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Original Research Article

TP53 overexpression and three-year survival in stage III and IV colorectal cancer: a retrospective cohort study

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ABSTRACT

Background: TP53 mutations are among the most common molecular alterations in colorectal cancer (CRC) and are frequently associated with tumor aggressiveness and poor prognosis. This study evaluated the influence of TP53 overexpression on three-year overall survival in patients with stage III and IV CRC.
Methods: A retrospective cohort study was conducted on 46 patients with stage III–IV CRC treated at Dr. Moewardi General Hospital, Surakarta, Indonesia, between 2020 and 2023. TP53 expression was assessed using immunohistochemistry and categorized as overexpression or non-overexpression. Survival outcomes were analyzed using Chi-square and Kaplan–Meier methods with log-rank testing.
Results: Seventeen patients (36.9%) demonstrated TP53 overexpression, whereas 29 (63.1%) showed non-overexpression. Mortality before three years was significantly higher in the overexpression group (82.4%) than in the non-overexpression group (31.0%). TP53 overexpression was significantly associated with reduced three-year survival (p=0.001; Cramer's V=0.495). Kaplan–Meier analysis demonstrated significantly shorter survival among patients with TP53 overexpression (log-rank p=0.002). Metastatic status and lymphovascular invasion were also associated with poorer survival.
Conclusions: TP53 overexpression is significantly associated with decreased three-year survival in advanced CRC and may serve as a useful prognostic biomarker for risk stratification and treatment planning.

Keywords: Colorectal cancer, TP53, p53 overexpression, Survival, Prognosis, Immunohistochemistry

INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies worldwide and remains a major public health concern. According to the Global Cancer Statistics 2024, CRC ranks as the third most commonly diagnosed cancer and the second leading cause of cancer-related mortality worldwide, accounting for approximately 1.9 million new cases and more than 900,000 deaths.[1,2] Despite substantial advances in screening, surgical techniques, chemotherapy, radiotherapy, and targeted

therapies, survival outcomes remain unsatisfactory in patients with advanced-stage disease.[3]

The development and progression of CRC result from the accumulation of multiple genetic and epigenetic alterations affecting key signaling pathways involved in cellular proliferation, apoptosis, and genomic stability.[4] Among these molecular abnormalities, mutations in the tumor suppressor gene TP53 represent one of the most frequent genetic events in colorectal carcinogenesis. 5TP53 mutations are detected in approximately 50–60% of colorectal cancers and are considered a hallmark of the adenoma-to-carcinoma sequence.[4,5]

The TP53 gene encodes the p53 protein, a critical regulator of cell-cycle arrest, DNA repair, apoptosis, senescence, and maintenance of genomic integrity. Loss of normal p53 function permits the survival and proliferation of genetically damaged cells, thereby promoting tumor progression and metastatic dissemination.[6,7]

Mutant p53 proteins often acquire a prolonged half-life and accumulate within the nucleus of tumor cells, making them detectable by immunohistochemical staining as p53 overexpression.[7] Consequently, p53 overexpression has become one of the most widely investigated surrogate markers of TP53 mutation status in routine pathology practice.[8] Previous studies have reported p53 overexpression in approximately 40–70% of colorectal cancer specimens depending on the study population and methodology used.[8,9]

Several meta-analyses have demonstrated that abnormal p53 expression is associated with advanced tumor stage, lymph node involvement, distant metastasis, disease recurrence, and poor overall survival.[10] Furthermore, TP53 abnormalities have been implicated in resistance to chemotherapy and radiotherapy, highlighting their potential utility as both prognostic and predictive biomarkers.[9,11]

Given the increasing emphasis on precision oncology and molecular prognostication, further evaluation of p53 overexpression in advanced colorectal cancer is warranted. Therefore, this study aimed to investigate the influence of TP53 overexpression on three-year overall survival among patients with stage III and IV colorectal cancer.

METHODS

Study design and setting

This study was an analytical observational study employing a retrospective cohort design. The study aimed to evaluate the association between TP53 overexpression and three-year overall survival among patients with stage III and IV colorectal cancer (CRC). Medical records and pathological specimens were obtained from Dr. Moewardi General Hospital, Surakarta, Indonesia, a tertiary referral center serving Central Java and surrounding regions. Data collection was conducted using medical records of patients diagnosed between January 2020 and December 2023. Immunohistochemical evaluation of TP53 expression was performed at the Department of Anatomical Pathology, Faculty of Medicine, Universitas Sebelas Maret, Surakarta.

Participants

Patients with histopathologically confirmed stage III or IV colorectal adenocarcinoma were screened for eligibility. Inclusion criteria were: (1) age ≥18 years; (2) histopathological diagnosis of stage III or IV colorectal adenocarcinoma; and (3) availability of formalin-fixed paraffin-embedded tumor tissue suitable for immunohistochemical analysis. Patients were excluded if medical records were incomplete or if paraffin tissue blocks were damaged and unsuitable for evaluation.

A purposive sampling technique was used to identify eligible patients. Based on sample size calculations and predefined eligibility criteria, a total of 46 patients were included in the final analysis. Patients were subsequently categorized into TP53 overexpression and non-overexpression groups according to immunohistochemical findings.

Immunohistochemical assessment of TP53 expression

TP53 expression was evaluated using immunohistochemical staining of formalin-fixed paraffin-embedded tumor specimens. Tissue sections were stained using Rabbit Anti-TP53 Polyclonal Antibody according to standardized laboratory protocols. Immunoreactivity was visualized using a horseradish peroxidase (HRP)-based detection system with 3,3'-diaminobenzidine (DAB) chromogen.

TP53 expression was assessed semi-quantitatively using the Intensity Distribution Score (IDS) method. Brown nuclear staining within tumor cells was considered positive. Microscopic evaluation was performed using an Olympus CX22 light microscope, and quantification was conducted using Scope Image 9.1 software. Based on the IDS assessment, patients were classified as having TP53 overexpression or non-overexpression.

Outcome measurement

The primary outcome was three-year overall survival (OS). Survival time was calculated from the date of diagnosis or initiation of definitive treatment until death from any cause or completion of the three-year follow-up period. Patients who remained alive at the end of follow-up were classified as survivors, whereas those who died before three years were classified as non-survivors. Patients lost to follow-up were treated as censored observations in survival analyses.

Statistical analysis

Data analysis was performed using SPSS software (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize demographic, clinicopathological, and molecular characteristics. Categorical variables were presented as frequencies and percentages. Associations between TP53 expression status and clinicopathological variables were analyzed using the Chi-square test or Fisher's exact test when appropriate. The strength of associations was assessed using Cramer's V coefficient.

Overall survival was estimated using the Kaplan–Meier method. Differences in survival distributions between TP53 expression groups were compared using the log-rank test. Variables demonstrating statistical significance in bivariate analyses were further evaluated in multivariable models to determine their independent association with survival outcomes. Statistical significance was defined as a two-tailed p value <0.05.

Ethical considerations

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Health Research Ethics Committee of Dr. Moewardi General Hospital, Surakarta, Indonesia (Approval No. 2.269/X/HREC/2025). Patient confidentiality was maintained throughout the study by anonymizing all identifiable information. As this study utilized retrospective medical record data and archived tissue specimens, informed consent requirements were waived by the ethics committee.

RESULTS

A total of 46 patients were included, comprising 23 survivors and 23 non-survivors at three years. Most patients were older than 45 years (73.9%) and male (58.7%). Stage III and stage IV disease were equally represented. TP53 overexpression was identified in 17 patients (36.9%), while 29 patients (63.1%) demonstrated non-overexpression. Among patients with TP53 overexpression, 14 of 17 (82.4%) died before three years, compared with 9 of 29 (31.0%) in the non-overexpression group. Three-year survival was observed in only 17.6% of patients with TP53 overexpression versus 69.0% of those without overexpression (Table 1).

Table 1: Baseline characteristics of patients according to three-year survival status.

Characteristics	Survival ≥3 Years N (%)	Survival <3 Years N (%)	Total N (%)	P value
Age (in years)				
18–45	7(30,4)	5(21,7)	12 (26,08)	0.502
>45	16(34,8)	18(34,8)	34 (73,91)	
Sex				
Male	13(47,8)	15 (65,2)	27 (58,7)	0.546
Female	10 (43,5)	8 (34,8)	19 (41,3)	
Clinical Stage				
Stage III	15 (65,2)	8 (34,8)	23 (50,0)	0.390
Stage IV	8 (34,8)	15 (65,2)	23 (50,0)	
Tumor Differentiation Grade				
Well–Moderately Differentiated	14 (60,9)	10 (43,5)	24 (52,2)	0.140
Poorly Differentiated	9 (39,1)	13 (56,5)	22 (47,8)	
Treatment Modality				
Surgery ± Chemotherapy	19 (82,6)	14 (60,9)	33 (71,7)	0.102
Chemotherapy Alone	4 (17,4)	9 (39,1)	13 (28,3)	
Primary Tumor Location				
Right Colon	7 (30,4)	11 (47,8)	18 (39,1)	0.479
Left Colon	9 (39,1)	7 (30,4)	16 (34,8)	
Rectum	7 (30,4)	5 (21,7)	12 (26,1)	
Lymph Node Status				0.038
N1	14 (60,9)	7 (30,4)	22 (47,8)	
N2	9 (39,1)	16 (69,6)	24 (52,2)	
Histopathological type				
Conventional Adenocarcinoma	16 (69,6)	11 (47,8)	27 (58,7)	0.134
Mucinous / Signet-Ring Cell Carcinoma	7 (30,4)	12 (52,2)	19 (41,3)	

Continued.

Characteristics	Survival ≥3 Years N (%)	Survival <3 Years N (%)	Total N (%)	P value
Lymphovascular Invasion (LVI)				
Absent	14 (60,9)	7 (30,4)	21 (45,7)	0.038
Present	9 (39,1)	16 (69,6)	25 (54,3)	
Perineural Invasion (PNI)				
Absent	15 (65,2)	9 (39,1)	24 (52,2)	0.077
Present	8 (34,8)	14 (60,9)	22 (47,8)	
Metastatic Status				
Single Metastasis	6 (26,1)	4 (17,4)	10 (21,7)	
Multiple Metastases	2 (8,7)	11 (47,8)	13 (28,3)	0.013
Non-metastatic (Stage III)	15 (65,2)	8 (34,8)	23 (50,0)	
Performance Status (ECOG)				
ECOG 0–1	17 (73,9)	13 (56,5)	30 (65,2)	0.216
ECOG ≥2	6 (26,1)	10 (43,5)	16 (34,8)	
TP53 Expression				
Overexpression	3 (13,04)	14 (60,9)	17 (36.9)	0.001
Non-overexpression	20 (86,96)	9 (39,1)	29 (63.0)	

*Abbreviations: ECOG, Eastern Cooperative Oncology Group; LVI, Lymphovascular invasion; PNI, perineural invasion; TP53, tumor protein p53.

Bivariate analysis demonstrated a significant association between TP53 overexpression and reduced survival (p=0.001; Cramer's V=0.495), indicating a moderate relationship. Additional factors significantly associated with survival included lymph node status (p=0.038), lymphovascular invasion (p=0.038), and metastatic status (p=0.013).

A significant association was observed between TP53 expression and three-year survival (p = 0.001). TP53 overexpression was identified in 60.9% of patients who died within three years, compared with only 13.0% of patients who survived for at least three years. The Cramer's V coefficient of 0.495 indicated a moderate strength of association between TP53 overexpression and poorer survival outcomes (Table 2).

Table 2: Association between TP53 expression and three-year survival.

TP53 expression	Alive ≥3 Years n (%)	Died <3 Years n (%)	Total n (%)	Cramer's V	P value
Overexpression	3 (13.0)	14 (60.9)	17 (37.0)	0.495	0.001
Non-overexpression	20 (87.0)	9 (39.1)	29 (63.0)		

*Abbreviation: TP53, tumor protein p53.

Kaplan-Meier survival analysis revealed significant separation of survival curves between TP53 expression groups. The mean survival time was 2.00 years (95% CI: 1.51-2.49) in the overexpression group compared with 3.17 years (95% CI: 2.71-3.63) in the non-overexpression group. The log-rank test confirmed a statistically significant difference (χ^2=9.518; p=0.002) (Table 3).

A multivariable logistic regression analysis was performed to evaluate the independent association of clinicopathological variables with three-year survival in patients with colorectal cancer. Variables entered into the model included tumor differentiation grade, treatment modality, lymph node status, histopathological type, perineural invasion, metastatic status, performance status, and TP53 expression.

None of the variables remained statistically significant in the multivariable model (all p>0.05). The regression coefficients demonstrated extremely large odds ratios and unstable confidence intervals, indicating model instability and possible complete or quasi-complete separation due to the relatively small sample size and sparse distribution of events across categories. Consequently, the independent effects of these variables could not be reliably estimated in the final multivariable model.

These findings indicate that TP53 overexpression is strongly associated with earlier mortality and shorter survival duration in patients with advanced colorectal cancer.

Table 3: Mean survival time according to TP53 expression status.

Ekspresi_P53 (Mantel–Cox): $\chi^2 = 9.518$, p=0.002.	Mean			P value Log Rank (Mantel-Cox)
	Estimate	95% Confidence Interval		
		Lower Bound	Upper Bound	
Overexpression	2.000	1.511	2.489	0.002 $\chi^2 = 9,518$
Non-Overexpression	3.172	2.713	3.631	
Overall	2.739	2.361	3.118	

*Abbreviations: CI, confidence interval; TP53, tumor protein p53. Statistically significant at $p < 0.05$.

Table 4: Multivariable logistic regression analysis of factors associated with three-year survival in patients with colorectal cancer.

Variables	B	Sig.	OR	95% C.I. for EXP (B)	
				Lower	Upper
Tumor Differentiation Grade	-14.309	1.000	0.000	.000	.
Treatment Modality	-22.797	1.000	0.000	.000	.
Lymph Node Status	-1.322	1.000	0.267	.000	.
Histopathological Type	.000	1.000	1.000	.000	.
Perineural Invasion	13.408	1.000	665363.61	.000	.
Metastatic Status (Single Metastasis)	-1.719	1.000	0.179	.000	.
Metastatic Status (Multiple Metastases)	17.874	0.999	57915128.74	.000	.
Performance Status (ECOG ≥2)	-12.507	1.000	0.000	.000	.
TP53 Overexpression	38.841	0.998	73835156875211 680.000	.000	.

*OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

DISCUSSION

The present study demonstrated that TP53 overexpression was significantly associated with reduced three-year survival among patients with stage III and IV colorectal cancer (CRC). Patients exhibiting TP53 overexpression experienced substantially higher mortality rates and shorter survival durations than those without overexpression. Furthermore, Kaplan-Meier analysis revealed a significant separation of survival curves, indicating that TP53 overexpression may serve as a clinically meaningful prognostic biomarker in advanced CRC.[6]

The biological rationale underlying these findings is closely related to the fundamental role of TP53 as the "guardian of the genome." Under physiological conditions, wild-type p53 maintains genomic stability by inducing cell-cycle arrest, DNA repair, senescence, and apoptosis in response to cellular stress and DNA damage. Activation of p53 stimulates transcription of multiple downstream targets, including CDKN1A (p21), BAX, PUMA, and GADD45, thereby preventing the propagation of genetically unstable cells. Loss of TP53 function through mutation disrupts these protective mechanisms, allowing tumor cells to evade apoptosis, accumulate additional genetic abnormalities, and acquire a more aggressive phenotype.[5,12]

In colorectal carcinogenesis, TP53 mutation is generally considered a late molecular event occurring during the adenoma-to-carcinoma transition. Most TP53 mutations are missense mutations located within the DNA-binding domain, resulting in the production of structurally altered proteins with prolonged half-lives. Unlike wild-type p53, which is rapidly degraded, mutant p53 accumulates within the nucleus and can be detected as overexpression by immunohistochemistry. Consequently, p53 overexpression is frequently used as a surrogate marker for TP53 mutation in clinical pathology practice.[13]

Beyond the simple loss of tumor-suppressive activity, mutant p53 may acquire oncogenic "gain-of-function" properties that actively promote tumor progression. Experimental studies have demonstrated that mutant p53 enhances colorectal cancer aggressiveness through multiple mechanisms, including activation of Wnt/β-catenin signaling, NF-κB-mediated inflammatory pathways, epithelial-mesenchymal transition (EMT), and remodeling of the tumor microenvironment. Aberrant activation of Wnt signaling promotes cancer stem-cell maintenance, uncontrolled proliferation, and increased invasive potential. Simultaneously, activation of NF-κB stimulates the production of pro-inflammatory cytokines that create a protumorigenic microenvironment and facilitate tumor growth, angiogenesis, and metastatic dissemination.[14,15]

Another important mechanism linking TP53 abnormalities with poor survival is chromosomal instability (CIN), which characterizes approximately 80-85% of colorectal cancers.[5,16] TP53 dysfunction impairs DNA damage checkpoints, allowing the accumulation of chromosomal aberrations, aneuploidy, and loss of heterozygosity. These alterations increase intratumoral heterogeneity and enable the emergence of highly aggressive cellular subclones with enhanced metastatic potential and therapeutic resistance. Therefore, tumors exhibiting TP53 overexpression are biologically more likely to progress rapidly and develop distant metastases, ultimately contributing to reduced survival.[17]

The present findings are consistent with previous reports indicating that TP53 mutations occur in approximately 50-60% of colorectal cancers and may be identified in up to 80% of metastatic tumors. Several meta-analyses have demonstrated that abnormal p53 expression is associated with advanced tumor stage, lymph node involvement, distant metastasis, disease recurrence, and poorer overall survival. Our findings further support the growing body of evidence suggesting that TP53 abnormalities represent a key molecular determinant of disease progression and adverse clinical outcomes in advanced CRC.[17,18]

The significant relationship between metastatic status and survival observed in this study is also biologically plausible. Metastasis remains the leading cause of death in colorectal cancer and reflects the culmination of molecular alterations enabling tumor cells to invade surrounding tissues, enter the circulation, and colonize distant organs. TP53-mutated tumors exhibit enhanced migratory and invasive behavior through EMT induction and matrix metalloproteinase activation.[3,17]

Similarly, lymphovascular invasion (LVI) was significantly associated with poor survival in the present study. LVI is a well-established marker of aggressive tumor biology and has been correlated with increased recurrence and reduced survival in colorectal cancer.[17,18] Previous evidence suggests that TP53 dysfunction may facilitate vascular and lymphatic dissemination, thereby contributing to both LVI and metastatic spread.[17]

Another possible explanation for the poor prognosis observed among patients with TP53 overexpression is treatment resistance. Many cytotoxic agents exert their antitumor effects through DNA damage-induced apoptosis, a process that largely depends on intact p53 signaling. Consequently, TP53-mutated tumors frequently exhibit reduced chemosensitivity and impaired apoptotic responses, resulting in poorer treatment outcomes.[11,19]

The approximately one-year difference in mean survival observed between TP53 expression groups highlights the clinical relevance of this biomarker. Given that immunohistochemical assessment of p53 is inexpensive, widely available, and routinely performed in pathology laboratories, TP53 overexpression may represent a practical prognostic marker for identifying high-risk patients who may benefit from intensified surveillance and individualized treatment strategies.[8,20]

CONCLUSION

TP53 overexpression is significantly associated with decreased three-year survival in patients with stage III and IV colorectal cancer. Patients with TP53 overexpression experience substantially higher mortality rates and shorter survival durations than those without overexpression. TP53 expression assessment may serve as a valuable prognostic biomarker for identifying high-risk patients and optimizing clinical management strategies in advanced colorectal cancer.

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