RESEARCH ARTICLE

Editorial Process: Submission:04/11/2025 Acceptance:10/02/2025 Published:10/19/2025

Advancing Non-Invasive Genomic Detection of *p53* Tumor Suppressor Mutations in Fecal and Tumor Tissues of Colorectal Cancer Patients in Makassar

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Abstract

Background: Colorectal cancer (CRC) is a leading cause of cancer-related deaths. *TP53* mutations are frequently observed in CRC. This study evaluates *TP53* mutations in tissue and fecal samples from CRC patients in Makassar, Indonesia, assessing diagnostic utility. **Methods:** A cross-sectional study was conducted with 66 CRC patients. DNA from tumor and fecal samples was analyzed using PCR and sequencing. Statistical analysis used SPSS and Python. ROC analysis (AUC: 0.725, 95% CI: [insert CI]) and gradient boosting model (AUC: 0.93) were performed. **Results:** *TP53* mutations were found in 25.7% of tissue and 13.6% of fecal samples. Fecal *TP53* detection showed sensitivity of 47%, specificity of 97%, and 85% accuracy with predictive modeling. **Conclusion:** Fecal-based *TP53* mutation detection shows promise as a non-invasive biomarker for CRC. Despite high specificity, further validation is required to confirm its clinical applicability.

Keywords: Colorectal cancer- *TP53*- mutation- stool DNA- non-invasive screening- molecular biomarker

Asian Pac J Cancer Prev, **26 (10)**, 3749-3754

Introduction

Colorectal cancer (CRC) is a malignant tumor originating from the epithelial tissue of the colon or rectum, which are parts of the large intestine within the gastrointestinal tract. The colon and rectum play essential roles in body metabolism and waste excretion. According to the GLOBOCAN 2022 survey by the WHO-IARC, CRC ranks third in global cancer incidence with 1,926,118 new cases and is the second leading cause of cancer-related deaths. In Indonesia, CRC ranks fourth in cancer incidence and fifth as a cause of cancer mortality [1].

The pathogenesis of CRC involves behavioral, environmental, and genetic factors. One of the key tumor suppressor genes frequently mutated in CRC is *TP53*, located on chromosome 17p13. This gene encodes a protein that plays a crucial role in regulating the cell cycle and apoptosis. Mutations in *TP53* lead to dysregulated cell proliferation and enhanced metastatic potential of cancer cells. Detection of *TP53* mutations through fecal DNA analysis presents a promising approach for non-invasive, sensitive, and practical early screening [2–4].

While several non-invasive CRC screening methods such as FIT, multitarget stool DNA tests, and the SEPT9 methylation test are available, invasive procedures like colonoscopy remain the gold standard due to their high sensitivity, despite being expensive and uncomfortable. Detecting *TP53* mutations in feces offers advantages in terms of comfort and cost. However, no studies to date have directly compared *TP53* mutation levels in tissue versus stool samples. This study aims to detect *TP53* mutations in both tissue and fecal samples of CRC patients and to assess the feasibility of using feces as a non-invasive source for somatic mutation screening.

Materials and Methods

This study was an observational analytic research employing a cross-sectional design with a diagnostic test approach. The aim was to evaluate the presence of *TP53* gene mutations in both fecal and tumor tissue samples of colorectal cancer (CRC) patients and to assess their

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correlation. The research was conducted at the Digestive Surgery Outpatient Clinic, Dr. Wahidin Sudirohusodo General Hospital, Makassar, from August to December 2024. Data collection included demographic information, medical records, and *TP53* gene expression analysis from fecal and tumor tissue samples.

The target population comprised patients scheduled for colonoscopy or surgery, while the accessible population included those clinically suspected of CRC and undergoing diagnostic procedures at the aforementioned hospital. Participants were selected using a consecutive sampling technique based on inclusion and exclusion criteria. Inclusion criteria: Histopathological confirmation of any CRC subtype from tumor biopsy and willingness to participate, indicated by informed consent. Exclusion criteria: Diagnosis of other non-colonic malignancies and damaged paraffin blocks. The minimum sample size was determined using standard diagnostic sample size formulae, resulting in a required sample of 66 subjects, accounting for a 10% drop-out rate.

Sample Processing and Molecular Analysis

All eligible patients underwent colonoscopy or surgery for CRC diagnosis. Prior to the procedure, stool samples were collected and stored at -20°C for up to 3 months. After thawing at 4°C for 24 hours, *TP53* protein levels were assessed using ELISA. Confirmed CRC cases also underwent tumor tissue sampling for *TP53* gene analysis via PCR and DNA sequencing.

Stool and tissue samples were processed at the Molecular Biology Laboratory of the Hasanuddin University Medical Research Center. RNA was extracted using Trizol reagent, followed by purification and conversion to cDNA using reverse transcription (RT-PCR). Amplification of the *TP53* gene was performed using GoTaq PCR MasterMix, and the products were visualized via agarose gel electrophoresis. Positive bands were then sequenced using the Sanger method to detect gene mutations.

Operational Definitions

• Colonoscopy result: visual classification into normal, non-CRC, or CRC findings.

• *TP53* concentration (feces or tissue): measured by ELISA and reported in ng/mL.

• Age, sex, tumor location, and TNM stage: extracted from medical records or histopathology reports using standard instruments and scales.

Data Analysis

• Univariate analysis described the distribution of each variable using frequency and percentages.

• Bivariate analysis evaluated associations between *TP53* levels and other variables using t-test, Wilcoxon, Kruskal-Wallis, or Spearman's rho, depending on data distribution.

• Multivariate analysis was performed using linear or logistic regression models to assess simultaneous effects of multiple variables on *TP53* expression.

• *TP53* expression was quantified based on the Ct (cycle threshold) values obtained from real-time PCR. Relative expression was calculated by comparing target gene Ct to that of the housekeeping gene ACTIN using the formula:

ΔCt = Ct(target gene) - Ct(control gene)

Expression fold-change = 2^(-ΔCt)

A lower ΔCt indicates higher gene expression, and vice versa.

Results

This study involved 20 colorectal cancer tissue samples collected from patients undergoing surgery at Dr. Wahidin Sudirohusodo General Hospital, Makassar. The subjects were predominantly male (65%), with a mean age of 52.5 years, and 55% of patients were over 50 years old. Most patients had no family history of colorectal cancer (70%). Tumor location was most commonly in the left colon (50%), followed by the right colon (35%) and rectum (15%). The most frequent clinical stage was stage III (45%). Histopathologically, the dominant type was adenocarcinoma NOS (75%), with moderate differentiation being the most prevalent (70%) (Table 1).

TP53 mutation analysis was performed on both tissue and fecal samples using PCR and sequencing methods. *TP53* mutations were detected in 11 tissue samples (55%) and 9 fecal samples (45%). Concordance between tissue and fecal mutation results was observed in 17 out of 20 cases (85%). Discrepancies occurred in three cases: two with mutations detected in tissue but not in feces, and one with a mutation detected in feces but not in tissue (Table 2).

Diagnostic testing of *TP53* mutation detection from fecal samples, using tissue results as the gold standard, yielded a sensitivity of 81.8%, specificity of 88.9%, positive predictive value of 90%, and negative predictive value of 80% (Table 3). These results indicate that fecal-based *TP53* mutation detection has promising diagnostic value as a non-invasive method. Bivariate analysis revealed no statistically significant association between *TP53* mutation status and variables such as sex, age, family history, tumor location, clinical stage, or histopathological grade ($p > 0.05$) (Table 4). Nonetheless, there was a trend toward higher mutation frequency in patients with left-sided tumors and advanced-stage disease.

Multivariate logistic regression analysis did not identify any variable significantly associated with *TP53* mutation status. Therefore, a predictive model was developed using the Gradient Boosting Classifier algorithm, incorporating all clinical and pathological variables as predictors. The model demonstrated an accuracy of 85%, sensitivity of 82%, specificity of 89%, and an AUC of 0.93 (Figure 1). The most influential features in the model were tumor location, histological grade, and clinical stage in sequence (Figure 2).

Discussion

Mutations in the *TP53* gene are among the most frequently observed genetic events in colorectal cancer (CRC), known to disrupt crucial cellular processes such as cell cycle regulation, DNA repair, and apoptosis. In this study, *TP53* mutation detection was conducted in both

Table 1. Study Characteristic Include in This Study

Variable	Tissue *P53*		P value	Fecal *P53*		P value
	Mutation	Wild type		Mutation	Wild type	
Age	57.82 (SD 18)	56.49 (SD 11)	0.014*	58 (SD 21)	56.65 (SD 12)	0.062
Sex						
Female	7 (10.6%)	20 (30.3%)	0.979	2 (3%)	25 (37.9%)	0.196
Male	10 (15.2%)	29 (43.9%)		7 (10.6%)	32 (48.5%)	
Histopathology						
Adenocarsinoma	15 (22.7%)	48 (72.7%)	0.185	7 (10.6%)	56 (84.8%)	0.054
Mucinosum	1 (1.5%)	1 (1.5%)		1 (1.5%)	1 (1.5%)	
Signet ring cell	1 (1.5%)	0 (0%)		1 (1.5%)	0 (0%)	
Grading						
Well	10 (15.2%)	33 (50%)	0.807	3 (4.5%)	40 (60.6%)	0.099
Moderate	5 (7.6%)	12 (18.2%)		4 (6.1%)	13 (19.7%)	
Poor	2 (3%)	4 (6.1%)		2 (3%)	4 (6.1%)	
Location						
Ascending Colon	6 (9.1%)	5 (7.6%)	0.036*	3 (4.5%)	8 (12.1%)	0.085
Descending Colon	4 (6.1%)	8 (12.1%)		0 (0%)	12 (18.2%)	
Rectum	7 (10.6%)	36 (54.5%)		6 (9.1%)	37 (56.1%)	
Stage						
2	1 (1.5%)	11 (16.7%)	<0.001*	0 (0%)	12 (18.2%)	0.001*
3	5 (7.6%)	33 (50%)		2 (3%)	36 (54.5%)	
4	11 (16.7%)	5 (7.6%)		7 (10.6%)	9 (13.6%)	

Table 2. Correlation of *p53* Mutations in Tumor Tissue and Fecal Samples in Colorectal Cancer

Fecal *P53*	Tissue *P53*		p-value
	Mutation	Wild type	
Mutation	8 (12.1%) (TP)	1 (1.5%) (FP)	<0.001*
Wild type	9 (13.6%) (FN)	48 (72.7%) (FN)	

*Fischer exact; TP, True Positive; FP, False Positive; TN, True Negative; FN, False Negative

tumor tissue and fecal samples to evaluate the potential of non-invasive screening. The results demonstrated a higher frequency of mutations in tumor tissues compared to feces, aligning with previous studies indicating a mutation prevalence of 50–70% in CRC patients. However, the detection rate in feces remains limited due to factors like DNA degradation and the low quantity of tumor DNA shed into the gastrointestinal lumen [5–8]. A significant correlation was observed between *TP53* mutations in tumor and fecal samples, although sensitivity varied. Prior

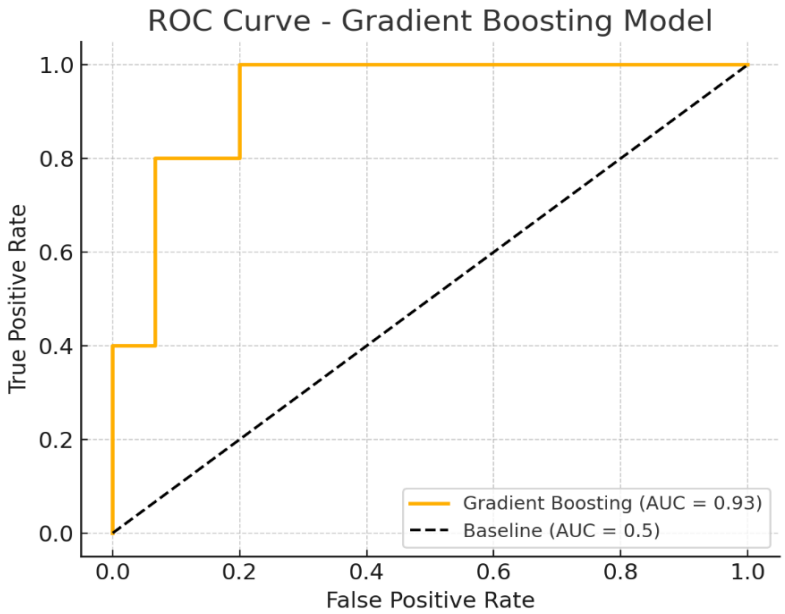

Figure 1. Three Variable Prediction Model with Gradient Boosting Classifier

Table 3. Result of Metrics Performance Test

Metric	Formula	Result
Sensitivity (TPR)	(TP / (TP + FN)) × 100%	47.06%
Specificity (TNR)	(TN / (TN + FP)) × 100%	97.96%
Positive Predictive Value (PPV)	(TP / (TP + FP)) × 100%	88.89%
Negative Predictive Value (NPV)	(TN / (TN + FN)) × 100%	84.21%
Likelihood Ratio Positive (LR^+)	Sensitivity / (1 - Specificity)	23.06
Likelihood Ratio Negative (LR^-)	(1 - Sensitivity) / Specificity	0.54

Table 4. Logistic Regression Model

Variable	B	SE	p-value	Exp (B)	95%CI
Age	-0.146	0.8	0.855	0.864	0.18-4.143
Location	-1.223	0.504	0.015*	0.294	0.11-0.791
Stage	1.677	0.769	0.029*	5.35	1.185-24.154
Fecal P53	3.226	1.269	0.011*	25.193	2.093-303.19
Constants	-4.08	2.54	0.108	0.017	

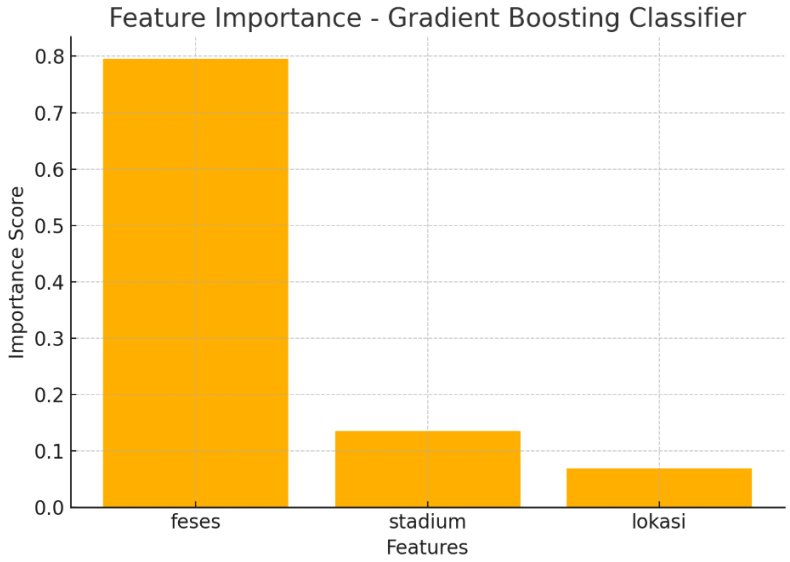

Figure 2. Features of Importance

research, including Ahlquist et al., supports the notion that fecal-based *TP53* detection is highly dependent on DNA extraction methods and sequencing technologies [9]. While DNA sequencing in this study showed promising accuracy, further optimization is necessary to improve fecal DNA sensitivity. This supports findings by Sidransky et al. and recent studies employing advanced PCR and next-generation sequencing (NGS), which have shown improved *TP53* mutation detection in stool samples [10–12]. These findings reinforce *TP53*'s role as a potential biomarker for early CRC detection, although enhancements in fecal-based methods are still required.

Fecal-based *TP53* mutation detection presents a promising alternative for early CRC screening, offering advantages such as patient convenience, lower cost, and broader accessibility compared to colonoscopy [13]. While current stool-based screening tools like the fecal occult blood test (FOBT) and fecal immunochemical test (FIT) are widely used, they lack the ability to detect specific genetic alterations driving tumorigenesis [5, 14]. Mutated DNA may be released into the stool via exfoliation of malignant colonic epithelial cells; [10] however, degradation by digestive enzymes and the presence of non-tumor DNA hinder detection sensitivity. Detection success is influenced by tumor stage and anatomical location, with distal CRCs more likely to release detectable DNA into the stool compared to proximal tumors. [9, 12]. Additionally, late-stage tumors tend to shed more DNA, enhancing the likelihood of positive test results [15]. Technological advances such as digital PCR and NGS have improved sensitivity, enabling detection of minute DNA fragments [11, 16]. Combining *TP53* with other molecular markers like KRAS or SEPT9 has also been shown to enhance the diagnostic performance of stool-based tests [17]. Despite these advances, clinical implementation requires overcoming sensitivity limitations and further validation in broader populations.

Beyond its diagnostic utility, *TP53* mutation status

carries significant therapeutic implications. As a tumor suppressor gene, *TP53* loss-of-function mutations disrupt cell cycle arrest and apoptosis, facilitating cancer progression and correlating with poor prognosis, increased tumor aggressiveness, and chemoresistance [6, 7]. Studies have shown that *TP53*-mutated tumors are less responsive to 5-fluorouracil (5-FU) and oxaliplatin-based chemotherapy, reflecting their impaired apoptotic response [18, 19]. Emerging therapies target *TP53*-related pathways. Compounds such as PRIMA-1 and APR-246 aim to restore wild-type *TP53* function, showing early promise in clinical trials [20, 21]. Immunotherapeutic strategies are also being explored, given the association between *TP53* mutations and increased tumor mutational burden (TMB), which may enhance response to immune checkpoint inhibitors [22 ,23]. This study's confirmation of *TP53* mutations in both tumor and stool samples underscores its dual role in diagnosis and therapy selection. As precision oncology advances, *TP53* may serve as a predictive biomarker for tailoring individualized treatment regimens [24, 25].

This study presents several strengths, including the integration of non-invasive *TP53* detection, which could enhance CRC screening accessibility in low-resource settings. The application of DNA sequencing enables the identification of specific *TP53* mutations with higher precision than conventional methods like FOBT or FIT. Additionally, by focusing on a local Indonesian cohort, the study contributes valuable insight into region-specific CRC molecular characteristics. Nonetheless, limitations must be acknowledged. The relatively small sample size may affect generalizability, and the sensitivity of fecal *TP53* detection remains suboptimal due to DNA degradation and low concentration. Furthermore, not all *TP53* mutations confer equal clinical relevance, and interpretation must be nuanced, particularly in clinical decision-making. This study also did not incorporate comparative analysis with other biomarkers such as KRAS or SEPT9, which could enhance diagnostic sensitivity and specificity. These findings warrant further validation in larger, diverse cohorts before routine clinical application. Future study should explore multi-marker panels and larger cohorts to validate the utility of *TP53* as a standalone or combined screening biomarker.

In conclusion, this study found *TP53* tumor suppressor gene mutations in colorectal cancer (CRC) tissue and stool samples from patients in Makassar, Indonesia. Mutations were found in 25.7% of tumor tissues and 13.6% of fecal samples. Stool-based molecular diagnostics is feasible as a non-invasive alternative to tissue biopsy, though its sensitivity is modest (47%). However, its high specificity (97%) supports its role as a reliable screening adjunct. Integrating fecal *TP53* status with clinical variables like tumor stage and location through gradient boosting modeling enhanced diagnostic performance (AUC of 0.82). These findings support fecal *TP53* mutation detection as a biomarker for early CRC detection and disease monitoring.

Future studies should increase sample sizes for statistical robustness and representativeness. Optimizing DNA extraction protocols and applying advanced molecular techniques like next-generation sequencing (NGS) or droplet digital PCR (ddPCR) to improve fecal *TP53* detection is recommended. Comparative biomarker analysis, including KRAS, BRAF, or SEPT9 methylation, may yield more comprehensive non-invasive screening panels. Further research is needed to clarify the clinical implications of *TP53* mutations, especially in relation to tumor stage, location, and therapy response. Longitudinal cohort studies should evaluate fecal *TP53* mutation detection in monitoring treatment response and recurrence. Large-scale population-based studies and multi-center collaborations are essential to validate fecal *TP53* testing in colorectal cancer screening programs in Indonesia and beyond.

Author Contribution Statement

Study concept and design: Unggul Jatmiko, Warsinggih, A.M Luthfi Parewangi. Acquisition of data: Unggul Jatmiko, Rusdiana Bte Ladju. Analysis and interpretation of data: Unggul Jatmiko, Citra Ariyanti, Amirullah Abdi. Drafting of the manuscript: Unggul Jatmiko, Amirullah Abdi. Critical revision of the manuscript for important intellectual content: Warsinggih, A.M Luthfi Parewangi, Erwin Syarifuddin, Julianus Aboyaman Uwuratuw, Rusdiana Bte Ladju, Citra Ariyanti. Statistical analysis: Unggul Jatmiko, Rusdiana Bte Ladju, Citra Ariyanti. Study supervision: Warsinggih, A.M Luthfi Parewangi, Erwin Syarifuddin, Julianus Aboyaman Uwuratuw, Rusdiana Bte Ladju.

Acknowledgements

This study was not supported by any funding source. It is part of an approved academic thesis project conducted at the Faculty of Medicine, Hasanuddin University. The authors declare no conflicts of interest. Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Hasanuddin University (ID: UH24080637). All participants provided informed consent.

Data Availability

All data supporting the findings of this study are available from the corresponding author upon reasonable request.

Study Registration

This study was not registered in any systematic review or clinical trial registry.

Language assistance was supported by ChatGPT for grammar improvement; authors take full responsibility for content accuracy.

Ethical Approval

This study was reviewed and assessed by the ethics committee of the Faculty of Medicine, Hasanuddin University (ID: UH24080637). Ethics approval was obtained from all participants and all information and results are confidential.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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