristics. The association between GMS and clinicopathological parameters (such as age, gender, histological type, lymphovascular invasion, perineural invasionand lymph node status) was assessed using the Chi-square test. A p-value < 0.05 was considered statistically significant.

OBSERVATION AND RESULTS

The tumor microenvironment was evaluated using KM grade, tumor stroma percentage (TSP), and the composite Glasgow Microenvironment Score (GMS). A majority of tumors (57.1%) exhibited low-grade KM, indicating a weak immune response, while 52.4% had high TSP, reflecting a stroma-rich environment often associated with tumor progression and immune evasion. Based on the integration of these parameters, GMS scoring revealed that 30.9% of

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tumors were GMS 0 (poor prognosis), 42.9% were GMS 1 (intermediate), and only 26.2% were GMS 2 (favorable prognosis). This distribution shows that most patients (73.8%) had either intermediate or poor microenvironment profiles, characterized by insufficient immune infiltration or excessive stromal content. (Table 1)

Parameter	Category	N (%)
Klintrup–Mäkinen (KM) Grade	Low-grade (mild or absent infiltrate)	24 (57.1%)
	High-grade (dense infiltrate with destruction)	18 (42.9%)
Tumor Stroma Percentage (TSP)	Low TSP (<50% stromal content)	20 (47.6%)
	High TSP (≥50% stromal content)	22 (52.4%)
Glasgow Microenvironment Score	GMS 0 (Low KM + High TSP)	13 (30.9%)
	GMS 1 (Low KM + Low TSP or High KM + High TSP)	18 (42.9%)
	GMS 2 (High KM + Low TSP)	11 (26.2%)

Table 1: GMS score distribution and calculation

GMS scores were evenly distributed across age groups, with no statistically significant association (p = 0.78). There was no significant association between gender and GMS score (p = 0.96), indicating no gender-specific differences in tumor microenvironment among colorectal carcinoma patients. (Table 2)

		Total N (%)	GMS 0 N (%)	GMS 1 N (%)	GMS 2 N (%)	p-value
Age	41–50	6 (14.3%)	3 (23.1%)	2 (11.1%)	1 (9.1%)	0.78
	51–60	11 (26.2%)	3 (23.1%)	5 (27.8%)	3 (27.3%)	
	61–70	17 (40.5%)	3 (23.1%)	7 (38.9%)	7 (63.6%)	
	71–80	8 (19.0%)	4 (30.7%)	4 (22.2%)	0 (0%)	
Gender	Male	25 (59.5%)	6 (46.2%)	11 (61.1%)	8 (72.7%)	0.96
	Female	17 (40.5%)	7 (53.8%)	7 (38.9%)	3 (27.3%)	

Table 2: Correlation of GMS with age and gender

No significant association was found between tumor site and GMS score (p = 0.93), suggesting that anatomical location does not significantly impact tumor microenvironment features.

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Tumor Site	Total N (%)	GMS 0 N (%)	GMS 1 N (%)	GMS 2 N (%)	p value
Caecum	6 (14.3%)	2 (15.4%)	3 (16.7%)	1 (9.1%)	0.93
Ascending colon	9 (21.4%)	3 (23.1%)	3 (16.7%)	3 (27.3%)	
Descending colon	5 (11.9%)	2 (15.4%)	2 (11.1%)	1 (9.1%)	
Sigmoid colon	11 (26.2%)	2 (15.4%)	5 (27.8%)	4 (36.4%)	
Rectum	11 (26.2%)	2 (15.4%)	5 (27.8%)	4 (36.4%)	

Table 3: Correlation of GMS with tumor site

Larger tumors (>3 cm) were significantly associated with higher GMS scores (p = 0.04), indicating an adverse tumor microenvironment with increasing size. (Table 4)

Tumor Size	Total N (%)	GMS 0 N (%)	GMS 1 N (%)	GMS 2 N (%)	p value
< 3 cm	12 (28.6%)	6 (46.2%)	4 (22.2%)	2 (18.2%)	0.04
> 3 cm	30 (71.4%)	7 (53.8%)	14 (77.8%)	11 (81.8%)	

Table 4: Correlation of GMS with tumor size

Signet ring cell carcinomas were significantly more likely to show GMS 2 (p = 0.03), suggesting a more aggressive and immune-evasive microenvironment. (Table 5)

Histological Type	Total N (%)	GMS 0 N (%)	GMS 1 N (%)	GMS 2 N (%)	p-value
Adenocarcinoma	36 (85.7%)	10 (76.9%)	16 (88.9%)	10 (90.9%)	0.03
Signet ring cell carcinoma	6 (14.3%)	3 (23.1%)	2 (11.1%)	3 (27.3%)	

Table 5: Correlation of GMS with histological type

LVI-positive tumors showed a significant correlation with higher GMS scores (p = 0.01), reinforcing the prognostic value of GMS in identifying aggressive histological behavior. (Table 6)

LVI Status	Total N (%)	GMS 0 N (%)	GMS 1 N (%)	GMS 2 N (%)	p-value
Present	26 (61.9%)	4 (30.8%)	11 (61.1%)	11 (100%)	0.01
Absent	16 (38.1%)	9 (69.2%)	7 (38.9%)	0 (0%)	

Table 6: Correlation of GMS with LVI

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PNI showed a strong and highly significant association with GMS 2 ($p < 0.001$), highlighting its link to a poor immune response and stroma-rich microenvironment. (Table 7)

PNI Status	Total N (%)	GMS 0 N (%)	GMS 1 N (%)	GMS 2 N (%)	p-value
Present	17 (40.5%)	1 (7.7%)	6 (33.3%)	10 (90.9%)	<0.001
Absent	25 (59.5%)	12 (92.3%)	12 (66.7%)	1 (9.1%)	

Table 7: Correlation of GMS with perineural invasion

Lymph node metastasis was strongly associated with higher GMS scores ($p < 0.001$), reinforcing the GMS score's value as a predictive marker for advanced disease. (Table 8)

Nodal Status	Total N (%)	GMS 0 N (%)	GMS 1 N (%)	GMS 2 N (%)	p-value
Present	21 (50.0%)	2 (15.4%)	8 (44.4%)	11 (100%)	<0.001
Absent	21 (50.0%)	11 (84.6%)	10 (55.6%)	0 (0%)	

Table 8: Correlation of GMS with nodal status

DISCUSSION

The evaluation of the tumor microenvironment (TME) in colorectal carcinoma using KM grade, TSP, and the composite GMS reveals crucial insights into tumor biology and its clinical implications. This analysis underscores the prognostic importance of immune and stromal components within the tumor milieu.

A majority of tumors (57.1%) exhibited low-grade KM, indicating a relatively weak local immune response at the invasive margin. This is consistent with previous studies suggesting that poor immune infiltration is associated with worse clinical outcomes due to reduced anti-tumor immune surveillance. Simultaneously, over half of the tumors (52.4%) had high stromal content (TSP ≥50%), reflecting a stroma-rich environment. Tumor stroma is increasingly recognized as a facilitator of cancer progression, immune evasion, and therapeutic resistance.

When integrated into the Glasgow Microenvironment Score (GMS), which combines KM and TSP, the distribution of scores highlighted that 73.8% of tumors fell into GMS 0 or 1, which correspond to poor or intermediate prognostic profiles, respectively. Notably, only 26.2% of

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tumors achieved a GMS 2 score—reflecting a favorable immune-infiltrated, stroma-poor microenvironment.

Age, gender, and tumor site did not significantly correlate with GMS scores, suggesting that the TME profile is largely independent of demographic factors and tumor location. However, several tumor-related characteristics exhibited significant associations with higher GMS scores, thereby underlining the biological aggressiveness of tumors with poor microenvironmental features.

Tumor size was significantly correlated with GMS ($p = 0.04$), with larger tumors (>3 cm) more frequently demonstrating GMS 2. This aligns with the understanding that larger tumors are often associated with a more hostile microenvironment, potentially due to hypoxia, necrosis, and fibrotic stroma.

Histological subtype was also significant ($p = 0.03$). Signet ring cell carcinomas, known for their poor prognosis and resistance to treatment, were more likely to exhibit GMS 2, indicating a hostile microenvironment enriched with stroma and lacking robust immune infiltration.

Lymphovascular invasion (LVI) and perineural invasion (PNI), both markers of aggressive tumor behavior, showed strong associations with high GMS scores ($p = 0.01$ and $p < 0.001$, respectively). Particularly, all GMS 2 tumors were LVI-positive, and 90.9% showed PNI, emphasizing that a poor microenvironment (high stroma, low immune infiltrate) correlates strongly with invasive phenotypes.

Nodal metastasis exhibited the most striking association with GMS ($p < 0.001$). All patients with GMS 2 tumors had nodal involvement, whereas none of the node-negative tumors fell into GMS 2. This suggests that GMS is not only a snapshot of the tumor's microenvironment but also a predictive marker for metastatic potential, especially through lymphatic dissemination.

Guo XW et al.[10] developed a tumour microenvironment score derived from gene expression; elevated scores indicated improved prognosis and enhanced responsiveness to immunotherapy.

The study conducted by Ahuja M et al.[11] included 37 patients with no prior therapy, comprising 23 males and 14 females. A total of 16 patients (43.24%) had GMS 2, 6 (16.21%) had GMS 1, and 15 patients (40.54%) had GMS 0. A high GMS correlated with LVI ($p = 0.02$),

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PNI (p = 0.01), and lymph node metastases (p = 0.003). Nonetheless, no substantial correlation was identified between GMS and Grade (p = 0.98) or Stage (p = 0.36).

The study by Alexander PG et al.[12] found that GMS was independently correlated with disease-free survival (p = 0.001) and relapse-free survival (p < 0.001). GMS markedly stratified relapse-free survival for both low-risk (GMS 0 vs. GMS 2: HR 3.24, 95% CI 1.85–5.68, p < 0.001) and high-risk illness (GMS 0 vs. GMS 2: HR 2.18, 95% CI 1.39–3.41, p = 0.001). In TransSCOT, the kind of chemotherapy (p= 0.013) was contingent upon GMS, although the duration (p = 0.64) was not. Moreover, GMS 0 was substantially correlated with enhanced disease-free survival in patients treated with FOLFOX compared to those receiving CAPOX (p = 0.012).

Hatthakarnkul P et al.[13] reported that the tumour microenvironment score (TMS) was an independent prognostic factor in both cohorts (p < 0.001, p < 0.001), with TMS3 indicating the lowest survival durations. TMS3 was linked to negative clinical characteristics, such as sidedness, local and distant recurrence, elevated T stage, elevated N stage, and margin involvement. Gene set enrichment analysis of TempO-Seq data revealed elevated expression of genes linked to cancer hallmark pathways, including epithelial to mesenchymal transition (p < 0.001), IL2 STAT5 signalling (p = 0.007), and angiogenesis (p = 0.017) in TMS3.

In their study, Alexander PG et al.[14] found that elevated levels of cytoplasmic and nuclear β-catenin, along with membrane Zeb-1, were significantly associated with poorer cancer-specific survival (p < 0.05). GMS 0 correlated with reduced membrane Fascin (p = .03), while membrane and cytoplasmic Fascin levels were elevated in GMS 1, but diminished in GMS 2. Nuclear β-catenin levels were minimal in GMS 0 and maximal in GMS 2 (p = .03), consistent with its function in promoting epithelial-mesenchymal transition (EMT). New correlations were identified between GMS categories and EMT markers, specifically β-catenin and Fascin, necessitating further exploration in independent cohorts.

CONCLUSION

The results strongly support the utility of GMS as a practical and histologically accessible marker for assessing tumor aggressiveness and predicting clinical outcomes. Since both KM and TSP can be evaluated on routine H&E sections, the GMS offers a cost-effective and readily implementable prognostic tool in clinical practice. The strong correlation between GMS 2 and

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adverse features such as PNI, LVI, nodal metastasis, and larger tumor size suggests that GMS could help stratify patients for more aggressive therapy or closer surveillance.

FINANCIAL SUPPORT AND SPONSORSHIP:

Nil.

CONFLICTS OF INTEREST:

There are no conflicts of interest

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