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The elevated preoperative platelet to lymphocyte ratio predicts decreased time to recurrence in colon cancer patients

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Platelet to lymphocyte ratio;
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Prognostic factor

Abstract

BACKGROUND: Recent evidence indicates that tumor progression involves factors of systemic inflammation, such as platelets and lymphocytes. In this study, we investigated the prognostic relevance of the preoperative platelet to lymphocyte (P/L) ratio on time to recurrence (TTR) and overall survival (OS) in patients with stage II and III colon cancer (CC) who underwent curative resection.

METHODS: In this retrospective study, 372 CC patients were included. Kaplan–Meier curves and multivariate Cox proportional models were calculated for TTR and OS.

RESULTS: In univariate analysis, the elevated P/L ratio was significantly associated with decreased TTR (HR = 1.60, 95% CI = 1.02 to 2.51, $P = .040$) and remained significant in multivariate analysis (HR = 1.65, 95% CI = 1.05 to 2.58, $P = .030$), where HR and CI represent Hazard ratio and confidence interval, respectively. Patients with elevated P/L ratio showed a median TTR of 116 months. In contrast, patients with low P/L ratio had a median TTR of 132 months. In OS analysis, the elevated P/L ratio showed a trend toward decreased OS in univariate analysis (HR = 1.54, 95% CI = .95 to 2.48, $P = .079$).

CONCLUSION: In this study, we identified the preoperative P/L ratio as a prognostic marker for TTR in stage II and III CC patients.

Colorectal cancer (CRC) is the 3rd cause of cancer worldwide and the 2nd leading cause of cancer-related death in Europe and the United States.[1,2] State of the art treatment in nonmetastatic disease is surgery, with 5-year survival rates ranging from 44% to 93% depending on the clinical stage.[3] The high mortality is primarily related to complications of tumor dissemination.

5-Fluorouracil-based adjuvant treatment has demonstrated a significant benefit for stage III colon cancer (CC) patients,[4] but remains controversial in stage II CC.[5]

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Over the last decade, various expert opinion reports have been published in an attempt to define a high-risk stage II subgroup that may benefit from adjuvant 5-fluorouracil-based chemotherapy.[6,7] High tumor stage and histological grade, the number of resected lymph nodes, venous, lymphatic, or perineural invasion, emergency surgery (because of obstruction or perforation), and a high preoperative carcinoembryonic antigen level have been identified as unfavorable clinicopathological prognostic factors in previous studies.[3,8–11] In addition, a large number of translational research studies evaluated the association of various molecular markers with clinical outcome in CC, but high costs, lack of standardization, and regional availability limit the application in routine clinical practice.[12,13] Moreover, as most of the known prognostic factors are assessed postoperatively, we are in need of preoperative prognostic markers for an early and adequate risk stratification of tumor recurrence.

Tumor progression and metastasis comprise a cascade of steps that involve the interaction between the tumor and the host-derived stromal microenvironment, which includes factors that support angiogenesis and inflammation.[14,15] Previous studies have suggested that the preoperative indices of systemic inflammation, such as the platelet to lymphocyte (P/L) ratio, a combination of platelet and lymphocyte counts, might provide prognostic information on various cancer entities, showing a decreased survival in patients with elevated P/L ratio.[16–20]

Therefore, the aim of this study is to investigate the prognostic effect of the preoperative P/L ratio for time to recurrence (TTR) and overall survival (OS) in a large cohort of patients with stage II and III CC who underwent curative surgical resection.

Patients and Methods

Subjects

A total of 372 patients with histologically confirmed stage II and III CC were included in this retrospective study. All patients were treated and/or included in the CC surveillance program between 1996 and 2011 at the Division of Clinical Oncology, Department of Medicine, Medical University of Graz, Austria. Follow-up care was performed in regular intervals (3-month intervals in years 1 to 3, 6-month intervals in years 4 to 5, and 12-month intervals in years 6 to 10 after diagnosis). Follow-up investigations included clinical examination, laboratory data including carcinoembryonic antigen and carbohydrate-antigen (CA) 19-9, radiological assessment (liver scan or ultrasound and chest X-ray every 6 months within the 1st 3 years), and colonoscopy every 2 years. Clinical and histopathological features were retrospectively obtained from the patient's history. Follow-up data of all patients were available. The laboratory data, including preoperative platelets and lymphocytes count, were obtained by preoperative exploration within 3 days before surgery was performed. This study has been approved by the Institutional Review Board of the Medical University of Graz. All participants were Caucasians.

Statistical analysis

The primary endpoint of the study was TTR. TTR was calculated from the date of diagnosis of CC to the date of the 1st observation of tumor recurrence. TTR was censored at the time of death or at the last follow-up if the patient remained tumor-free at that time. The secondary endpoint was OS. OS was determined from the date of diagnosis of CC to the date of death of any cause. The optimal cut-off levels for the P/L ratios were calculated by applying receiver operating curve analysis. The association between dichotomized P/L ratio and clinical and histopathological features was analyzed with chi-square test. The impact of clinicopathological features (tumor location, tumor size, lymph node involvement, tumor grade, tumor stage, adjuvant chemotherapy), sex, age, and the P/L ratio on TTR and OS was analyzed using Kaplan–Meier curves and compared by the log-rank test. In the multivariate Cox-regression analysis, the impact of P/L ratio on TTR and OS was analyzed. In this analysis, the model was adjusted for clinicopathological factors ($P < .1$) associated with the endpoints in univariate analysis. Hazard ratios (HRs) estimated from the Cox analysis were reported as relative risks with corresponding 95% confidence intervals (CIs). All statistical analyses were performed using the Statistical Package for Social Sciences Version 20.0 (SPSS, Inc, Chicago, IL). A 2-sided P value of $<.05$ was considered statistically significant.

Results

Baseline patient characteristics and tumor biological factors are shown in Table 1. The median age at the time of diagnosis was 64 years (range, 27 to 95 years). The median follow-up time was 68 months (range, 1 to 190 months). The median P/L ratio was 211 (range, 1 to 1,555). By applying receiver operating curve analysis, the optimal cut-off levels for the P/L ratio was 176 for TTR and 225 for OS.

The primary tumor sites were localized at the appendix ($n = 2$), coecum ($n = 73$), colon ascendens ($n = 55$), flexura hepatica ($n = 19$), colon transversum ($n = 26$), flexura lienalis ($n = 22$), colon descendens ($n = 21$), sigmoid ($n = 128$), and rectosigmoid ($n = 26$).

The elevated P/L ratio of >176 was significantly associated with female patients and a higher tumor size ($P = .014$ and .047, respectively). None of the other clinicopathological features were associated with an elevated P/L ratio (data not shown).

Of the 372 CC patients, 94 (25.3%) developed tumor recurrence and 72 (19.4%) died within the follow-up period. The tumor recurred in 27 of 139 (19.4%) patients with a P/L ratio of ≤ 176 and in 64 of 217 (29.5%) patients