Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.4 No. 12 (2023): December 2023 Issue
https://doi.org/10.51168/sjhrafrica.v4i12.2449
Review Article

# Histological differentiation and Ki-67 expression in rectal cancer based on time-dependent diffusion MRI-derived microstructure parameters: A systematic review.

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## Abstract

### Background
Histological differentiation and Ki-67 expression are key indicators of tumor aggressiveness in rectal cancer but are currently assessed postoperatively. Time-dependent diffusion MRI (td-dMRI) has emerged as an advanced imaging technique capable of probing tissue microstructure beyond conventional apparent diffusion coefficient (ADC) measurements.
Purpose: To systematically evaluate the diagnostic and predictive value of td-dMRI–derived microstructure parameters for assessing histological differentiation and Ki-67 expression in rectal cancer.

### Methods
A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar were searched from database inception to 31 January 2026. Eligible studies included peer-reviewed human investigations evaluating time-dependent diffusion magnetic resonance imaging (MRI) techniques with quantitative microstructure parameter extraction and histopathological correlation for tumor differentiation and/or Ki-67 expression in rectal cancer. Risk of bias was assessed using the QUADAS-2 tool. Due to methodological heterogeneity, findings were synthesized narratively.

### Results
Three single-center studies published between 2025 and 2026 were included. Across studies, intracellular volume fraction and cellularity-related parameters consistently demonstrated significant associations with histological differentiation and, in one study, Ki-67 expression. Multiparametric models incorporating microstructure parameters outperformed ADC-only approaches for characterizing tumor aggressiveness.

### Conclusion
td-dMRI-derived microstructure parameters, particularly intracellular volume fraction, showed promise as non-invasive imaging biomarkers of histological differentiation and proliferative activity in rectal cancer. Larger, standardized multicentre studies are required to validate their clinical utility.

***Keywords:*** *Diffusion-weighted imaging; Histological differentiation; Intracellular volume fraction; Ki-67; Microstructure imaging; Rectal cancer; Time-dependent diffusion magnetic resonance imaging*
***Submitted:*** *September 20, 2023* ***Accepted:*** *November 29, 2023* ***Published:*** *December 30, 2023*

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## Introduction

Rectal cancer remains a significant global health burden and continues to contribute substantially to cancer-related morbidity and mortality despite advances in diagnostic

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imaging, surgical techniques, and multimodal oncologic therapy [1,2]. Accurate preoperative risk stratification is essential for optimizing individualized treatment strategies, particularly in determining eligibility for neoadjuvant chemoradiotherapy, tailoring surgical approaches and predicting long-term oncologic outcomes. Among the pathological features of rectal cancer, histological differentiation and tumor proliferative activity are recognized as key indicators of biological aggressiveness and prognostic significance [3-5].

Histological differentiation reflects the degree of resemblance between tumor cells and normal glandular epithelium and is closely associated with tumor invasiveness, metastatic potential, and treatment response [6,7]. Poorly differentiated tumours are generally associated with unfavourable prognosis, higher recurrence rates, and reduced survival [8,9]. In parallel, Ki-67, a nuclear protein expressed during active phases of the cell cycle, serves as a widely accepted marker of cellular proliferation. Elevated Ki-67 expression has been linked to increased tumor aggressiveness, resistance to therapy, and adverse clinical outcomes in rectal cancer [10-12]. However, assessment of differentiation grade and Ki-67 expression currently rely on postoperative histopathological examination, limiting their utility for preoperative decision-making [13,14].

Magnetic resonance imaging (MRI) is the cornerstone of locoregional staging in rectal cancer and plays a critical role in evaluating tumor extent, mesorectal fascia involvement, extramural vascular invasion, and nodal status [15,16]. Diffusion-weighted imaging (DWI), through the calculation of apparent diffusion coefficient (ADC) values, provides functional information related to the mobility of water molecules within tissues and is commonly used as a surrogate marker of tumor cellularity [17-19]. Lower ADC values are often associated with higher cell density and restricted diffusion in malignant tissues [20,21]. Nevertheless, ADC represents a composite parameter influenced by multiple microenvironmental factors, including cellular density, extracellular volume fraction, perfusion effects, membrane permeability, and tissue heterogeneity. As a result, conventional ADC lacks specificity for underlying tumor microarchitecture and may inadequately capture the complex biological features that determine tumor aggressiveness [22].

Time-dependent diffusion MRI (td-dMRI) has emerged as an advanced diffusion imaging approach designed to overcome the limitations of conventional DWI[23,24]. By probing water diffusion at different diffusion times or frequencies using pulsed-gradient spin-echo (PGSE) and oscillating-gradient spin-echo (OGSE) techniques, td-dMRI enables interrogation of tissue microstructure across multiple spatial scales. These acquisitions allow the derivation of biologically meaningful microstructure-related parameters, including intracellular volume fraction, extracellular diffusivity, cellularity surrogates, and cell size-related metrics[25-27]. Unlike ADC, these parameters aim to disentangle specific microstructural contributors to diffusion restriction and thereby provide a more direct representation of tissue architecture[28-29].

In oncologic imaging, td-dMRI has demonstrated potential for characterizing tumor microstructure, assessing cellular heterogeneity, and reflecting biological processes such as proliferation and differentiation[30]. In rectal cancer, emerging studies employing td-dMRI techniques including MR cytometry and IMPULSED-based modelling, have reported associations between microstructural diffusion parameters and histopathological features. These approaches offer the possibility of noninvasively assessing tumor aggressiveness and proliferative activity, potentially bridging the gap between imaging findings and molecular pathology [31].

Despite growing interest in td-dMRI for rectal cancer evaluation, the existing evidence remains fragmented, and the collective ability of td-dMRI–derived microstructure parameters to predict histological differentiation and Ki-67 expression has not been systematically synthesized. A comprehensive evaluation of the available literature is therefore warranted to clarify the current state of evidence, identify consistent imaging biomarkers, and highlight gaps requiring further investigation. Accordingly, the present systematic review aimed to critically evaluate published human studies assessing time-dependent diffusion MRI–derived microstructure parameters for predicting histological differentiation degree and Ki-67 expression in rectal cancer, with a focus on their potential role as non-invasive imaging biomarkers of tumor aggressiveness.

## Materials and methods

### Study design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [32].

### Review question

What is the diagnostic and predictive value of time-dependent diffusion MRI–derived microstructure parameters for assessing histological differentiation degree and Ki-67 expression in rectal cancer?

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## Information sources

The following electronic databases were systematically searched:

- PubMed/MEDLINE
- Scopus
- Web of Science
- Google Scholar

Manual screening of reference lists from eligible articles was also performed.
The search strategy combined controlled vocabulary terms and free-text keywords related to diffusion MRI techniques, rectal cancer, and histopathological outcomes. The following search terms were used in various combinations:

- "Time-dependent diffusion MRI"
- "Oscillating gradient"
- "OGSE"
- "pulsed gradient"
- "PGSE"
- "MR cytometry"
- "cell size imaging"
- "IMPULSED"
- "rectal cancer"
- "tumor differentiation"
- "histological grade"
- "Ki-67"

Boolean operators (AND/OR) were applied as appropriate. Additionally, the reference lists of all eligible articles were manually screened to identify further relevant studies.

## Search dates

All databases were searched from inception to 31 January 2026. The final search was conducted on 31 January 2026.

## Eligibility criteria (Expanded for PRISMA compliance)

## Inclusion criteria

- Peer-reviewed original human research
- Patients with histologically confirmed rectal cancer or rectal lesions
- Use of time-dependent diffusion magnetic resonance imaging techniques, including oscillating-gradient spin-echo or pulsed-gradient spin-echo acquisitions
- Quantitative extraction of microstructure-derived diffusion parameters
- Histopathological correlation with tumor differentiation grade and/or Ki-67 expression
- English language publications

## Exclusion criteria

- Animal, phantom, or simulation studies
- Studies using conventional diffusion-weighted imaging without diffusion-time or frequency dependence
- Reviews, editorials, letters, conference abstracts
- Studies lacking histopathological reference standards
- Studies without extractable outcome data

## Study selection

All retrieved records were imported into a reference management system, and duplicate articles were removed. Titles and abstracts were screened independently to exclude clearly irrelevant studies. Full-text articles of potentially eligible studies were then assessed against the predefined inclusion and exclusion criteria. Any disagreements were resolved through discussion and consensus.

## Data extraction

Data extraction was performed using a standardized data collection form. The following information was extracted from each included study:
Author and year of publication
Study design and sample size
MRI acquisition protocol and diffusion modelling approach
Microstructure parameters evaluated
Histopathological reference standards
Primary outcomes (differentiation grade and/or Ki-67 expression)
Diagnostic performance metrics

## Risk of bias assessment

Methodological quality and risk of bias were assessed qualitatively using a QUADAS-2–informed framework [33], focusing on:

- Patient selection
- Conduct and interpretation of the index test
- Reference standard
- Flow and timing

## Data synthesis

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Due to heterogeneity in imaging protocols, diffusion models, outcome definitions, and statistical analyses, quantitative meta-analysis was not feasible. Therefore, findings were synthesized using a qualitative narrative approach.

## Certainty in the body of evidence

Certainty of evidence for the primary outcomes was qualitatively assessed considering study design, sample size, risk of bias, methodological consistency, and precision of reported diagnostic performance metrics. Given the small number of single-center studies and heterogeneity in diffusion acquisition protocols and modeling approaches, the overall certainty of evidence was judged to be low to moderate.

# Results

## Study selection

The electronic database search identified 214 records across PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. After the removal of 62 duplicate records, 152 unique studies remained for title and abstract screening.

During initial screening, 134 records were excluded due to irrelevance to the review question, non-human study design, use of conventional ADC-only diffusion techniques, or lack of histopathological correlation.

The full texts of 18 articles were assessed for eligibility. Of these, 15 studies were excluded for the following reasons: absence of time-dependent diffusion MRI techniques (n = 9), lack of microstructure parameter analysis (n = 3), absence of histopathological outcomes (n = 2), and non-original article type (n = 1).

Ultimately, 3 studies met all inclusion criteria and were included in the final qualitative synthesis. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

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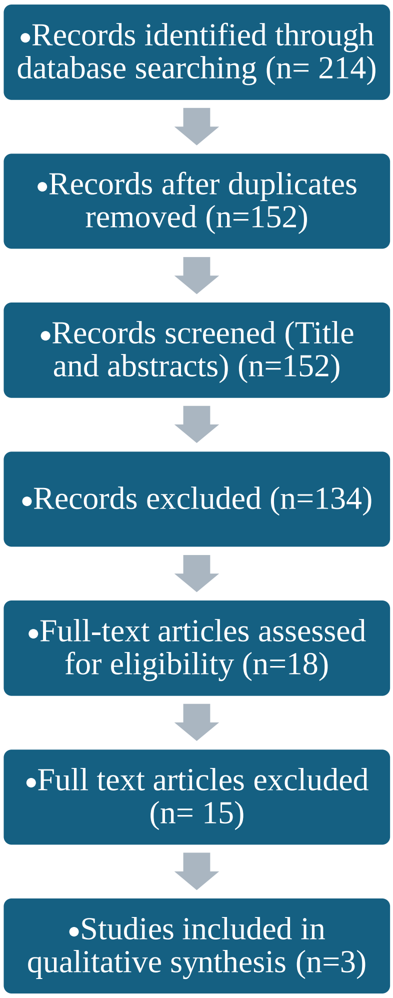


**Figure 1: PRISMA Flowchart**

## Study characteristics

The characteristics of the included studies are summarized in Table 1. The studies were published between 2025 and 2026 and were conducted as single-center prospective or retrospective analyses. Sample sizes ranged from 66 to 86 participants.

All studies employed time-dependent diffusion MRI techniques, incorporating combinations of oscillating-gradient spin-echo (OGSE) and pulsed-gradient spin-echo (PGSE) acquisitions. Diffusion modeling approaches included MR cytometry, IMPULSED, and related microstructure-based frameworks.

Across the included studies, poorly differentiated rectal cancers demonstrated distinct microstructural characteristics compared with well or moderately-differentiated tumors. Intracellular volume fraction and cellularity-related parameters consistently differed between differentiation groups. Multiparametric models combining microstructure parameters with conventional diffusion metrics achieved higher diagnostic accuracy than ADC alone.

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**Table 1. Characteristics of included studies**

| Author (Year) | Study Design | Sample Size | Population | td-dMRI Technique | Microstructure Parameters | Histopathological Outcome(s) | Key Findings |
|---|---|---|---|---|---|---|---|
| Lu et al. (2026)[34] | Retrospective cohort | 73 | Rectal cancer | OGSE + PGSE td-dMRI | Intracellular volume fraction, cellularity, ADC (time-dependent) | Differentiation grade, Ki-67 | Higher cellularity/ADC metrics were observed in the low differentiation group; ICVF was lower in the high Ki-67 group (P=0.001); combined model AUC 0.831 (differentiation) and 0.820 (Ki-67) |
| Zhao et al. (2026)[35] | Prospective exploratory | 86 | Rectal adenocarcinoma | OGSE + PGSE MR cytometry (IMPULSED, JOINT, EXCHANGE) | Intracellular volume fraction, extracellular diffusivity, and cellularity | Differentiation grade | Intracellular volume fraction best single predictor (AUC 0.812); combined models have an AUC of up to 0.883 |
| Kou et al. (2025)[36] | Retrospective preliminary study | 66 | Rectal lesions | OGSE + PGSE IMPULSED | Cell size metrics, intracellular fraction, extracellular diffusivity, and cellularity | Histologic type and grade-related parameters | Microstructure parameters differentiated malignant vs benign lesions and cancer subtypes. |

Abbreviations: td-dMRI = time-dependent diffusion MRI; OGSE = oscillating-gradient spin-echo; PGSE = pulsed-gradient spin-echo; ICVF = intracellular volume fraction; AUC = area under the curve.

## Risk of bias assessment

The risk of bias assessment is summarized in Table 2. Overall, the included studies demonstrated low to moderate risk of bias.

Patient selection bias was mainly related to single-center study designs and limited sample sizes. The conduct and interpretation of the index test were generally appropriate, although variability in diffusion modeling and region-of-interest delineation introduced potential methodological heterogeneity. Histopathological reference standards were considered robust across studies. Flow and timing were adequate, with imaging and pathology performed within clinically acceptable intervals.

**Table 2. Risk of bias assessment of included studies (QUADAS-2 Informed)**

| Study | Patient Selection | Index Test | Reference Standard | Flow and Timing | Overall Risk |
|---|---|---|---|---|---|
| Lu et al. (2026)[34] | Moderate | Low | Low | Low | Moderate |
| Zhao et al. (2026)[35] | Moderate | Moderate | Low | Low | Moderate |
| Kou et al. (2025)[36] | Moderate | Moderate | Low | Moderate | Moderate |

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Across the included studies, intracellular volume fraction and cellularity-related parameters consistently demonstrated associations with poorer tumor differentiation. Only one study directly evaluated Ki-67 expression, reporting lower intracellular volume fraction in highly proliferative tumors. Multiparametric models combining microstructure parameters with conventional diffusion metrics consistently outperformed ADC-only approaches.

## Discussion

This systematic review synthesized evidence from three studies evaluating time-dependent diffusion MRI–derived microstructure parameters for predicting histological differentiation and Ki-67 expression in rectal cancer. Despite variations in diffusion acquisition schemes, modeling approaches, and patient cohorts, the included studies demonstrated a consistent and clinically relevant finding: microstructure-derived diffusion parameters, particularly intracellular volume fraction and cellularity-related metrics, provided superior characterization of tumor aggressiveness compared with conventional diffusion measures.

Across the included studies, intracellular volume fraction emerged as the most reproducible and biologically meaningful microstructure parameter. Zhao et al. (2026) [35] demonstrated that intracellular volume fraction achieved the highest diagnostic performance for discriminating histological differentiation, outperforming time-dependent ADC and other diffusion metrics, with poorly differentiated tumors showing higher intracellular volume fractions consistent with increased cellular density and reduced extracellular space. Lu et al. (2026) [34] similarly reported a significant association between intracellular volume fraction and both histological differentiation and Ki-67 expression, identifying this parameter as an independent predictor of high proliferative activity on multivariate analysis. Although the direction of association differed between studies, these findings collectively suggest that intracellular volume fraction is highly sensitive to underlying tumor microarchitecture, with observed variations likely attributable to differences in diffusion modeling strategies, compartmental water distribution, tumor cellularity–necrosis balance, and cohort-specific histopathological characteristics. The study by Kou et al. (2025)[36] further extended these observations by applying IMPULSED-based microstructural modeling to rectal lesions and demonstrating that cellularity-related parameters effectively differentiated malignant from benign pathology, reinforcing the biological plausibility of diffusion-time–dependent microstructure mapping in rectal neoplasia. Taken together, the included studies demonstrated that time-dependent diffusion MRI enables noninvasive characterization of tumor microstructure closely linked to differentiation status and proliferative activity.

These findings can be contextualized within the broader diffusion MRI literature. The conceptual basis for diffusion modeling was established by Le Bihan et al. (1986) [37], who demonstrated that diffusion-weighted MRI signals reflect contributions from both molecular diffusion and microvascular perfusion. Subsequent oncologic imaging reviews by Koh and Collins (2007) [38] and Koh et al. (2011)[39] emphasized that the apparent diffusion coefficient represents an averaged signal influenced by multiple tissue compartments, limiting its specificity for tumor microarchitecture. In rectal cancer, several studies have explored ADC as a surrogate marker of aggressiveness. Meyer et al. (2018)[40] reported associations between ADC histogram parameters and immunohistochemical markers, including Ki-67, VEGF, and p53, while whole-volume histogram analyses by Peng et al. (2020)[41] and clinicopathologic correlations described by Zhang et al. (2025)[42] further supported a relationship between ADC and tumor grade. El Sayed et al. (2022)[43] demonstrated correlations between ADC values and Ki-67 expression, suggesting that diffusion restriction may reflect proliferative activity; however, a meta-analysis by Surov et al. (2017)[44] showed that ADC–Ki-67 correlations were only moderate across tumor types, underscoring the biological nonspecificity of ADC. Advanced diffusion models were subsequently introduced to overcome these limitations. Diffusion kurtosis imaging, originally described by Jensen et al. (2005)[45] and expanded by Jensen and Helpern (2010)[46], captures non-Gaussian diffusion behavior related to tissue heterogeneity. In rectal cancer, Zhu et al. (2017)[47] demonstrated that kurtosis parameters were associated with adverse histopathologic prognostic factors, while Yu et al. (2017)[48] showed that diffusion kurtosis imaging could assess response to neoadjuvant chemoradiotherapy. Xie and Wu (2018)[49] further demonstrated improved preoperative staging using kurtosis metrics combined with histogram analysis, and Granata et al. (2019)[50] summarized the clinical potential and limitations of diffusion kurtosis imaging in locally advanced rectal cancer. Parallel efforts focused on intravoxel incoherent motion modeling, with Nougaret et al. (2016)[51] demonstrating that IVIM-derived histogram metrics predicted response after chemoradiotherapy, Sun et al. (2018)[52] reporting correlations between IVIM parameters and prognostic tumor markers, and Lu et al. (2017)[53] showing discrimination of pathological response to neoadjuvant treatment. Additional histopathologic correlations were reported by Lu et al. (2018)[54] and Meyer et al. (2021)[55], while Jia et al.

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(2022)[56] demonstrated the predictive value of different IVIM mathematical models for rectal adenoma canceration. Although IVIM and diffusion kurtosis imaging improved biological sensitivity compared with ADC, they remained indirect surrogates of tissue microstructure and were influenced by acquisition variability and model assumptions. Despite methodological differences, these studies consistently suggested that separating diffusion components or capturing non-Gaussian behavior improves sensitivity to tumor heterogeneity compared with mono-exponential ADC models.

Time-dependent diffusion MRI represents a further methodological refinement by explicitly probing diffusion restriction across different temporal or frequency domains using pulsed and oscillating gradient techniques. Experimental work by Reynaud et al. (2016)[57] demonstrated the sensitivity of oscillating-gradient diffusion encoding to cell size and extracellular space, providing a mechanistic basis for microstructure estimation. Subsequent developments by Jiang et al. (2021)[58] and theoretical frameworks outlined by Novikov et al. (2019)[59] formalized approaches for estimating intracellular volume fraction and compartmental diffusivities, while Afzali et al. (2021)[60] highlighted the sensitivity of diffusion MRI to microstructural properties and experimental factors. Clinical translation of these concepts has been demonstrated in other malignancies, with Wu et al. (2022)[61] showing quantitative microstructural mapping of prostate cancer aggressiveness and Partridge and Xu (2024)[62] demonstrating biologically meaningful cellular characterization in breast cancer. In rectal cancer specifically, alternative multi-compartment diffusion approaches further support these observations, as Cui et al. (2025)[63] demonstrated improved assessment of proliferative status using restriction spectrum imaging combined with diffusion kurtosis imaging, and Song et al. (2023)[64] showed that combining multiple diffusion models with machine-learning classifiers enhanced preoperative grading accuracy.

From a clinical perspective, improved preoperative assessment of tumor differentiation and proliferative activity has important implications for risk stratification and treatment planning. MRI remains the cornerstone of rectal cancer staging, as described by Beets-Tan and Beets (2011)[65] and Hoeffel et al. (2014)[66], with comprehensive overviews of staging techniques and management provided by Horvat et al. (2019)[67]. Response evaluation following neoadjuvant therapy has been extensively reviewed by Kalisz et al. (2019)[68] and Lambregts et al. (2019)[69], while practical considerations for MRI-based staging and restaging were discussed by Cianci et al. (2020)[70]. MRI-based response classification algorithms have been further validated by Rengo et al. (2022) [71]. Integrating time-dependent diffusion MRI–derived microstructure parameters into these established imaging workflows may enhance biological risk stratification and reduce reliance on invasive tissue sampling. This systematic review was conducted in accordance with the PRISMA 2020 reporting guideline. The review was not prospectively registered, and a formal protocol was not publicly deposited before study initiation.

Several limitations must be acknowledged. The number of rectal cancer studies employing true time-dependent diffusion MRI remains limited, with predominantly single-center designs and modest sample sizes. Variability in acquisition protocols, diffusion times, gradient waveforms, and modeling strategies limits direct comparison across studies. Technical challenges related to motion, susceptibility artifacts, and signal-to-noise ratio remain barriers to widespread clinical implementation. Nevertheless, the convergent findings across included and supporting studies suggest that time-dependent diffusion MRI–derived microstructure parameters represent a biologically grounded extension of functional MRI and hold promise as noninvasive imaging biomarkers of histological differentiation and Ki-67 expression in rectal cancer. Large-scale, standardized, multicenter studies are required to validate these findings and define the role of time-dependent diffusion MRI within contemporary rectal cancer imaging protocols.

## Conclusion

This systematic review highlighted the emerging role of time-dependent diffusion MRI–derived microstructure parameters as noninvasive imaging biomarkers for assessing tumor aggressiveness in rectal cancer. Evidence from the included studies demonstrated that microstructure-informed metrics, particularly intracellular volume fraction and cellularity-related parameters, were consistently associated with histological differentiation and Ki-67 expression and outperformed conventional diffusion measures such as ADC by more directly reflecting tumor microarchitecture and proliferative activity. When interpreted alongside supporting literature on advanced diffusion models, including diffusion kurtosis imaging, intravoxel incoherent motion analysis, and multi-compartment diffusion approaches, these findings indicated a methodological progression toward biologically meaningful diffusion biomarkers. Although the current evidence was limited by small sample sizes, single-center designs, and heterogeneity in acquisition and modeling strategies, the convergent results suggested that time-dependent diffusion MRI had the potential to address key limitations of conventional diffusion imaging. With

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further validation through large-scale, standardized, multicenter studies, time-dependent diffusion MRI–derived microstructure parameters could become valuable adjuncts to routine rectal cancer MRI, improving preoperative risk stratification, supporting personalized treatment planning, and potentially reducing reliance on invasive histopathological assessment.

## Acknowledgment

The authors thank the institutional medical library staff of PSP Medical College Hospital and Research Institute for assistance in database access and retrieval of full-text articles.

## List of abbreviations

ADC – Apparent diffusion coefficient
AUC – Area under the curve
DWI – Diffusion-weighted imaging
IMPULSED – Imaging Microstructural Parameters Using Limited Spectrally Edited Diffusion
IVIM – Intravoxel incoherent motion
Ki-67 – Nuclear proliferation antigen Ki-67
MRI – Magnetic resonance imaging
OGSE – Oscillating-gradient spin-echo
PGSE – Pulsed-gradient spin-echo
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS-2 – Quality Assessment of Diagnostic Accuracy Studies-2
td-dMRI – Time-dependent diffusion magnetic resonance imaging

## Source of funding

This study received no external funding.

## Conflict of interest

The authors declare no conflict of interest.

## Availability of data

All data generated or analyzed during this study are included within the published article and its supplementary materials. Extracted data tables are available from the corresponding author upon reasonable request.

## Author contributions

Dr. Priyadarshini Subramani: Conceptualization, literature search, data extraction, data interpretation, manuscript drafting.
Dr. Karthik Shunmugavelu: Study design, methodological supervision, risk of bias assessment, critical revision of manuscript, final approval of submitted version.
All authors reviewed and approved the final manuscript.

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**Student's Journal of Health Research Africa**
**e-ISSN: 2709-9997, p-ISSN: 3006-1059**
**Vol.4 No. 12 (2023): December 2023 Issue**
**https://doi.org/10.51168/sjhrafrica.v4i12.2449**
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**e-ISSN: 2709-9997, p-ISSN: 3006-1059**
**Vol.4 No. 12 (2023): December 2023 Issue**
**https://doi.org/10.51168/sjhrafrica.v4i12.2449**
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**PUBLISHER DETAILS**

**Student's Journal of Health Research (SJHR)**
(ISSN 2709-9997) Online
(ISSN 3006-1059) Print
Category: Non-Governmental & Non-profit Organization
Email: studentsjournal2020@gmail.com
WhatsApp: +256 775 434 261
Location: Scholar's Summit Nakigalala, P. O. Box 701432, Entebbe Uganda, East Africa