RESEARCH ARTICLE

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Development and Validation of Platelet-Index Based Colorectal Cancer Survival Prognostic Nomogram

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Abstract

Introduction: A prognostic model is essential for postoperative treatment planning, follow-up strategies, and aiding physicians in communicating survival rates to patients. Recent studies suggest that platelet indices may serve as valuable prognostic markers. This study aims to develop and validate a nomogram incorporating platelet indices to predict survival outcomes in CRC patients. **Methods:** This prospective cohort study included subjects diagnosed with CRC between 2019 and 2024 at Wahidin Sudirohusodo Hospital, Makassar. Subjects were randomly divided into training and validation sets. Demographic data (age, gender), clinical data (tumor invasion [T], node [N], metastases [M], tumor location, histological grading, history of surgery, chemotherapy, ileus or peritonitis), and platelet indices were collected. Independent prognostic factors were determined using the Cox regression model in SPSS 25.0. Nomogram development and validation were conducted using the "rms" (Regression Modeling Strategies) and "survival" packages in R Studio. **Results:** Thirteen prognostic factors, including gender, tumor location, T, N, M, histological grade, history of ileus or peritonitis, history of tumor resection, history of chemotherapy, and platelet indices, significantly impacted CRC survival. A nomogram was constructed with a C-index of 0.9 in the training set and 0.91 in the validation set. **Conclusions:** A prognostic survival nomogram for Indonesian CRC patients was developed and validated, enabling predictions of CRC survival probabilities.

Keywords: Nomogram- survival- colorectal cancer- platelet indices

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and ranks second in cancer-related mortality [1]. The American Cancer Society projects an increase in CRC cases and mortality rates by 2035 [2]. Developing countries, including Indonesia, have seen a rising CRC incidence due to lifestyle changes and increased life expectancy. In Indonesia, CRC ranks sixth in cancer incidence and mortality [3].

In Indonesia, the incidence and mortality rate for colorectal cancer ranked sixth, with a rate of 4.2% and 3.8%, respectively [4]. Rahadiani et al. (2021) showed that this incidence had increased remarkably by 9.2% in the past 10 years [5]. The overall survival rate of CRC across the Indonesian population in the last 10 years ranged from 35.3-45% [6, 7] compared to an average of 69% survival rate in the developed country [8]. Nevertheless, the survival rate was affected by many factors related to diagnosis, the extent of the disease, the patient, and particular circumstances.

Accurate prognostic models are essential for CRC management. Nomograms have shown promise over traditional TNM staging systems by incorporating various independent factors to provide personalized survival estimates [9]. They have been built for various cancers and have shown advantages over the TNM staging system [10]. This study aims to identify prognostic factors associated with Indonesian CRC survival and develop a nomogram suitable for outpatient use.

Materials and Methods

Study design

This prospective cohort study included CRC patients diagnosed from 2019 to 2024 at Wahidin Sudirohusodo General Hospital. Ethical clearance was obtained from the Local Ethics Committee for Medical Research,

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Hasanuddin University. Subjects were divided into training and validation sets and followed until June 2024.

Participants

Eligibility criteria included a histopathologically confirmed diagnosis of colorectal cancer (ICD10 C18, C19, C20), complete clinical data, and no significant missing information. Patients with other primary tumors or immune disorders were excluded.

Variables

Collected variables included demographic data (age, gender), clinical data (tumor invasion [T], node [N], metastases [M], tumor location, histological grade, history of surgery, chemotherapy, ileus or peritonitis), and platelet indices.

Bias

To overcome the bias, we did a paired-match case and control data, based on the variables' history of smoking, alcoholic drinking, and ethnicity. Then, we divided the total data based on 7:3 proportion to the training and validation set.

Statistics

Statistical analyses were performed using SPSS 25.0 (IBM, Chicago, Illinois) and R Studio (Rstudio, PBC, New Zealand). Kaplan-Meier analysis estimated overall survival (OS). Variables significant in univariate analysis ($p < 0.05$) were included in Cox regression. The "rms" package in R Studio was used to build the nomogram and calculate 1- and 5-year survival probabilities [11]. Calibration plots and Harrel's C-index assessed the nomogram's accuracy.

Study Size and Bias Mitigation

The minimum sample size was determined based on the rule of thumb of 10 events per variable, with a 10% addition for bias adjustment. To reduce bias, cases and controls were paired based on smoking history, alcohol consumption, and ethnicity.

Results

Patient Characteristics

A total of 1,230 CRC patients were included. The training set comprised 861 subjects (70%), while the validation set included 369 subjects (30%). Significant prognostic factors included age, tumor location, T, N, M, histological grade, history of surgery, chemotherapy, ileus, and platelet indices. Most subjects with poor survival were male, aged >45 years old, tumor site at rectum histological grade 3, T4, N1, M1, had history of ileus or peritonitis, no history of tumor resection, no history of chemotherapy, and had high platelet index (Table 1).

Univariate and multivariate survival analysis

For univariate analysis, a Kaplan-Meier survival analysis was carried out. For the gender variable, no significant difference in survival was shown. The statistical analysis could not be done for tumor invasion because all T1 stage was found in the survived group. As many as 13 prognostic factors were analyzed by log-rank analysis and all prognostic factors were shown to be significant factors

Table 1. Charateristics of Subjects in This Study

Variables	Survived	Died	Hazard Ratio
Age			
<45 years old	433 (50.3%)	415 (48.2%)	-
>45 years old	428 (49.7%)	446 (51.8%)	
Gender			
Male	264 (30.7%)	565 (65.6%)	1.32
Female	597 (69.3%)	382 (44.4%)	
Tumor location			
Right colon	203 (23.6%)	129 (15.0%)	1.03
Left colon	251 (29.2%)	180 (20.9%)	
Rectum	406 (47.2%)	552 (64.1%)	
Tumor size			
T2	127 (14.8%)	0 (0%)	1.46
T3	578 (67.1%)	259 (30.1%)	
T4	156 (18.1%)	602 (69.9%)	
Node			
Negative	443 (51.4%)	51 (5.9%)	2.16
Positive	418 (48.6%)	810 (94.1%)	
Metastasis			
Negative	829 (96.3%)	422 (49.0%)	1.38
Positive	32 (3.7%)	439 (51.0%)	
Histological grade			
1	411 (47.7%)	70 (8.1%)	1.01
2	406 (47.2%)	466 (54.1%)	
3	44 (5.1%)	325 (37.8%)	
Platelet count			
Low	702 (81.5%)	158 (18.3%)	1.14
High	159 (18.5%)	703 (81.7%)	
Platelet distribution width			
Low	705 (78.2%)	180 (20.9%)	1.8
High	156 (21.8%)	681 (79.1%)	
Mean platelet volume			
Low	673 (78.2%)	186 (21.6%)	1.14
High	188 (21.8%)	675 (78.4%)	
Plateletcrit			
Low	641 (74.5%)	152 (17.6%)	1
High	220 (25.5%)	709 (82.4%)	
History of curative surgery			
Yes	761 (88.4%)	406 (47.1%)	1.13
No	100 (11.6%)	455 (52.9%)	
History of chemotherapy			
Yes	758 (11.8%)	102 (11.8%)	11.14
No	103 (88.2%)	759 (88.2%)	
History of ileus or peritonitis			
Yes	841 (97.7%)	737 (85.6%)	2.07
No	20 (2.3%)	124 (14.4%)	

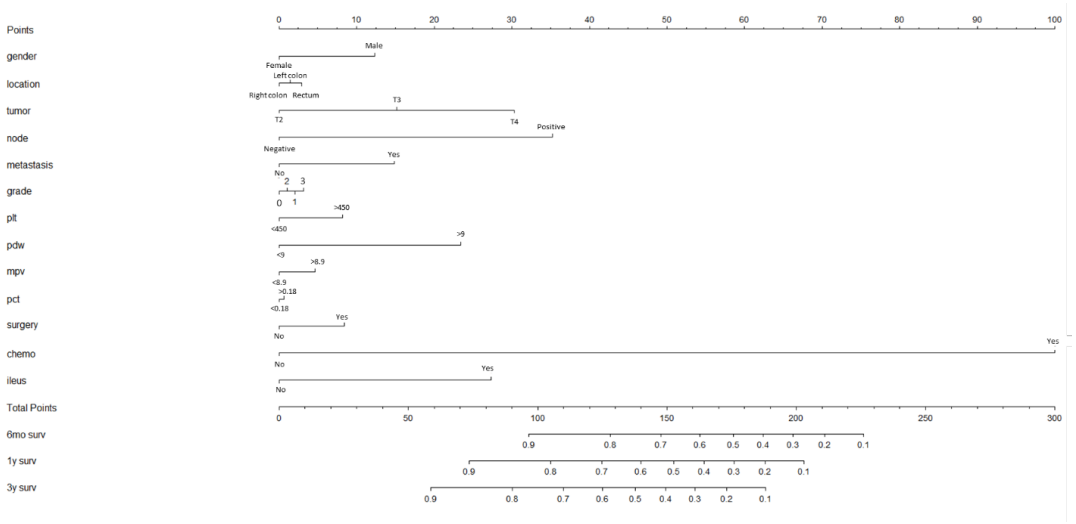

Figure 1. Nomogram for CRC Survival Determination

affecting overall survival (p<0.001). A multifactorial Cox regression analysis was performed using the enter method following univariate analysis. All variables except age were significant independent prognostic factors with patient survival prognosis (P<0.05) (Table 1).

Building nomogram and android application for CRC survival

According to the results of COX multivariate analysis, 13 independent risk factors were integrated to create the nomogram. The nomogram was created using R studio with the probability of survival at 1 and 5 years. The scores assigned to each variable can be seen in the nomogram. At the very bottom, a range of total scores is given to describe survival rates. In accordance with the results of the Cox regression analysis, the pathological type has the greatest weight, which can be seen from the nomogram line from 0 to 100. The results of the nomogram can be seen in Figure 1.

The strength of a nomogram is determined by calculating the Harrel Index C statistical estimate, which means the area under the curve on the receiving operating curve. In the training set, the C-index of the nomogram was 0.9 (SD 0.21), and C-index in the validation set was 0.91 (SD 0.19). We used the calibration plots to check the accuracy of the nomogram that was shown in Figure 2.

Discussion

The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging is the most basic staging system for evaluating the prognosis of colon cancer [12]. Of note, the TNM staging system has an inherent limitation, as it assesses individual patients' risk by only three variables (TNM) and cannot be combined with other clinopathological factors [13]. Therefore, the nomogram has emerged as a more advanced method owing to its ability to estimate individualized risk based on more comprehensive disease and patient characteristics.

In this study, we showed that there were 13 prognostic factors that contributed to the estimated survival of CRC, consisting of age at diagnosis, tumor location, histological

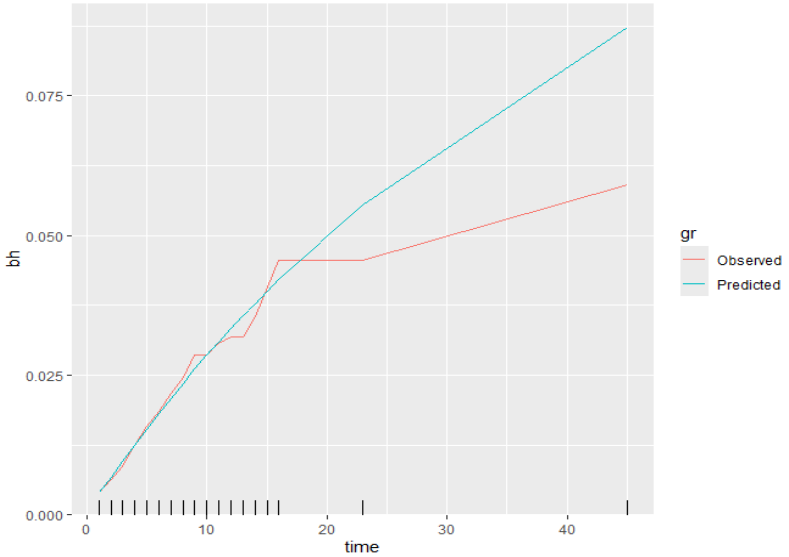

Figure 2. Calibration Plot of the Nomogram by Calculating Observed and Predictive Value

Table 2. Description of the Previously Built Nomogram

Authors	Stage limitation	Factors included in nomogram	C-index in training set	C-index in validation set
[15]	Locally advanced rectal cancers	Age, gender, carcinoembryonic antigen value, tumor location, T stage, N stage, metastatic lymph nodes ratio, adjuvant chemotherapy and chemoradiotherapy	0.7	0.76
[18]	All	Sex, age, race, marital status, preoperative carcinoembryonic antigen status, surgical extent, tumor size, location, histology, differentiation, infiltration depth, lymph node count, lymph node ratio, and metastasis	0.816	0.777
[16]	Non metastatic	Age, first-degree relative cancer history, differentiation grade, vessels/nerves invasion, TNM stage, CEA, CA19-9 and PNI	0.75	0.79
[19]	Stage III	Tumor differentiation grade, lymph node metastasis ratio, intravascular emboli (IVE), preoperative serum carcinoembryonic antigen (CEA) level, albumin to globulin ratio (AGR), T stage and N stage	0.734	0.714
[20]	All	APC, ATM, BRAF, PTEN, TP53 (LOF), mutation count (high: >3, low: < =3), age, CEA, and the location of the tumor	0.887	NA
[14]	Stage II-III	Preoperative mean platelet volume, preoperative platelet distribution width, monocytes, and postoperative adjuvant chemotherapy	0.67	0.69
[21]	All	Age, gender, histological grade, T stage, number of retrieved lymph nodes, tumor size, and N stage	0.729	0.745
[22]	All	Race, age, tumor site, tumor size, gender, histology, tumor extension, lymph node, and radiation	0.722	0.721
[23]	All	Body mass index (BMI), family history, tumor grading, tumor stage, primary site,diabetes history, T stage, N stage, and type of treatment	0.692	0.627
[24]	Signet-ring cell	Age, marital status, tumor size, surgery, T, N, M	0.737	0.796
[25]	Liver metastasis	age, sex, primary site, T category, N category, metastasis of bone, brain or lung, surgery, and chemotherapy	0.811	0.727
[26]	Distant metastasis	Age at diagnosis, marital status, race, primary tumour site, tumour grade, CEA level, T stage, N stage, presence of bone, brain, liver and lung metastasis	0.742	0.746
[27]	All	Race, primary site, histology, grade, tumor size, regional nodes examined, LNR, liver metastasis, lung metastasis, bone metastasis, brain metastasis, stage, T, N, CEA, perineural invasion, and median household income	0.868	0.84
[28]	Peritoneal metastasis	Age, carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 125 (CA125), cytoreductive surgery (CRS), hyperthermic intraperitoneal chemotherapy (HIPEC), and chemotherapy	0.701	0.716
[29]	Metastatic	Age, primary site, extra-lung metastasis, CEA, primary tumor size, regional nodes	0.648	0.793
[30]	All	Age, primary site, grade, surgery, T, N, M, bone metastasis, brain metastasis, liver metastasis, lung metastasis, dan chemotherapy	0.731	0.736

grade, tumor stage (T), nodes stage (N), metastasis stage (M), history of ileus or peritonitis, history of curative surgery, history of chemotherapy, and platelet index. Study demonstated that age was not a significant prognostic factor for survival. The highest prognostic factors value for colorectal cancer survival were history of chemotherapy, presence of lymph node, and tumor size. The lowest prognostic factors value for colorectal cancer survival were tumor location, histological grade, and plateletcrit.

Platelet indices, such as mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit, have been implicated in cancer progression through various biological mechanisms. Elevated platelet indices often reflect a hypercoagulable state, which promotes tumor angiogenesis, immune evasion, and metastasis by shielding circulating tumor cells from immune surveillance and facilitating their colonization at distant sites [14]. Platelets secrete growth factors such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), which enhance tumor vascularization and proliferation [15]. Furthermore, increased MPV levels have been linked to systemic inflammation, a critical factor in the tumor microenvironment that fosters cellular proliferation and metastatic potential, while variations in PDW may indicate platelet heterogeneity influencing tumor interactions [16]. These mechanisms underscore

the prognostic relevance of platelet indices in colorectal cancer and highlight their potential as therapeutic targets, emphasizing the value of their inclusion in predictive models like the one presented in this study.

Nomogram is a simple graphical representation of a statistical prediction model that generates a numerical probability of a clinical event and has been recently applied in prognosis-associated clinical studies with comparable results [17]. In this study, a nomogram was built using 13 significant survival prognostic factors which revealed to be a significant independent prognostic factor associated with patient survival prognosis ($p<0.05$). The strength index for the nomogram, Harrel C-index is quite good, the C-index of the nomogram was 0.9 (SD 0.21), and C-index in the validation set was 0.91 (SD 0.18). The C-index in this study was higher than other studies [15, 18, 16, 19, 20, 14, 21-28] except from Wu et al. (2021). However, they include CEA, which was not available routinely in our country [27]. This study included history of acute abdomen and progressivity that were not available in other studies that focused on including molecular markers. Others previously built nomograms were provided in Table 2 [16, 19, 20, 15, 18, 29, 14, 21, 30, 22, 24, 25, 27, 28, 23, 26].

Although we successfully developed and validated nomograms to predict survival. Our study does have several limitations. First, it is retrospective in design from a single institution, so that selection bias may be underestimated. Second, we only used partially outside data sets from other hospitals but used our data for external validation. However, we conducted strictly randomized grouping to allocate it into 2 sets so that it can be regarded as an external validation to some extent. Third, several molecular prognostic factors, such as KRAS, BRAF, and microsatellite instability, were unavailable. Fourth, the chemotherapy regimens were not based on guidelines, as our national medical insurance did not cover the drugs.

The strength of the nomogram in our study is that we strictly paired all subjects in each training and validation set to control other competing variables. Then, this is the first nomogram of CRC survival in Indonesian population. The calibration index showed promising solid results. Thus we hope for another validation in larger sets of multicenter data.

In conclusion, a prognostic survival nomogram for Indonesian CRC patients was developed and validated to determine the survival probability of CRC patients. The predictive model presented satisfactory discrimination and calibration, which can be used for survival estimation and individualized treatment decision-making in CRC patients.

Author Contribution Statement

Erwin Syarifuddin: Concept, design, statistical analysis, discussion, manuscript preparation, and editing. Warsinggih: Concept, data collection, discussion, and conclusion. Rina Masadah, Ronald Erasio Lusikooy, and Muhammad Husni Cangara: Design, data analysis, and manuscript review.

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Ethics Approval

Ethical approval for this research was obtained from the Local Ethics Committee for Medical Research, Hasanuddin University.

Data Availability

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

Conflict of Interest

The authors declare no conflicts of interest associated with this study.

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