RESEARCH ARTICLE

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Predictive Value of Serum MTHFR and CEA Levels for Tumor Size Reduction Following Neoadjuvant CAPEOX Therapy in Advanced Colorectal Cancer Patients in Makassar

Albert Julyson Wishnu Cahypoetro[1]*, Ronald Erasio Lusikooy[1,2], Ilham Jaya Patelongi[3], Ibrahim Labeda[1,2], Samuel Sampetoding[1,2], Arham Arsyad[1], Amirullah Abdi[4]

Abstract

Background: This study aimed to evaluate the predictive value of serum levels of methylenetetrahydrofolate reductase (MTHFR) and carcinoembryonic antigen (CEA) for tumor size reduction following neoadjuvant CAPEOX chemotherapy in patients with advanced colorectal cancer. **Methods:** A prospective observational study was conducted involving 36 patients with histologically confirmed stage III–IV colorectal cancer who underwent neoadjuvant CAPEOX therapy. Serum MTHFR and CEA levels were measured before chemotherapy. Tumor response was assessed by comparing pre- and post-treatment imaging, based on RECIST criteria. Correlations between the biomarkers and the percentage of tumor reduction were analyzed using Spearman's test, followed by multivariate linear regression to develop a predictive model. **Results:** The mean age of participants was 45.6 ± 8.0 years, with a predominance of male patients (66.7%). Both serum MTHFR and CEA levels showed significant correlations with tumor size reduction (MTHFR: $\rho = 0.764$, $p < 0.001$; CEA: $\rho = 0.654$, $p < 0.001$). The final regression model demonstrated strong predictive performance: Tumor size reduction (%) = $-165.68 + (1.10 \times \text{CEA}) + (15.38 \times \text{MTHFR})$, with an adjusted R^2 of 0.714 ($p < 0.001$). A nomogram derived from this model yielded a Harrell's C-index of 0.836, indicating high discriminative ability in predicting therapeutic response. **Conclusion:** Serum MTHFR and CEA levels serve as complementary biomarkers for predicting tumor size reduction following neoadjuvant CAPEOX chemotherapy in advanced colorectal cancer. Their combined use provides a simple, cost-effective tool for individualized treatment planning and advances biomarker-based precision oncology in resource-limited clinical settings.

Keywords: Colorectal cancer- CAPEOX regimen- MTHFR enzyme- CEA marker- Tumor prediction

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Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide and remains a leading cause of cancer-related mortality. According to GLOBOCAN 2020, more than 1.9 million new CRC cases and 940,000 deaths were reported, accounting for approximately 10% of all cancer incidences and 9% of global cancer deaths [1]. Although CRC incidence is higher in high-income countries, its mortality burden is disproportionately greater in low- and middle-income regions due to limited access to early screening and comprehensive treatment [2]. In Indonesia, CRC accounted for 8.6% of all new cancer cases and 7.9% of cancer-related deaths in 2020 [3]. These data underscore the urgent need for predictive, cost-effective, and individualized therapeutic strategies to improve clinical outcomes [4, 5].

Neoadjuvant chemotherapy has become an integral component in the management of advanced CRC, as it enhances tumor resectability and improves survival outcomes [6]. The CAPEOX regimen a combination of capecitabine and oxaliplatin is widely used as standard neoadjuvant therapy, yet patient responses vary substantially. This variability is driven by complex molecular and biochemical factors that influence drug metabolism and resistance. Therefore, identifying predictive biomarkers capable of forecasting individual responses to CAPEOX therapy is crucial for optimizing treatment planning. In this context, 5-fluorouracil (5-FU), the active metabolite of capecitabine, plays a central role by inhibiting thymidylate synthase, an enzyme essential for DNA synthesis and cellular proliferation [7].

*[1]Department of Digestive Surgery, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia. [2]Department of Digestive Surgery, Wahidin Sudirohusodo Hospital, Makassar, Indonesia. [3]Department of Physiology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia. [4]Department of Surgery, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia. *For Correspondence: albertwisnu@gmail.com*

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the folate cycle that catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, thereby influencing DNA methylation and repair [8, 9]. Polymorphisms in the MTHFR gene, such as 677C>T and 1298A>C, are known to alter enzymatic activity and affect 5-FU efficacy [10]. Recent studies suggest that serum MTHFR levels may reflect functional enzyme status and thus serve as a noninvasive biomarker of chemosensitivity [11]. Lower MTHFR concentrations may increase intracellular 5,10-methylenetetrahydrofolate availability, enhancing 5-FU–induced DNA damage and apoptosis in tumor cells. However, evidence linking serum MTHFR concentrations with neoadjuvant response in CRC remains limited.

Alongside enzymatic biomarkers, classical tumor markers such as carcinoembryonic antigen (CEA) continue to play an important role in monitoring CRC progression. CEA, a cell-adhesion glycoprotein overexpressed in epithelial malignancies, promotes tumor invasion, metastasis, and resistance to apoptosis through ERK/MAPK and PI3K/AKT signaling pathways [12]. High baseline CEA levels and insufficient clearance following chemotherapy are associated with poor therapeutic response and unfavorable prognosis [13]. Therefore, integrating functional biomarkers such as serum MTHFR with conventional tumor markers like CEA may enhance predictive accuracy for treatment outcomes and advance personalized cancer therapy [14].

Despite growing global interest in predictive oncology, there remains a lack of studies evaluating both serum MTHFR and CEA as combined predictors of neoadjuvant chemotherapy response, particularly among Indonesian CRC patients. Findings from this investigation are expected to support biomarker-based stratification strategies and contribute to the advancement of precision oncology in resource-limited settings. The aim of this study was to determine the predictive role of serum MTHFR and CEA levels in tumor size reduction following neoadjuvant CAPEOX chemotherapy in patients with advanced colorectal cancer.

Materials and Methods

Study Design and Setting

This prospective analytical cohort study was conducted at the Digestive Surgery Division, Faculty of Medicine, Hasanuddin University, in collaboration with the Human Metabolic Research Center (HUMRC), Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia, from June to December 2025.

Participants

Patients aged ≥18 years with histologically confirmed stage III–IV colorectal adenocarcinoma scheduled for neoadjuvant CAPEOX chemotherapy were consecutively enrolled. Inclusion criteria were completion of planned chemotherapy cycles and availability of complete baseline and post-treatment imaging and laboratory data. Exclusion criteria included treatment interruption, chemotherapy regimen modification, or loss to follow-up.

Given the exploratory nature of this study and limited patient availability, no formal a priori power calculation was performed. The analysis should therefore be interpreted as hypothesis-generating rather than confirmatory.

Treatment Protocol

All patients received the CAPEOX regimen consisting of capecitabine 1000 $mg \cdot m^{-2}$ orally twice daily on days 1–14 and oxaliplatin 130 $mg \cdot m^{-2}$ intravenously on day 1 of a 21-day cycle, for up to six cycles. Supportive treatment followed institutional protocols.

Tumor Response Assessment

Tumor response was evaluated using contrast-enhanced computed tomography before initiation and after completion of neoadjuvant chemotherapy, according to RECIST version 1.1. Tumor size change was calculated as the percentage change from baseline maximal tumor diameter.

Tumor shrinkage was coded as a negative percentage, while tumor growth was coded as a positive percentage. Accordingly, more negative values indicate greater tumor reduction. This coding directly affects the interpretation of correlation coefficients and regression estimates in subsequent analyses.

Biochemical Assays

Venous blood samples were collected prior to chemotherapy initiation. Serum MTHFR concentrations were measured using a commercial ELISA kit (MyBioSource, San Diego, USA), and serum CEA levels were quantified using a chemiluminescent immunoassay (Abbott Diagnostics, Chicago, USA). All assays were performed in duplicate with appropriate quality controls.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics version 25.0 and R Studio version 4.3. Normality was assessed using the Shapiro–Wilk test. Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate. Nonparametric tests were applied due to non-normal distribution of key variables.

Associations between serum biomarkers and tumor size change were evaluated using Spearman's rank correlation coefficient. Multiple linear regression analysis was conducted to identify independent predictors of tumor size change. Regression assumptions were assessed, including linearity, homoscedasticity, and multicollinearity; variance inflation factors (VIFs) < 2 were considered acceptable. Regression results are reported with unstandardized coefficients, standardized β coefficients, 95% confidence intervals (CI), and p-values. A two-tailed p-value < 0.05 was considered statistically significant.

A nomogram was constructed based on the final regression model. Internal validation using bootstrapping or cross-validation was not performed due to sample size limitations; therefore, model performance metrics should be interpreted cautiously.

Results

Baseline Characteristics

A total of 36 patients with advanced colorectal cancer were included. The mean age was 45.6 ± 8.0 years, and 66.7% were male. The rectum was the most common tumor site (47.3%). Mean baseline serum CEA and MTHFR levels were 8.67 ± 6.02 ng·mL^{-1} and 8.23 ± 0.98 ng·mL^{-1}, respectively. The mean tumor size change following neoadjuvant CAPEOX therapy was −31.9% ± 23.8%, indicating substantial heterogeneity in treatment response (Table 1).

Effect of Demographic Variables

Nonparametric analyses (Table 2) demonstrated no significant associations between tumor size change and age ($\rho = 0.142$, $p = 0.407$), sex (Mann–Whitney U, $p = 0.420$), or tumor location (Kruskal–Wallis $H = 1.376$, $p = 0.502$). These variables were therefore not included in the multivariate regression model.

Correlation Between Biomarkers and Tumor Size Change

Serum MTHFR level ranged from 6.46 to 11.69 ng·mL^{-1}. Figure 1 illustrates the relationship between serum MTHFR levels and tumor size reduction following neoadjuvant CAPEOX chemotherapy. Most patients experienced tumor reduction between −60% and 0%, with a few outliers showing minimal or opposite changes. A clear trend was observed in which lower MTHFR levels were associated with greater tumor shrinkage. As presented in Table 3, serum MTHFR levels showed a significant correlation with the percentage of tumor size reduction ($\rho = 0.764$, $p < 0.001$). This indicates a strong, positive, and statistically significant relationship, suggesting that reduced MTHFR expression was associated with improved chemotherapy response.

Serum CEA levels ranged from 1.56 to 34.10 ng·mL^{-1}. Figure 2 shows the association between serum CEA levels and tumor size reduction. The scatter distribution demonstrated higher variability, with most patients clustering at low to moderate CEA levels. Elevated CEA concentrations tended to correspond to smaller or negative tumor reductions, indicating poorer chemotherapy response. Nonetheless, several data points deviated from this trend, implying potential influence from other biological factors. As shown in Table 4, serum CEA also correlated significantly with tumor size reduction ($\rho = 0.654$, $p < 0.001$). This moderate positive correlation suggests that lower pre-treatment CEA levels were associated with greater tumor shrinkage after chemotherapy.

Multivariate Regression Model

The percentage change in tumor size among participants

Table 1. Baseline Characteristics of Participants (n = 36)

Variable	n	% / Mean ± SD
Sex		
Male	24	66.7
Female	12	33.3
Tumor location		
Right colon	10	27.7
Left colon	9	25
Rectum	17	47.3
Age (years)	–	45.64 ± 8.02
CEA (ng·mL^{-1})	–	8.67 ± 6.02
MTHFR (ng·mL^{-1})	–	8.23 ± 0.98
Tumor size reduction (%)	–	31.87 ± 23.80

Table 2. Correlation of Patient Demographic Factors and Tumor Site with Tumor Size Reduction

Variable	Statistical test	p-value
Age	Spearman	0.407
Sex	Mann–Whitney	0.42
Tumor location	Kruskal–Wallis	0.502

Table 3. Correlation between Serum MTHFR Levels and Tumor Size Reduction

Variable	n	Correlation (rho)	p-value
MTHFR	36	0.764	<0.001*

*Spearman correlation test

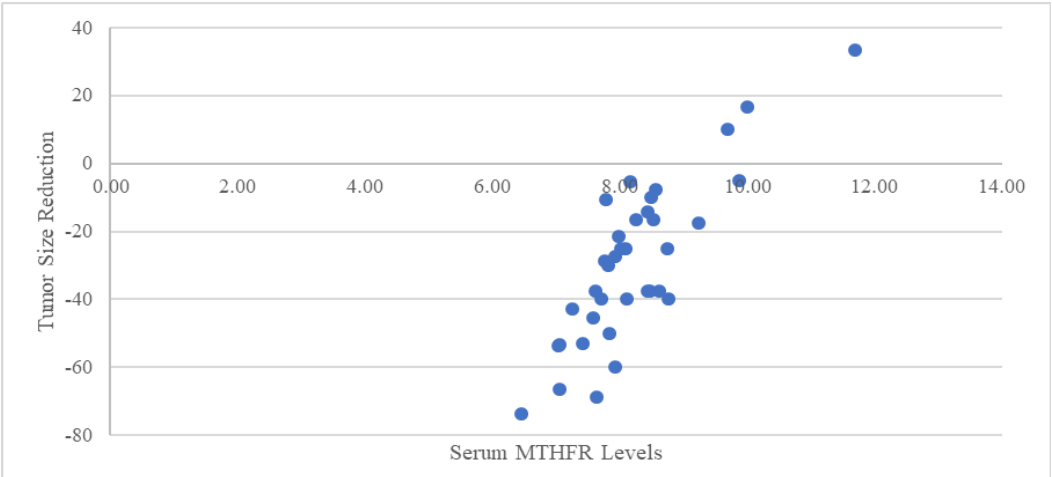

Figure 1. Relationship between Serum MTHFR Levels and Tumor Size Reduction

Table 4. Correlation between Serum CEA Levels and Tumor Size Reduction

Variable	n	Correlation (rho)	p-value
CEA	36	0.654	<0.001*

*Spearman correlation test

Table 5. Multiple Linear Regression Predicting Tumor Size Reduction

Coefficient	Estimate	SE	t-value	p-value
Intercept	−165.68	16.5	−9.57	<0.001*
CEA	1.1	0.52	2.14	0.039
MTHFR	15.38	3.17	4.85	<0.001*

*Multiple linear regression

ranged from −73.7% to +33.3%. As confounding variables were not significant in bivariate analysis, only serum CEA and MTHFR levels were included in the multivariate model. Multiple linear regression yielded the following predictive equation:

Tumor size reduction (%) = −165.68 + (1.10 × CEA) + (15.38 × MTHFR).

The model demonstrated strong explanatory power (adjusted $R^2 = 0.714$, $F = 44.65$, $p < 0.001$). Serum CEA (standardized $\beta = 0.32$, 95% CI: 0.05–2.15, $p = 0.039$) and MTHFR (standardized $\beta = 0.61$, 95% CI: 9.01–21.75, $p < 0.001$) remained significant predictors, with no evidence of multicollinearity (VIF < 2) (Table 5). Lower baseline values of both biomarkers were associated with greater tumor shrinkage.

Normogram Performance

A graphical nomogram was developed to facilitate clinical prediction of tumor size reduction based on the regression model (Figure 3). Each biomarker (CEA and MTHFR) was plotted on a point scale from 0 to 100, with the total score corresponding to the predicted tumor reduction percentage. For instance, a patient with CEA = 5 ng·mL^{-1} (5 points) and MTHFR = 7.5 ng·mL^{-1} (20 points) would have a total score of 25 points, corresponding to a predicted tumor reduction of approximately −50%. Conversely, a patient with CEA = 30 ng·mL^{-1} (35 points) and MTHFR = 10 ng·mL^{-1} (65 points) would have a total score of 100 points, corresponding to an estimated tumor size increase of +20%.

Model performance was further evaluated using Harrell's concordance index (C-index) to assess discriminative ability. The nomogram achieved a C-index of 0.836 (SE = 0.08), indicating excellent model discrimination. This implies that in 83.6% of cases, the model correctly distinguished differences in tumor size reduction based on serum MTHFR and CEA levels.

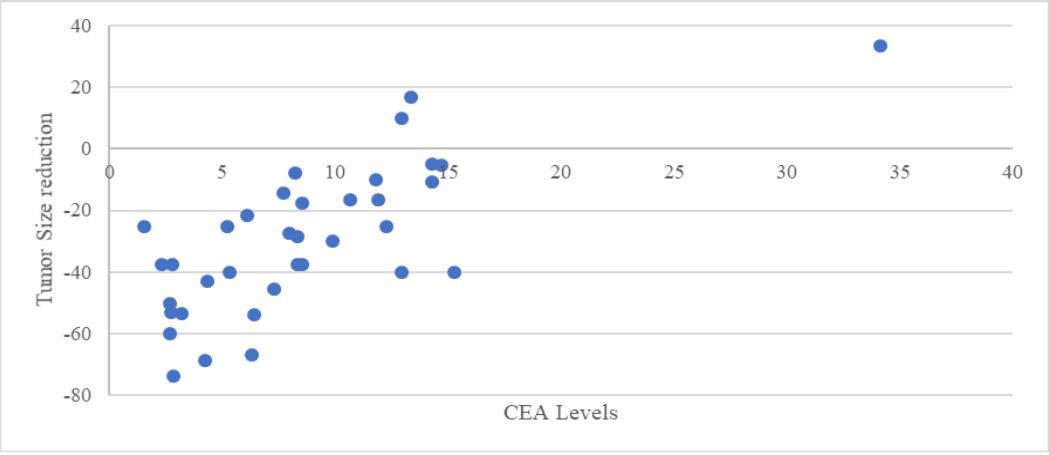

Figure 2. Relationship between Serum CEA Levels and Tumor Size Reduction

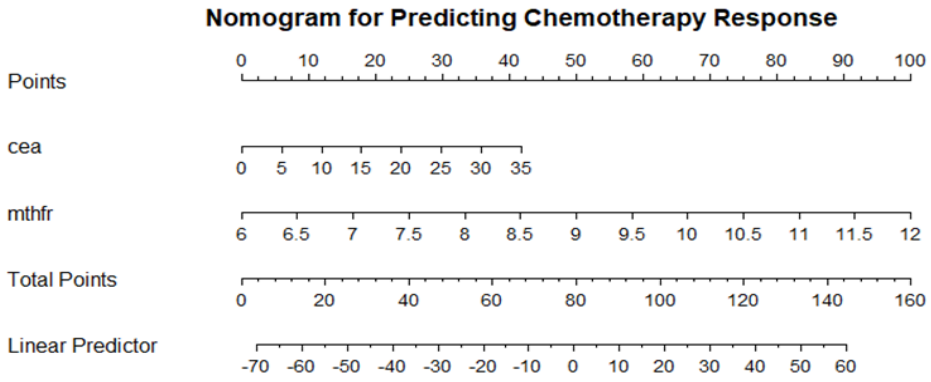

Figure 3. Nomogram for Predicting Percentage Reduction in Tumor Size after CAPEOX Chemotherapy in Advanced Colorectal Cancer

Discussion

Colorectal cancer remains one of the leading causes of cancer-related mortality worldwide, and neoadjuvant chemotherapy with the CAPEOX regimen has become a cornerstone in downstaging tumors prior to surgery. However, considerable inter-patient variability in therapeutic response highlights the need for reliable predictive biomarkers. The enzyme methylenetetrahydrofolate reductase (MTHFR) plays a crucial role in folate metabolism and DNA synthesis, potentially influencing the activity of capecitabine, a prodrug of 5-fluorouracil (5-FU) [15-17]. Reduced MTHFR activity increases intracellular 5,10-methylenetetrahydrofolate concentrations, enhancing thymidylate synthase inhibition and augmenting the cytotoxic effects of 5-FU [16]. This biochemical mechanism plausibly explains the present study's finding that patients with lower serum MTHFR concentrations exhibited greater tumor size reduction following CAPEOX therapy [18].

The findings align with prior research indicating that genetic or enzymatic alterations in MTHFR affect chemotherapy sensitivity [19]. Cohen et al. [20] and Zhang et al. demonstrated that patients with MTHFR C677T variants or reduced enzymatic activity showed improved responses to 5-FU–based regimens. Similarly, in vitro evidence by Liu et al. (2020) revealed that MTHFR knockdown markedly increased capecitabine sensitivity in colorectal cancer cell lines. Lower MTHFR expression may also impair DNA repair capacity, enhancing susceptibility to oxaliplatin-induced DNA damage. Collectively, these findings suggest that serum MTHFR concentration, reflecting functional enzymatic activity, may serve as a practical, noninvasive biomarker for predicting treatment response and supporting personalized chemotherapy strategies.

Carcinoembryonic antigen (CEA) remains a widely used tumor marker in colorectal cancer and continues to provide valuable prognostic and predictive insights [21, 22]. Elevated baseline CEA levels often correlate with advanced disease and chemoresistance, whereas lower concentrations generally indicate a more favorable therapeutic response. In this study, pretreatment CEA levels were inversely correlated with tumor size reduction, corroborating earlier evidence that baseline CEA serves as an independent predictor of tumor regression following CAPEOX therapy [12]. Mechanistically, increased CEA expression may activate pro-survival signaling pathways such as Wnt/β-catenin and PI3K/AKT, enhancing anti-apoptotic mechanisms and reducing chemotherapy efficacy [12]. Therefore, pre-treatment CEA quantification remains a valuable tool for risk stratification and therapeutic planning [23].

Integrating serum MTHFR and CEA into a combined predictive model offers a novel and pragmatic framework for quantifying neoadjuvant chemotherapy response [24]. The nomogram developed in this study, based on these two parameters, achieved a concordance index (AUC) of 0.836—superior to traditional clinical systems such as GERCOR (AUC 0.65–0.70). This improvement underscores the benefit of combining biochemical and molecular data rather than relying solely on clinical staging. Previous single-biomarker models, including those using only CEA or thymidylate synthase (TYMS), have demonstrated moderate predictive accuracy, whereas the MTHFR–CEA model achieved higher sensitivity (85% vs. 72%) in distinguishing partial from complete responders [12]. In contrast to commercial genomic assays such as Oncotype DX Colon, which primarily estimate recurrence risk, this model provides a direct, cost-effective method for predicting immediate therapeutic response in real-world clinical settings [25].

Nomogram-based prediction offers several clinical advantages [26, 27]. It enables individualized, quantitative estimation of tumor reduction rather than categorical classification, thereby enhancing decision-making precision. Because serum MTHFR and CEA are routinely measurable biomarkers, this predictive approach is feasible even in resource-limited settings. The model may be further refined by incorporating additional variables such as KRAS mutation status, microsatellite instability, or radiomic features. Future integration of artificial intelligence and machine learning algorithms could also enhance its ability to capture complex nonlinear interactions and improve cross-population robustness [28, 29].

The novelty of this study lies in its integrative design that combines biochemical biomarkers, statistical modeling, and visual representation through a nomogram to predict tumor size reduction after neoadjuvant chemotherapy. Unlike previous studies that examined MTHFR or CEA individually, this work demonstrates their combined predictive utility within a validated regression model. The capacity to estimate quantitative outcomes such as the percentage of tumor shrinkage adds greater clinical relevance than simple binary classifications of "responder" versus "non-responder." This contribution represents a meaningful advancement toward accessible precision oncology, particularly in low-resource healthcare environments.

Despite these encouraging findings, several limitations merit consideration. The single-center design and modest sample size limit generalizability and preclude definitive conclusions. The absence of internal validation raises the possibility of overfitting, and the predictive performance of the nomogram should therefore be interpreted cautiously. Additionally, potential confounders such as nutritional folate status, genetic polymorphisms, and tumor molecular characteristics were not assessed and may have influenced treatment response. Future multicenter studies with larger and more diverse cohorts, external validation, and integration of genomic or radiomic variables are needed to confirm and refine the clinical utility of this model. Overall, this study should be viewed as hypothesis-generating. It provides preliminary evidence that combined assessment of serum MTHFR and CEA may offer a pragmatic and cost-effective strategy for predicting neoadjuvant chemotherapy response in advanced colorectal cancer, warranting further investigation.

In conclusion, this study demonstrated that serum methylenetetrahydrofolate reductase (MTHFR) and

carcinoembryonic antigen (CEA) levels are significant predictors of tumor size reduction following neoadjuvant CAPEOX chemotherapy in patients with advanced colorectal cancer. Lower serum concentrations of both biomarkers were associated with greater tumor shrinkage, supporting their complementary roles in predicting chemotherapy response. The developed multivariate model and corresponding nomogram achieved high predictive accuracy (C-index = 0.836), offering a practical, quantitative tool for individualized assessment of treatment efficacy.

These findings highlight the potential of integrating biochemical and clinical markers to guide precision oncology, particularly in resource-limited settings where molecular testing is not widely available. Routine measurement of serum MTHFR and CEA can assist clinicians in identifying patients likely to respond favorably to CAPEOX therapy, optimizing therapeutic decisions, and improving cost-effectiveness of care.

Further multicenter studies with larger and more diverse populations are warranted to externally validate this model and to explore additional predictive parameters, such as genomic alterations and radiomic features, to enhance its generalizability and clinical applicability.

Author Contribution Statement

Study concept and design: Albert Julyson Wishnu Cahyopoetro, Ronald Erasio Lusikooy, Ilhamjaya Patelongi. Acquisition of data: Albert Julyson Wishnu Cahyopoetro. Analysis and interpretation of data: Albert Julyson Wishnu Cahyopoetro, Amirullah Abdi. Drafting of the manuscript: Albert Julyson Wishnu Cahyopoetro, Amirullah Abdi. Critical revision of the manuscript for important intellectual content: Ronald Erasio Lusikooy, Ilhamjaya Patelongi, Ibrahim Labeda, Samuel Sampetoding, Arham Arsyad. Statistical analysis: Ilhamjaya Patelongi, Amirullah Abdi. Study supervision: Ronald Erasio Lusikooy, Ilhamjaya Patelongi, Ibrahim Labeda, Samuel Sampetoding, Arham Arsyad.

Acknowledgements

Ethical Approval

This study was reviewed and assessed by the ethics committee of the Faculty of Medicine, Hasanuddin University (No. UH25050328). Ethics approval was obtained from all participants and all information and results are confidential.

Scientific approval / Thesis

This study is part of an approved academic thesis conducted at the Faculty of Medicine, Hasanuddin University.

Data Availability

All data supporting the findings of this study are available from the corresponding author upon reasonable request. Language assistance was supported by ChatGPT for grammar improvement; authors take full responsibility for content accuracy.

Study Registration

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

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