

The Relationship Between Carcinoembryonic Antigen and Prognosis in Colorectal Cancer

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Dear Editor,

I read with great interest the article by Aydın et al., which examined the association between preoperative carcinoembryonic antigen (CEA) levels and prognosis in 226 patients with colon cancer.¹ The authors stratified patients into three groups by CEA level (3–10, 10–20, and >20 µg/L) and found that higher CEA was significantly associated with venous, perineural, and lymphatic invasion, although no significant differences were observed in TNM stage, recurrence, or overall survival. This is a valuable contribution to the ongoing discussion on CEA as a prognostic biomarker in colorectal cancer, and I would like to raise several methodological points that I believe merit further consideration.

All patients in this cohort had elevated preoperative CEA (≥ 3 µg/L); patients with normal CEA levels were not included. Because the analysis compares only degrees of CEA elevation, it cannot address whether CEA elevation itself — relative to normal levels — carries prognostic value. Previous studies have shown that even within the normal range, higher CEA values are associated with worse survival, suggesting that the relationship between CEA and prognosis is continuous rather than threshold-based^{2,3}. Including a normal-CEA reference group in future analyses would allow a more complete assessment of this continuum.

The three groups were highly unequal in size (n=168, 18, and 39, respectively). This imbalance limits statistical power to detect differences in the smaller groups and increases the risk of type II error, particularly for outcomes such as overall survival and recurrence, where the highest-CEA group had numerically shorter survival without reaching statistical significance (p=0.153).

The associations reported — between CEA level and lymphovascular or perineural invasion — were assessed only with univariate tests. Survival and recurrence in colorectal cancer are influenced by multiple interrelated factors, including TNM stage, lymphovascular invasion, tumor differentiation, and M stage. A multivariable analysis adjusting for these covariates would be needed to determine whether preoperative CEA level is an independent prognostic factor, as has been shown in other large series^{4,5}. Postoperative CEA kinetics, including normalization after surgery, may also add prognostic information beyond a single preoperative measurement^{6,7}.

Liver metastasis was significantly more frequent in the lowest-CEA group, a result that runs counter to the general literature linking higher CEA with greater metastatic burden^{5,8}. Given the small size of the higher-CEA subgroups, this finding may at least partly reflect a statistical artifact of unequal group sizes rather than a genuine biological

relationship, and I believe this alternative explanation warrants more cautious discussion in the manuscript.

Patients were recruited over a decade (2012–2022), during which colorectal cancer surgery, staging (reflected in the concurrent use of the 7th and 8th TNM editions), and follow-up protocols evolved considerably. These temporal changes could confound the survival and recurrence comparisons; stratifying or adjusting for treatment era would strengthen the validity of the conclusions.

These limitations do not diminish the relevance of the findings, which support a link between high preoperative CEA and adverse histopathological features in colon cancer. Rather, they highlight the need for a prospective, multicenter study incorporating both normal- and high-CEA patients, adequately powered subgroups, and multivariable survival analysis to clarify the independent prognostic role of preoperative CEA. I thank the authors for their contribution and hope these comments will stimulate further discussion on the optimal use of CEA as a prognostic biomarker in colorectal cancer.

Sincerely,

Keywords: carcinoembryonic antigen; colon cancer; prognosis; multivariable analysis

Conflict of Interest: The author declares no conflicts of interest.

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