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# Prognostic and predictive role of hyponatremia in cancer patients

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## Abstract

Hyponatremia is the most frequent electrolyte disorder encountered in hospitalized patients. Several studies have demonstrated that hyponatremia is a negative prognostic factor in different clinical scenarios. Noteworthy, not only severe and acute hyponatremia has been associated with an increased risk of mortality, but also moderate or even mild chronic hyponatremia may increase the risk of death. This has been demonstrated in different categories of patients, including cancer patients. There is growing evidence that both progression free survival and overall survival are significantly reduced in cancer patients with hyponatremia compared to patients with normonatremia. One important, and still open, question is whether the worse outcome associated with hyponatremia in cancer patients is directly attributable to the electrolyte disorder itself or might be a sign of the severity of the underlying disease. With regard to this point, some basic research studies suggested that low sodium concentration stimulates per se cancer cells proliferation and invasiveness. Recent clinical evidence appears to indicate that the correction of hyponatremia is an independent and favourable prognostic factor in cancer patients. Admittedly, robust confirmatory data from clinical practice are needed, in order to validate the hypothesis that cancer patients may die for hyponatremia and not just with hyponatremia.

**Keywords:** Hyponatremia, cancer, mortality, prognosis, vasopressin

## INTRODUCTION

Hyponatremia, which is the most frequent electrolyte disorder in hospitalized patients<sup>[1]</sup>, frequently occurs also in cancer patients at different stages of disease. For instance, a recent retrospective study, performed



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at a large University Hospital in Germany in inpatients receiving specialist palliative care, showed that the prevalence of hyponatremia was 38.7% (e.g., 275 out of 710 patients) and that low serum sodium concentration  $[\text{Na}^+]$  was associated with symptom severity<sup>[2]</sup>. Several studies have demonstrated that hyponatremia is a negative prognostic factor in different clinical scenarios. Noteworthy, not only severe and acute hyponatremia has been associated with an increased risk of mortality, but there is evidence that also moderate or even mild chronic hyponatremia may increase the risk of death. This has been shown for instance in a large cohort study, which included more than 50,000 inpatients at a teaching academic medical center. This study showed that mildly reduced serum  $[\text{Na}^+]$  was associated with an increased in-hospital mortality. In addition, each mmol/L reduction of serum  $[\text{Na}^+]$  increased the risk of death by 2.3%<sup>[3]</sup>. Among different clinical settings, hyponatremia has been associated with an increased risk of death in patients with heart failure<sup>[4-6]</sup>, acute myocardial infarction<sup>[7,8]</sup>, pneumonia<sup>[9]</sup>, cirrhosis<sup>[10,11]</sup>, renal failure<sup>[12]</sup>, pulmonary embolism<sup>[13]</sup>, intracerebral hemorrhage<sup>[14]</sup>, in the elderly<sup>[15]</sup>, in intensive care patients<sup>[16]</sup>, in patients undergoing surgery<sup>[17]</sup> or cardiovascular procedures<sup>[18]</sup>. An extensive meta-analysis, including more than 850,000 patients, of whom 17.4% with hyponatremia, confirmed an increased mortality rate associated with reduced serum  $[\text{Na}^+]$ <sup>[19]</sup>.

The literature addressing cancer patients indicated that hyponatremia is a negative prognostic factor also in this subset of patients. This chapter will review the published data, so far, with the exception of patients with lung cancer, which is the specific topic of another chapter.

## **HYPONATREMIA AS A PROGNOSTIC AND PREDICTIVE FACTOR IN CANCER PATIENTS**

Ten years ago Waikar *et al.*<sup>[7]</sup> published the results of a prospective cohort study, conducted in two teaching hospitals in Boston, MS, in which the association between serum  $[\text{Na}^+]$  and mortality was investigated. The main outcome measures were in-hospital 1-year and 5-year mortality of patients with hyponatremia vs those with normal serum  $[\text{Na}^+]$ . Patients with hyponatremia had higher in-hospital mortality rates either at 1 year and at 5 years, even when serum  $[\text{Na}^+]$  was only slightly reduced (130-134 mmol/L). Among the different clinical subgroups that were analyzed, the risk of in-hospital mortality was significantly higher in hyponatremic patients with metastatic cancer [hazard ratio (HR) 2.05, 95% confidence interval (CI): 1.67-2.53] compared to normonatremic patients.

Shortly after, another study addressed predictors of inpatients mortality in an acute palliative care unit at the M. D. Anderson Cancer Center of the University of Texas. Of the 500 cancer patients admitted, 124 (25%) died<sup>[20]</sup>. Hyponatremia was one of the multiple predictors of a negative outcome (HR 3.02, 95%CI: 1.76-5.17,  $P < 0.001$ ), together with younger age, hypernatremia, high blood urea nitrogen, high heart rate, high respiration rate, and supplemental oxygen use.

A retrospective analysis of patients admitted at the same Cancer Center during a three months period in 2006, aiming to correlate hyponatremia with 90-day mortality, was performed<sup>[21]</sup>. Serum  $[\text{Na}^+]$  was categorized into four groups, e.g., normonatremia (serum  $[\text{Na}^+]$  135-147 mmol/L), mild (130-134 mmol/L), moderate (120-129 mmol/L), and severe ( $< 120$  mmol/L) hyponatremia. In all hyponatremic groups the risk of mortality at 90 days was higher than in normonatremic patients (HR for mild, moderate, and severe hyponatremia: 2.04 (95%CI: 1.42-2.91;  $P < 0.01$ ); 4.74 (95%CI: 3.21-7.01;  $P < 0.01$ ), and 3.46 (95%CI: 1.05-11.44;  $P = 0.04$ ), respectively. Although the authors recognized limitations to the study (observational, retrospective study, inability to adjust for all comorbid conditions), and the fact that it has not been proven that hyponatremia correction can reduce mortality, these data further confirmed the clear relationship between hyponatremia and increased mortality in cancer patients.

An Italian study performed in Ancona analyzed 105 consecutive cancer patients, affected by gastrointestinal, lung, breast, female genital tract, renal, brain tumors, and sarcoma, hospitalized during a 6 month period<sup>[22]</sup>.

Median overall survival (OS) from the day of hospitalization was 50 days. Hyponatremic patients had a significantly reduced OS ( $P = 0.0255$ ) compared to normonatremic patients. In addition, the authors reported that the presence of metastases was associated with a reduced OS ( $P = 0.0418$ ). Similar results were obtained by Castillo *et al.*<sup>[23]</sup>, who analyzed a population of patients with lymphoma, breast cancer, colorectal cancer, small cell and non-small cell lung cancer. Hyponatremia was negatively associated with OS in all types of tumor, but the highest HRs were found in lymphoma (HR 4.5,  $P < 0.01$ ) and in breast cancer (HR 3.7,  $P < 0.1$ ).

In a retrospective cohort study, performed in a single center, 204 cancer patients affected by hyponatremia secondary to the syndrome of inappropriate anti-diuresis (SIAD), which is the most common cause of hyponatremia in oncology, were selected. Malignancies included lymphoma, leukemia, colorectal, breast, lung, pancreas, prostate, head and neck, bladder, esophagus, gastric cancer. About 75% of patients had malignancy-associated SIAD, whereas in roughly 25% SIAD was due to other etiologies (e.g., medications, pulmonary infections, pain or nausea). The authors found that patients with malignancy-associated SIAD had a significantly shorter median survival (58 days vs. 910 days,  $P < 0.001$ ). The authors hypothesized that the cause of SIAD in cancer patients might represent a useful prognostic factor<sup>[24]</sup>.

A correlation between hyponatremia and a negative outcome was found also in patients with terminal cancer. A retrospective observational study conducted in a tertiary hospital palliative care unit in the Republic of Korea reported that, in addition to serum C-reactive protein (HR 1.22;  $P < 0.001$ ) and Palliative Performance Scale (HR 0.69,  $P < 0.001$ ), serum  $[\text{Na}^+] \leq 125$  mmol/L was associated with a reduced survival time (HR = 1.91;  $P < 0.001$ ) among 576 terminally ill patients (pancreatic/hepatobiliary, gastric, colorectal, lung cancer)<sup>[25]</sup>.

In a retrospective study performed at a University Hospital in China, among patients affected by nasopharyngeal carcinoma, glioma or oral cancer, that had been subjected to radiotherapy and developed radiation-induced brain necrosis, the risk of progression (i.e., increase of edema area  $\geq 25\%$  on the MRI) was three-fold higher in patients with hyponatremia compared to those with normonatremia. Thus, the authors claimed that hyponatremia may be considered as a potential predictor for the progression of radiation-induced brain necrosis and recommended that hyponatremia is appropriately managed also in these patients<sup>[26]</sup>.

Other authors addressed their attention to a different subset of cancer patients, i.e., those who develop spontaneous tumor lysis syndrome, that induces acute uric acid nephropathy. This is a rare, yet potentially fatal complication in cancer patients, and it is important to determine the relevance of potential prognostic predictors. Although only 12 patients developed this condition among the 1,073 patients admitted with acute renal failure to a single hospital during a period of four years, hyponatremia and hypoalbuminemia on the first day of admission were the best predictors of poor prognosis<sup>[27]</sup>.

An interesting retrospective cohort study performed in a primary care setting in Copenhagen, Denmark, examined another issue, i.e., the predictive role of hyponatremia on the subsequent development of cancer. This type of analysis is facilitated in countries, like Denmark, which have a National Patient Registry. The authors showed that there is a level-dependent increased risk to develop cancer in patients with hyponatremia. The cumulative incidence increased in patients with mild (serum  $[\text{Na}^+] 130$ -135 mmol/L), moderate (125-129 mmol/L) or severe hyponatremia ( $< 125$  mmol/L) [HR 1.32 (95%CI: 1.26-1.39), 1.31 (95%CI: 1.17-1.47), 1.77 (95%CI: 1.39-2.24), respectively] at 12 months, compared to normonatremic subjects. When different cancers types were analyzed separately, this finding was confirmed in head and neck, pulmonary and gastrointestinal cancer<sup>[28]</sup>.

Some studies on the role of hyponatremia in cancer have addressed specific cancer types. With regard to renal cell carcinoma (RCC), 212 newly diagnosed patients with localized RCC undergoing nephrectomy were

recruited in a study aiming to examine the prognostic value of hematologic and biochemical parameters, and other tumor-related factors. Multivariate analyses showed that preoperative serum  $[\text{Na}^+]$  was an independent predictor of OS and disease-free survival, when considered either as a continuous variable or when patients were grouped based on a cut-off of serum  $[\text{Na}^+]$  of 139 mmol/L (median value). The estimates of 5-year OS were 67.6% (95%CI: 54.2-80.9) and 44.3% (95%CI: 32.8-55.8) for patients with serum  $[\text{Na}^+]$  above or below 139 mmol/L respectively<sup>[29]</sup>. A Danish study addressed patients with metastatic RCC, divided into two independent cohorts of 120 patients/each. In each cohort 20% and 14% of patients had hyponatremia. Patients with hyponatremia at baseline had a median OS of 5.5 and 4.8 months in the two cohorts, whereas patients with normonatremia at baseline had a median OS of 18.6 and 16.9 months, respectively<sup>[30]</sup>. In multivariate analysis, hyponatremia proved to be an independent prognostic factor (HR 1.90, 95%CI: 1.1-3.2,  $P = 0.014$ ), together with increased neutrophils (HR 1.75, CI: 1.1-2.8,  $P = 0.018$ ), lactate dehydrogenase  $> 1.5$  ULN (HR 2.09, 95%CI: 1.3-3.3,  $P = 0.002$ ), and number of metastatic sites (+3) (HR 1.92, 95%CI: 1.3-2.9,  $P = 0.003$ ). Finally, hyponatremia was significantly associated with lack of response to treatment in both cohorts. A more recent Japanese study confirmed that hyponatremia appears to be a powerful prognostic predictor in patients with metastatic RCC treated with tyrosine-kinase inhibitors following radical nephrectomy<sup>[31]</sup>. In this study both progression-free survival (PFS) and OS were significantly lower in hyponatremic patients (median 10.0 and 20.9 months, respectively) than in normonatremic patients (median 28.4 and 38.5 months, respectively).

Reduced serum  $[\text{Na}^+]$  was indicated as a negative prognostic marker also in patients with gastric cancer and bone marrow metastases [HR 4.57; 95%CI: 1.99-10.52;  $P < 0.001$ ]<sup>[32]</sup> and in patients with hepatocellular carcinoma<sup>[33]</sup>.

### WHY IS HYPONATREMIA ASSOCIATED WITH A WORSE OUTCOME IN CANCER PATIENTS?

Clinical data clearly indicate that hyponatremia may be viewed as a predictor of a negative outcome in cancer patients. Admittedly, one open question is whether the reduced PFS and OS, described by a number of publications, is directly attributable to the electrolyte disorder itself or might be a sign of the severity of the underlying disease. With regard to this point, a Belgian prospective study on hyponatremia in cancer patients, published almost 20 years ago, suggested that the increase mortality rate observed in cancer patients with hyponatremia (19.5% vs 6.3% in normonatremic patients) was not apparently due to reduced serum  $[\text{Na}^+]$ , thus indicating that hyponatremia was to be considered as a marker of general debility in advanced disease<sup>[34]</sup>. A retrospective review (entitled "Mortality and serum sodium: do patients die from or with hyponatremia?") of the medical records of patients admitted to a teaching hospital in Rochester, NY, for different pathologies and who died after developing hyponatremia, also suggested that the main determinant of the observed deaths was likely the severity of the underlying illness rather than the degree of hyponatremia<sup>[35]</sup>. Similarly, a retrospective study that included patients diagnosed with SIAD in a community hospital in Israel showed that long-term survival was determined by SIAD etiology rather than by hyponatremia severity<sup>[36]</sup>.

Recently, a study performed at two teaching hospitals in Italy and one teaching hospital in England demonstrated that serum  $[\text{Na}^+]$  normalization during first-line therapy is an independent prognostic factor for OS and PFS in patients with non-small cell lung cancer<sup>[37]</sup>. Similarly, normalization of serum  $[\text{Na}^+]$  was associated with a better prognosis in patients with metastatic RCC treated with everolimus<sup>[38]</sup>. These findings are in agreement with the results of a meta-analysis that analyzed articles reporting the outcome of patients with different diseases in which hyponatremia had been corrected. The meta-analysis indicated that any improvement of hyponatremia was associated with a reduced risk of overall mortality [HR = 0.57 (0.40-0.81)]<sup>[39]</sup>.

Anyway, this issue is still a matter of debate and prospective randomized studies in cancer patients with hyponatremia, aiming to evaluate whether correction of hyponatremia can counteract the progression of the disease, are necessary.

Interestingly, some basic research studies have evaluated whether a microenvironment with a low  $[Na^+]$  may affect cell proliferation and invasion ability. A study performed in prostate cancer cells *in vitro* demonstrated for instance that the exposure to a slightly hypertonic milieu induced a dormant state. Cell dormancy represents a limiting step of the metastatic process by preventing the proliferation of isolated cells outside the primary tumor. Conversely, the authors demonstrated that in the presence of a hypotonic milieu, obtained for instance by reducing  $[Na^+]$  in the culture medium, cell cloning significantly increased<sup>[40]</sup>. Another study showed that low  $[Na^+]$  reduced neuroblastoma cell adhesion and increased invasion ability<sup>[41]</sup>. A micro-array analysis was performed, in order to analyze the gene expression pattern of cells exposed to low  $[Na^+]$  compared to normal  $[Na^+]$ . Among the genes that had different expression levels in the presence of reduced  $[Na^+]$ , the heme-oxygenase 1 gene (HMOX-1), a marker of oxidative stress, was the gene with the greatest variation. In fact, HMOX-1 gene expression showed a 200-fold increase in cells exposed to low  $[Na^+]$ . Immunocytochemistry for HMOX-1 protein confirmed these results. It is known that oxidative stress favors carcinogenesis, cancer growth and invasion, angiogenesis, and overall creates a permissive environment for cancer cells<sup>[42]</sup>. Accordingly, selective inhibition of HMOX-1 has been proposed as a therapeutic target for cancer treatment<sup>[43]</sup>. Although additional studies are needed in order to confirm these data, in view of the above described results from basic research it can be hypothesized that also *in vivo* low  $[Na^+]$  might promote cancer cell progression through the same mechanisms. If so, then we might probably say that patients die not only with hyponatremia, but also for hyponatremia.

## CONCLUSION

In recent years evidence indicating that hyponatremia is a predictor of a worse outcome in cancer patients has accumulated. There is emerging evidence, mainly from basic research studies at this time, that hyponatremia may by itself increase the risk of mortality of patients, rather than being a simple bystander of the progression of the disease. However, robust confirmatory data from clinical practice are certainly needed in order to definitively validate the hypothesis that cancer patients may die for hyponatremia.

Meanwhile, the author is truly convinced that it is worth to correct hyponatremia in patients, including cancer patients, because of the overall beneficial effect on the quality of life, which includes clinical improvement, such as amelioration of neurocognitive and motor performance, reduced length of stay in the hospital and re-admission probability<sup>[44-46]</sup>.

## DECLARATIONS

### Authors' contributions

The author contributed solely to the article.

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.

### Conflicts of interest

The author declares that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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