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Original Investigation

Hyponatremia in Hospitalized Cancer Patients and Its Impact on Clinical Outcomes

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Background: Hyponatremia is the most common electrolyte abnormality in clinical practice, yet little is known about its frequency in patients with cancer or its impact on their clinical outcomes.

Study Design: Retrospective analysis of prospectively collected data.

Setting & Participants: Patients with cancer admitted to the University of Texas M.D. Anderson Cancer Center in 2006 for 3 months.

Predictor: Serum sodium levels categorized as eunatremia (serum sodium, 135-147 mEq/L) and mild (134-130 mEq/L), moderate (129-120 mEq/L), and severe (<120 mEq/L) hyponatremia.

Outcomes: (1) Length of hospital stay and (2) 90-day mortality.

Results: In 4,702 admissions in 3,357 patients with cancer, hyponatremia (serum sodium <135 mEq/L) was noted in 47% of admissions. It was mild in 36%, moderate in 10%, and severe in 1%. Hyponatremia was acquired during the hospital stay in 24%. Using the first admission data, mean length of stay was 5.6 ± 5.0 days for patients with eunatremia and 9.9 ± 9.2, 13.0 ± 14.1, and 11.5 ± 12.6 days for those with mild, moderate, and severe hyponatremia, respectively. The respective HRs in the multivariate Cox model for longer hospital stay, using patients with eunatremia as reference, were 1.92 (95% CI, 1.75-2.13; $P < 0.01$), 2.94 (95% CI, 2.56-3.45; $P < 0.01$), and 2.32 (95% CI, 1.32-4.00; $P = 0.01$). 283 (8.4%) deaths occurred during 90 days, and in the multivariate model, the respective HRs for 90-day mortality for mild, moderate, and severe hyponatremia were 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; $P = 0.04$). These findings were consistent when analyses were repeated with sodium levels in tertiles.

Limitations: Observational study, retrospective, inability to adjust for all comorbid conditions.

Conclusion: Hyponatremia in patients with cancer is associated with longer hospital stay and higher mortality. Whether long-term correction of hyponatremia would improve these outcomes remains to be determined.

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INDEX WORDS: Low serum sodium; hyponatremia; hypo-osmolality; cancer; risk factors; outcomes; mortality; morbidity; length of hospital stay; health care cost.

Editorial, p. 168

The concentration of serum sodium is tightly regulated, and a level <135 mEq/L constitutes hyponatremia.[1] Often, the presence of hyponatremia indicates excess total-body water in relation to sodium.[1,2] Hyponatremia is seen in various medical conditions, such as heart, liver, and kidney failure; malignancies; and with the use of medications.[1,2] It also is the most frequently observed electrolyte abnormality in hospitalized patients and is reported to be associated with higher morbidity and mortality.[3,4]

A large body of literature is available for hyponatremia in patients with noncancer conditions, but very little is known about hyponatremia in patients with cancer, especially its frequency or impact on clinical outcomes.[4-8] Cancer is a common diagnosis, considered the leading cause of worldwide mortality, and consumes a large share of the health care budget.[9] The objective of this study was to determine the frequency and severity of hyponatremia in patients with cancer admitted to the hospital and examine its effect on length of stay and mortality. Data were collected prospectively for 3,357 patients admitted to The University of Texas M.D. Anderson Cancer Center (MDACC) on 4,702 occasions during a 3-month period in 2006. Based on this analysis, we report a high frequency of hyponatremia in hospitalized patients with cancer and a strong and independent association between hyponatremia and longer length of stay and higher mortality.

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METHODS

Study Design and Participants

The Institutional Review Board at MDACC approved the prospective collection of data. Data were collected into an electronic database for all patients admitted to MDACC for 3 months (May-July 2006). An admission was defined as a stay longer than 23 hours in the hospital that included midnight. The reference range for serum sodium at MDACC laboratory is 135-147 mEq/L. Hyponatremia was defined as serum sodium level <135 mEq/L. For clinical classification of the severity of hyponatremia, serum sodium levels were grouped, as has been reported before, into eunatremic (135-147 mEq/L), mildly hyponatremic (130-134 mEq/L), moderately hyponatremic (120-129 mEq/L), and severely hyponatremic (<120 mEq/L).[4] Of 3,357 patients, 1,031 (30.7%) were hospitalized under surgical services; 2,276 (67.8%), under medical oncology; and 50 (1.5%), under rehabilitation services. The first admission data were used for all analyses.

Statistical Analysis

To analyze the influence of hyponatremia on length of hospital stay and mortality rate, patients were grouped according to the clinical definition of hyponatremia and verified using tertile of serum sodium; the lowest serum sodium level during patients' first hospital stays was used for this purpose. The binning function in the Statistical Package for Social Science (SPSS Inc, version 16.0, www.spss.com) program was used to generate default cutoff values for serum sodium: 1st tertile, 137-147 mEq/L; 2nd tertile, 134-136 mEq/L; and 3rd tertile, <134 mEq/L. Patient and clinical characteristics were tabulated and compared among the clinically defined
groups with χ^2 test. Numbers of days of hospital stay among the 3 groups were compared by analysis of variance with multiple comparisons adjusted using the Tukey-Kramer method or Games Howell test, the latter for groups with unequal variance. Time to discharge was measured from the date of admission to the date of discharge. Patients who died before discharge were censored at their dates of death. Time to 90 day mortality was measured from the date of first admission to the date of death or last follow-up at 90 days. The Kaplan-Meier product-limit method was used to estimate survival outcomes of all patients by serum sodium groups and comparisons among groups were achieved with the log-rank statistic. For Cox proportional hazard analysis, the proportional hazards assumption was tested with examination of Pearson correlation between Schoenfeld residuals and the rank of survival time for cases that progressed to an event. The models were fit to determine the association of serum sodium levels with time-to-event outcomes after adjusting for other patient and clinical characteristics. Results are expressed as hazard ratio (HR) and 95% confidence interval (CI). For all multivariate analyses, clinically relevant variables with $P < 0.05$ in univariate analyses were included in the final multivariate models for adjustment. In the Cox model for length of stay, discharge was considered as the event and time to hospital discharge was modeled. A patient would be censored if death occurred within the hospital stay. Because the HR we obtained was the hazard for being discharged, the reciprocals of those values were used and reported as HR for not being discharged or HR for longer hospital stay. We also compared survival in hyponatremic patients who showed improvement in status compared with those who had worsening of hyponatremia. Patients who were hyponatremic on admission were included in this analysis, and improvement was defined if the in-patient serum sodium level increased to higher than at admission, whereas a lower or unchanged serum sodium level was defined as no improvement. $P < 0{\cdot}05$ was considered statistically significant; all tests were 2 sided. Statistical analyses were carried out by using SPSS (version 16.0) and SAS, version 9·1 (SAS Institute Inc, www.sas.com).

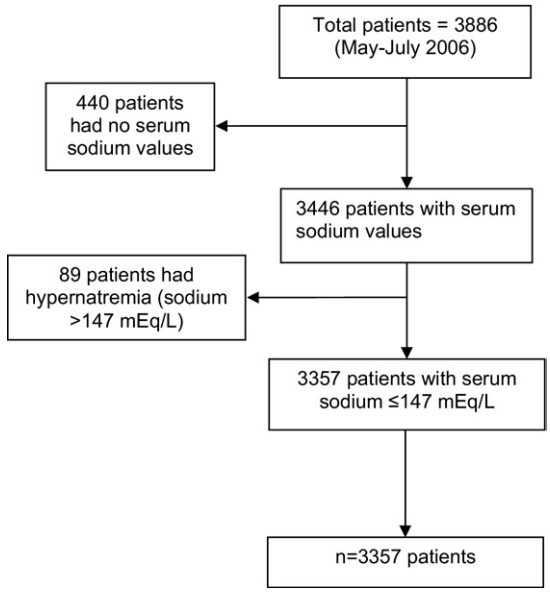

Figure 1. Flow chart of methodology for obtaining the first admission study data.

RESULTS

Patient Characteristics

Between May and July 2006, a total of 3,886 patients were admitted 5,384 times (Fig 1). After excluding patients with missing serum sodium values (11%) and those with hypernatremia (3%), 3,357 (86%) patients were available for final analysis. The group missing serum sodium levels not included in the analysis did not differ from the study population in general characteristics except for sex and cancer types (Table 1). There was a higher proportion of women in those excluded from the study; however, sex did not have an effect on the outcome analysis reported here. Table 1 lists demographic details of the study population as a whole and by groups of serum sodium levels.

Frequency, Severity, and Correction of Hyponatremia

The hyponatremia rate analyzed for the first hospitalization was 47%, and that included 23% at admission and 24% acquired in the hospital. Severity of hyponatremia based on clinical definition was mild in 36%, moderate in 10%, and severe in 1%. Patients with hematologic malignancies tended to have mild hyponatremia, whereas it was moderate to severe in patients with head-and-neck and gastrointestinal cancer (Table 1). Correction of hyponatremia, in other words, reaching ≥135 mEq/L of sodium, was noted in 70% of patients after admission. In 30% of patients admitted with hyponatremia, there was an increase in

Table 1. Patient Characteristics

	Excluded Patients	Included Patients	*P*	Eunatremia (135-147 mEq/L)	Hyponatremia (<135 mEq/L) Mild (134-130 mEq/L)	Moderate (129-120 mEq/L)	Severe (<120 mEq/L)	*P*[a]
No.	440	3,357		1,761	1,235	342	19	
Age (y)	55 ± 16	56 ± 17	0.2	55 ± 17	57 ± 16	59 ± 15	60 ± 18	<0.01
Men	174 (40)	1,742 (52)	<0.01	883 (50)	665 (54)	185 (54)	9 (47)	0.2
Race			0.6					0.7
White	333 (76)	2,442 (73)		1,283 (73)	890 (72)	253 (74)	16 (84)	
Black	37 (8)	323 (10)		178 (10)	117 (10)	28 (8)	0 (0)	
Hispanic	50 (11)	432 (13)		221 (13)	167 (14)	41 (12)	3 (16)	
Others[b]	20 (5)	160 (4)		79 (4)	61 (4)	20 (6)	0 (0)	
Primary cancer								
Hematologic malignancies[c]	11 (3)	587 (17)	<0.01	315 (18)	223 (18)	47 (14)	2 (11)	0.3
Genitourinary	92 (21)	614 (18)	0.2	334 (19)	224 (18)	55 (16)	1 (5)	0.3
Gastrointestinal	25 (6)	488 (15)	<0.01	217 (12)	204 (17)	64 (19)	3 (16)	<0.01
Head, neck, & lung	91 (21)	538 (16)	0.02	272 (15)	186 (15)	71 (21)	9 (47)	<0.01
Others[d]	211 (49)	1,130 (34)	<0.01	623 (36)	398 (32)	105 (31)	4 (21)	0.02

Note: Continuous variables given as mean ± standard deviation; categorical variables, as number (percentage).
[a]Overall *P* values.
[b]Include Asian, Filipino, Pacific Islander, and American Indian.
[c]Include leukemia, lymphoma, and myeloma.
[d]Include melanoma, breast, and thyroid malignancies.

serum sodium values, but values did not reach the 135-mEq/L level.

Outcome Analyses

Length of Stay

Overall length of stay for the first admission irrespective of serum sodium levels was 7.7 ± 8.2 days. The length of stay of patients with hyponatremia was significantly higher at 10.2 ± 10.2 days compared with 5.6 ± 5.0 days in patients with eunatremia ($P < 0.01$). When length of stay was analyzed by the clinical definition for hyponatremia severity, patients in the mild- and moderate-hyponatremia groups had significantly longer lengths of hospital stays; 9.9 ± 9.2 and 13.0 ± 14.1 days, respectively, compared with 5.6 ± 5.0 days for patients in the reference category of eunatremia (Fig 2A). The severe-hyponatremia group, which had fewer patients, had a mean stay of 11.5 ± 12.6 days but did not significantly differ statistically from the rest of the groups. Analyzed using tertile of serum sodium, there was a progressive and significant increase in length of stay in the second and third compared with the first tertile (Fig 2B). Similarly, using the multivariate model in the Cox analysis adjusted for age, type of malignancy, chemotherapy, antibiotic use, and serum creatinine, calcium, potassium, hematocrit, and blood glucose values (Table 2), HRs for longer hospital stay in patients with mild (HR, 1.92; 95% CI, 1.75-2.13; $P < 0.01$), moderate (HR, 2.94; 95% CI, 2.56-3.45; $P < 0.01$), and severe (HR, 2.32; 95% CI, 1.32-4.00; $P = 0.01$) hyponatremia was significantly higher than in patients with eunatremia (Table 2). When multivariate analysis was repeated using tertile of serum sodium levels, there was still a stepwise and significant increase in HRs for longer hospital stays (Table 2).

Mortality

There were 283 (8.4%) deaths during the 90 days (71, 121, 87, and 4 in the groups with eunatremia and mild, moderate, and severe hyponatremia, respectively). Kaplan-Meier survival analysis showed significantly decreased rates of survival in patients with mild, moderate, and severe hyponatremia compared with patients with eunatremia ($P < 0.01$; Fig 3A). Similar results were noted when data were reanalyzed using tertile of serum sodium values (Fig 3B). In the Cox proportional hazard models, serum sodium levels, whether introduced as a continuous or categorical variable, showed significant influence on 90-day mortality. After adjusting for age, type of malignancy, chemotherapy, antibiotic use, and serum creatinine, calcium, potassium, hematocrit, and blood glucose values, HRs for 90-day mortality in patients with mild (HR, 2.04; 95% CI, 1.42-2.91; $P < 0.01$), moderate (HR, 4.74; 95% CI, 3.21-7.01; $P < 0.01$), and severe (HR, 3.46; 95% CI, 1.05-11.44; $P = 0.04$) hyponatremia were significantly higher than for eunatremic patients (Table 2). Reanalyzed using

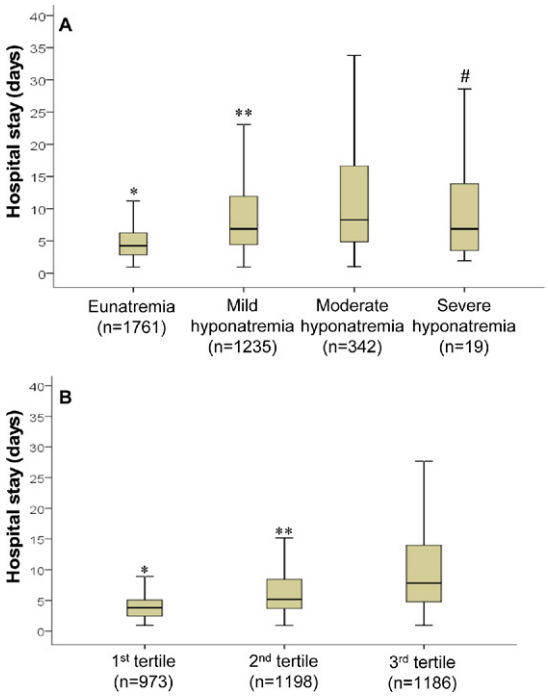

Figure 2. Length of hospital stay in patients. (A) Grouped by clinically defined groups of serum sodium levels (mild hyponatremia, serum sodium of 130-135 mEq/L; moderate hyponatremia, 120-129 mEq/L; and severe hyponatremia, <120 mEq/L). *Significantly different from mild ($P < 0.01$) and moderate ($P < 0.01$) hyponatremia. **Significantly different from moderate ($P < 0.01$) hyponatremia group. #No difference compared with eunatremia ($P = 0.2$) or mild ($P = 0.9$) or moderate ($P = 0.9$) hyponatremia groups. (B) Grouped by serum sodium tertile (1st tertile, serum sodium of 137-147 mEq/L; 2nd tertile, 134-136 mEq/L; and 3rd tertile, <134 mEq/L). *Significantly different from 2nd ($P < 0.01$) and 3rd ($P < 0.01$) tertiles of hyponatremia. **Significantly different from 3rd ($P < 0.01$) tertile of hyponatremia. *P* values signify analysis of variance and Games-Howell post hoc analysis; n = number of patients.

tertile of serum sodium values, this finding for 90-day mortality risk was confirmed (Table 2). Moreover, the HR for 90-day mortality was lower in the category of patients who had an increase in serum sodium levels from admission compared with the category of patients who did not have an increase (HR, 2.09; 95% CI, 1.40-3.15; $P < 0.01$ after adjusting for all variables listed in Table 2).

DISCUSSION

In our analysis, the hyponatremia rate in patients with cancer admitted for the first time to the hospital was 47%. Severity of hyponatremia was mild in 36% and moderate to severe in 11%. There also was a strong and independent inverse relationship between serum sodium levels and hospital stay and mortality.

The reported frequency of hyponatremia in patients admitted to the hospital varies widely due to variations in the definitions of hyponatremia used and whether hyponatremia after admission was included in the analysis.[4,10-13] Most studies have used the low end of the reference range for serum sodium, <135 mEq/L, as the cutoff value, with a reported rate of hyponatremia at admission ranging from 5.5%-28%.[4,10,11] Albeit this is widespread, these studies provided a range of estimates for the frequency of hyponatremia in patients hospitalized for general medical conditions. However, few studies to our knowledge have examined the frequency of hyponatremia in patients with cancer. Our analysis may be the first in this regard to report a higher frequency of hyponatremia in hospitalized patients with cancer. Although the cause of hyponatremia in our patients is not clear from our present database, several malignancies are associated with the syndrome of inappropriate antidiuretic hormone secretion. Also, many chemotherapeutic agents and often the accompanying hydration protocols can cause or aggravate hyponatremia. Malnutrition can be a contributing factor to hyponatremia in this population and needs careful analysis to discern its role. Moreover, cancer is common in elderly patients who often have other medical comorbid conditions that in turn can contribute to hyponatremia. Furthermore, cancer-related pain, especially when treated with morphine derivatives, can potentiate antidiuretic hormone and thus contribute to the higher frequency of hyponatremia in these patients.

We chose serum sodium tertile and the clinical definition of hyponatremia for statistical analyses. Both analyses provided similar results that the severity of hyponatremia is linked to length of hospital stay and mortality. Although studies have reported similar findings in patients with noncancer conditions,[3,4,11,12] our finding of a strong and independent association between hyponatremia and mortality in patients with cancer is of importance because the high mortality in patients with cancer is considered due at least in part to several potentially treatable medical comorbid conditions that are not directly related to cancer. An analysis assessing the financial burden of hyponatremia in patients without cancer indicated that even a single-day increase in hospital stay is associated with a significant increase in hospital cost, which was estimated to be $2,289 per day per admission.[11] Thus, part of the cost of patients with cancer staying in the hospital could be attributed to hyponatremia because in our study, nearly half of our hospitalized patients with cancer had hyponatremia, and it was associated with on average of 5 additional days of hospital stay. The slow and unpredictable correction of hyponatremia with current therapies may account in part for the longer hospital stay. Studies to examine whether the use of recently available V2-receptor antagonists, shown to produce a steady and predictable correction of hyponatremia, would decrease the length of hospi-

Table 2. HRs for Longer Hospital Stay and 90-Day Mortality for Serum Sodium Levels

	Time to First Discharge		Time to 90-d Mortality	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Clinical Definition for Hyponatremia Severity				
Serum sodium[a]				
Eunatremia (135-147 mEq/L)	1.00 (reference)		1.00 (reference)	
Mild hyponatremia (130-135 mEq/L)	1.92 (1.75-2.13)	<0.01	2.04 (1.42-2.91)	<0.01
Moderate hyponatremia (120-129 mEq/L)	2.94 (2.56-3.45)	<0.01	4.74 (3.21-7.01)	<0.01
Severe hyponatremia (<120 mEq/L)	2.32 (1.32-4.00)	0.01	3.46 (1.05-11.44)	0.04
Age (/1-y)	1.003 (1.00-1.005)	0.1	1.01 (0.99-1.02)	0.2
Malignancies (hematologic vs nonhematologic)	1.05 (0.93-1.20)	0.4	1.28 (0.90-1.81)	0.2
Chemotherapy (yes vs no)	1.59 (1.43-1.79)	<0.01	1.08 (0.77-1.50)	0.7
Antibiotic use (yes vs no)	2.08 (1.89-2.32)	<0.01	1.94 (1.25-3.02)	<0.01
Serum creatinine[b] (/1-mg/dL)	1.04 (0.98-1.11)	0.2	1.22 (1.08-1.38)	<0.01
Serum calcium[b] (/1-mg/dL)	0.94 (0.88-1.02)	0.2	1.04 (0.84-1.31)	0.7
Serum potassium[b] (/1-mEq/L)	1.14 (1.05-1.20)	<0.01	1.20 (1.02-1.43)	0.03
Hematocrit[b] (/1%)	0.98 (0.97-0.99)	<0.01	0.90 (0.87-0.94)	<0.01
Blood glucose[b] (/1-mg/dL)	1.01 (1.00-1.01)	0.05	1.003 (1.001-1.006)	0.02
Tertile of Serum Sodium Level				
Serum sodium[a]				
1st tertile (137-145 mEq/L)	1.00 (reference)		1.00 (reference)	
2nd tertile (134-136 mEq/L)	1.78 (1.58-2.01)	<0.01	2.19 (1.32-3.63)	0.01
3rd tertile (<134 mEq/L)	3.21 (2.83-3.62)	<0.01	3.51 (2.18-5.67)	<0.01
Age (/1-y)	1.003 (1.001-1.006)	0.01	1.01 (1.00-1.02)	0.03
Malignancies (hematologic vs nonhematologic)	1.03 (0.91-1.17)	0.6	1.33 (0.94-1.89)	0.1
Chemotherapy (yes vs no)	1.68 (1.50-1.88)	<0.01	1.02 (0.73-1.42)	0.9
Antibiotic use (yes vs no)	2.01 (1.79-2.24)	<0.01	1.31 (0.90-1.91)	0.2
Serum creatinine[b] (/1-mg/dL)	1.05 (0.98-1.12)	0.2	1.21 (1.06-1.38)	0.01
Serum calcium[b] (/1-mg/dL)	0.97 (0.90-1.04)	0.4	1.36 (1.12-1.66)	0.01
Serum potassium[b] (/1-mEq/L)	1.13 (1.06-1.21)	<0.01	1.14 (0.95-1.36)	0.2
Hematocrit[b] (/1%)	0.985 (0.977-0.994)	0.01	0.92 (0.89-0.95)	<0.01
Blood glucose[b] (/1-mg/dL)	1.01 (1.01-1.02)	0.03	1.005 (1.002-1.007)	<0.01

Note: Based on multivariate Cox proportional hazard analysis involving 3,357 patients.
Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]Lowest serum sodium level during hospital stay.
[b]Mean of all values during hospital stay.

tal stay and hence hospital costs are of considerable interest.[14] Such a study also will help us discern the cause-and-effect relationship between hyponatremia and associated adverse clinical outcomes.

The adjusted 90-day mortality rate was significantly higher in our patients with hyponatremia (Fig 3; Table 2). We chose 90 days because adequate outcome end points had occurred during this period. Previous studies have reported similar strong and independent associations between hyponatremia and mortality.[4,11] Although mortality correlates with severity of hyponatremia, it could be argued that worsening of underlying disease could have worsened both hyponatremia and mortality. Alternatively, because adjusting for confounding variables and comorbid conditions did not attenuate the strong inverse relationship between hyponatremia and mortality, the higher mortality with hyponatremia could be argued to be independent of comorbid conditions.[11,12] Supporting this possibility is the finding in our study and that of Waikar et al[4] that resolution of admission hyponatremia during hospitalization is associated with better survival. A counterpoint is that easy correction of hyponatremia may demarcate less sick patients and hence better survival. Although the cause-and-effect relationship between hyponatremia and mortality is unsettled, there is unanimity in studies across the disease spectrum for the strong association between hyponatremia and mortality, now including cancer. The critical question is whether correction and maintenance of serum sodium levels to near the reference range through an intervention such as V2-receptor

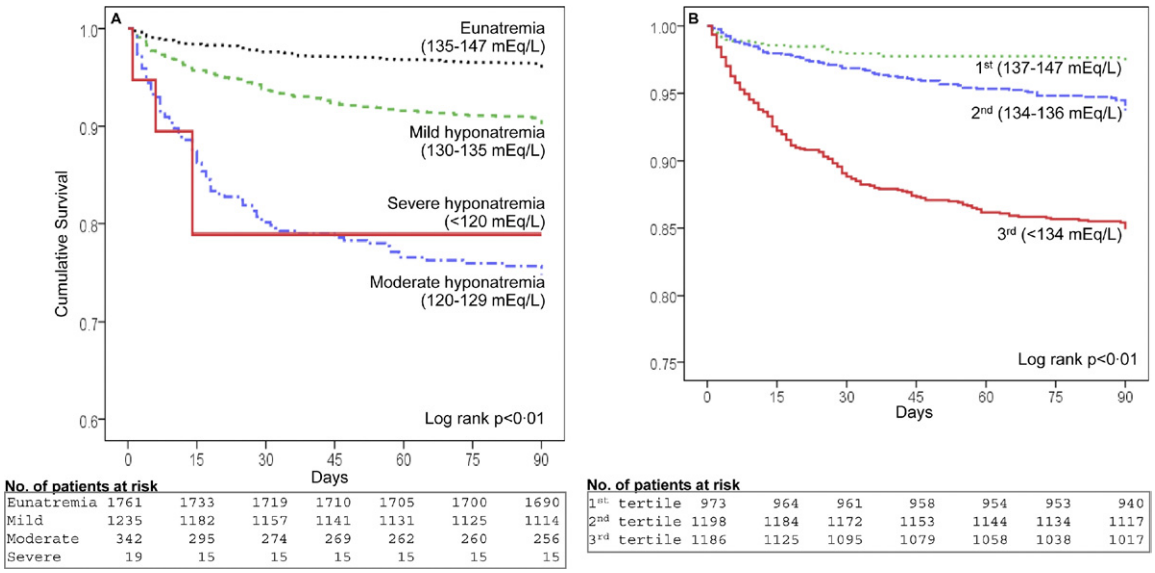

Figure 3. Kaplan-Meier survival analysis for 90 days: patients were grouped using the lowest serum sodium levels during their hospital stays, grouping by (A) clinical classification of hyponatremia and (B) tertile.

antagonist will alter the mortality of these patients. This is all the more logical when one considers the experimental evidence for the effect of long-term hyponatremia on perturbations in acid-base balance and serum aldosterone levels and the emerging clinical data for the deleterious effects of long-term hyponatremia on distant organs, such as bone.[15,16] That hyponatremia may have far-reaching metabolic and possible genetic consequences on cells beyond the immediate osmolar milieu supports the hypothesis that long-term hyponatremia through metabolic and genetic perturbations may cause deleterious effects on cells and tissues, leading to higher mortality.

The strengths of our study are that data were collected prospectively using a systematic approach and were validated before analysis. Most patients admitted to the hospital during the study period were included in the analysis. Data are collected from a large comprehensive cancer center with wider representation of patients with cancer. The study was able to track hospital correction of hyponatremia and compare outcomes with patients with uncorrected hyponatremia. Clinical outcomes are based on hard end points. For statistical analysis, we undertook alternate approaches and sensitivity analyses. One of the main limitations of our study is that our data do not provide details for the causes of hyponatremia in this population. Although prospectively collected, the analysis is still based on a database and hence the findings and hypotheses generated here are to be confirmed in prospective studies. Our inability to incorporate all patient characteristics, comorbid conditions, and severity of comorbid conditions might have led to some unmeasured confounding in multivariate analyses. However, we included common variables relevant to the survival of the cancer population, including other electrolyte abnormalities that often accompany hyponatremia.

In summary, our report on hyponatremia in patients with cancer indicates a higher rate of hyponatremia in this patient population and suggests a significant and independent association between hyponatremia and longer hospital stay and higher mortality. Patients who had correction of hyponatremia in the hospital had a decreased risk of mortality. Future interventional studies are warranted to determine whether long-term correction of hyponatremia, especially with the recently available oral V2-receptor antagonist, will modify clinical outcomes in these patients.[17]

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