



# Impact of hyponatremia in resected colorectal cancer patients

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Comment on: Li Q, Dai, W, Jia H, *et al.* Prognostic Impact of Hyponatremia in Patients With Stage I to III Colorectal Cancer After Radical Resection. *Dis Colon Rectum* 2018;61:1273-80.

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It is a great honor to comment on the article entitled “Prognostic impact of hyponatremia in patients with stage I to III colorectal cancer after radical resection” by Qingguo Li and his colleagues in the *Diseases of Colon and Rectum* (1).

This retrospective study investigated the prognostic role of electrolyte disorders in patients with stage I to III colorectal cancer (CRC) who underwent radical surgical resection. The study included 5,089 such patients at a single institution from April 2007 to April 2014. The Kaplan-Meier method was employed to estimate the overall survival (OS) and disease-free survival (DFS) with and without propensity score (PS) matching. In the pre-matching analysis, patients with hyponatremia ( $<102$  mmol/L) showed shorter OS (HR =0.943; 95% CI, 0.908–0.980;  $P=0.003$ ) and DFS (HR =0.957; 95% CI, 0.933–0.981;  $P<0.001$ ). The PS matching analysis performed on 770 patients in each group (low serum chloride *vs.* normal serum chloride) confirmed that hyponatremia was significantly associated with worse OS (HR =0.646; 95% CI, 0.489–0.855;  $P=0.002$ ) and DFS (HR =0.0.782; 95% CI, 0.647–0.944;  $P=0.01$ ). The authors concluded that hyponatremia diagnosed before treatment could independently predict the OS and DFS for patients with stage I to III CRC after radical resection.

Chloride is the most abundant anion in plasma and interstitial fluid, accounting for approximately one-third of plasma tonicity, and it affects acid-base changes (2,3). Although chloride is an electrolyte that is mostly measured in daily practice, its role and metabolism have not been an area of focus and research when compared to other electrolytes, such as sodium, potassium, and calcium. Nonetheless, metabolic alkalemia is often observed in the

perioperative course, and it has been widely known that it is primarily associated with electrolyte disturbances, such as hypokalemia and hyponatremia (4,5). An association has been previously reported between hyponatremia and mortality in critically ill patients (6-8). The authors speculated that hyponatremia was related to poor prognosis because (I) it could be a surrogate marker of malnutrition, and preoperative lower body mass index and older age may reflect nutritional deficiency in the patient before surgery (9); (II) it could be related to the status of preoperative chronic kidney disease (CKD) (10); and (III) some comorbidities such as liver disease (liver cirrhosis or hepatocellular carcinoma), diabetes mellitus, hypertension, and known heart failure had negative correlations with preoperative chloride levels.

However, the association between hyponatremia and increased mortality in patients with CRC has not been fully explored. In the study, the authors pointed out three elements to explain the association, including (I) stress, (II) hyponatremia reflecting the severity of CRC, and (III) abnormal expression of some ion channel proteins. At this time, as referred to in the article, there have been some reports about the abnormal expression of some ion channel proteins causing electrolyte disorders and leading to poor survival outcomes. However, we could not find any reports in PubMed that revealed the precise mechanism of hyponatremia leading to poor prognosis in CRC. Further basic and prospective clinical research is strongly expected.

Meanwhile, in addition to limitations that may have affected the results of the study, there are some points that we need to consider. First, because the original article mentioned that chemotherapy based on 5-fluorouracil

was applied to patients with high risk stage II and III disease after radical resection, the absence of adjuvant chemotherapy with oxaliplatin base regimens may have led to poor prognosis, which could influence the results of the study. The authors did not mention the completion rate of treatment; this is another point of interest. Recently, Oh TK *et al.* reported that preoperative hyponatremia was related to an increased risk for postoperative acute renal dysfunction, and preoperative serum chloride level exhibited an independent relationship with mortality and morbidity after noncardiac surgery (11). Chemotherapy based on 5-fluorouracil is contraindicated, or reduced use is recommended for patients with kidney dysfunction; therefore, clarifying this point may lead to more persuasion. The influence of underlying CKD is another point of interest that was not mentioned in the article because previous studies have reported that hyponatremia in preoperative CKD causes poor prognosis for patients who are critically ill.

Second, the cutoff value of hyponatremia (102 mmol/L) is different from previous studies. Although there are no established cutoff values for hypo-, normo-, or hypernatremia (8,12,13), most studies use cutoff values of 98 mmol/L for hyponatremia and 110 mmol/L for hypernatremia (12,13). The authors showed a mound-shaped histogram with the cutoff value of 102 mmol/L to define hyponatremia, which was derived from a large sample ( $n > 800$ ). However, a value of 102 mmol/L is generally regarded as normonatremia. Oh HJ *et al.* reported that the 28-day mortality rate in a hyponatremic group ( $< 97$  mmol/L) was significantly decreased by 5.4% at 24 h with an increase of 1 mmol/L in the chloride level after adjusting for age, sex, body mass index, systolic blood pressure, sequential organ failure assessment score, coronary arterial disease, serum albumin, and total  $\text{CO}_2$ . However, there was no significant effect on 28-day mortality of 1-mmol/L increase in the chloride level at 48 h. In addition, in the normonatremic group (98–110 mmol/L), an increase of chloride level was not significantly associated with 28-day mortality at any time (6). The effect of 1-mmol/L increase in the chloride concentration may be another point of interest in the original article for further study.

Third, as patients with stage I to III disease are grouped together in the study, subgroup analysis according to the T stage and N stage would be of interest. According to the 2016 Japanese Society for Cancer of the Colon and Rectum guidelines for the treatment of colorectal cancer (14), the

recurrence rate after curative resection varies from 3.7% in stage I to 30.8% in stage III. The 5-year survival rate is 91.6% in stage I, while it is 60.0% in stage IIIb.

Moreover, it is widely known that tumor location is another important factor that influences prognosis. It may be better to investigate the relationship with hyponatremia and these associated factors.

Discovering a simple and cost-effective predictable marker for patient prognosis is certainly a desirable goal. This article has focused on electrolyte disorders and prognosis in patients with stage I to III CRC. It may be the first article to emphasize serum chloride levels because we have not located any similar studies that have been previously published. Although the precise physiology and metabolic mechanism are unknown, the results of this study may be a milestone for further studies, leading to better outcomes in patients with CRC.

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## Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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