

Hypernatremia at admission predicts poor survival in patients with terminal cancer: a retrospective cohort study

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Abstract

Background Although palliative care providers, patients, and their families rely heavily on accurate prognostication, the prognostic value of electrolyte imbalance has received little attention. **Methods** As a retrospective review, we screened inpatients with terminal cancer admitted between January 2017 and May 2019 to one hospice-palliative care unit. Clinical characteristics and laboratory results were obtained from medical records for multivariable Cox regression analysis of independent prognostic factors. **Results** Of the 487 patients who qualified, 15 (3%) were hypernatremic upon admission. Median survival time was 26 days. Parameters associated with shortened survival included male sex, advanced age (> 70 years), lung cancer, poor performance status, elevated inflammatory markers, azotemia, impaired liver function, and hypernatremia. In a multivariable Cox proportional hazards model, male sex (hazard ratio [HR]=1.53, 95% confidence interval [CI]: 1.15–2.04), poor performance status (HR=1.45, 95% CI: 1.09–1.94), leukocytosis (HR=1.98, 95% CI: 1.47–2.66), hypoalbuminemia (HR=2.06, 95% CI: 1.49–2.73) and hypernatremia (HR=1.55, 95% CI: 1.18–2.03) emerged as significant predictors of poor prognosis. **Conclusion** Hypernatremia may be a useful gauge of prognosis in patients with terminal cancer. Further corroborative studies of large scale and prospective design are needed.

Background

Accurately predicting the prognosis of patients with terminal cancer is helpful to clinical decisions and management plans of palliative care workers. Over the past few decades, a number of studies have been conducted in this setting to identify patient-related prognostic factors of potential use, such as performance status, anorexia-cachexia, delirium, and dyspnea [1]; and various laboratory abnormalities have similarly been identified. Serum markers of systemic inflammation (i.e., leukocytosis, lymphopenia, C-reactive protein (CRP) elevation, and inflammatory cytokines) are well-known indices of poor survival [2]. Biomarkers of hepatic dysfunction (elevated lactate dehydrogenase [LDH], prolonged international normalized ratio [INR], hypoalbuminemia) and renal impairment (serum urea, creatinine, and uric acid elevations) have been implicated as well [2, 3].

Electrolyte abnormalities are common among the terminal cancer patients and represent yet another significant means of predicting survival [4]. In an earlier study, 79 % of such patients showed at least one electrolyte abnormality upon referral for palliative care [5]. Hyponatremia is the most frequent electrolyte disorder of patients with terminal cancer, having dire consequences [6]. In fact, its early detection and proper correction may actually prolong median survival time [7]. In cancer patients, hypernatremia caused by various etiology such as sodium overloading by fluid, excessive loss of free water, the use of osmotic agents, decreased release of antidiuretic hormone and renal dysfunction to ADH [8]. Although hypernatremia is otherwise a rarity in these patients, offering little opportunity for study, there is evidence to suggest that the prognostic ramifications again are negative due to a failure of feedback to compensate the imbalance [9, 10]. Potassium imbalance is also a highly prevalent electrolyte disorder. Especially in cancer patients, hypokalemia often presents in conjunction with hyponatremia and hypomagnesemia [4]. According to some, hyperkalemia is a prognostically unfavorable determinant, but

this view remains controversial [11, 12]. Research on the prognostic utility of other electrolyte disorders including hypercalcemia and hypermagnesemia, has likewise proved inconclusive [5, 13].

The present study was undertaken to assess the prevalence of electrolyte imbalance in terminally ill cancer patients, investigating the potential prognostic significance.

Methods

As a retrospective review, we examined medical records of 515 patients admitted to the palliative care unit of Incheon regional cancer center between January 2017 and May 2019. All participants were terminally ill with cancer and were not expected to survive beyond 6 months by clinical decision of medical oncologist and surgeon [14]. Ultimately, 10 patients who lacked serum electrolyte data and 18 patients transferred from other medical institutions were excluded, leaving 487 patients eligible for final analysis. In addition, patients who had no survival information available due to discharge to home or other institutions were censored (n=19). The institutional review board of Gachon University Gil Medical Center approved this study (GCIRB2019-149), waiving the need for informed patient consent as designed.

Electronic medical records provided the following patient data: age, sex, primary cancer site, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), evidence of active infection, survival times, and laboratory diagnostic results. ECOG-PS is a scale (0–4) used to assess physical ability. On day of admission, an experienced member of the palliative care team, including physicians and registered nurses, scored each patient functionally. Survival time was defined as the period from admission-day blood testing (electrolytes included) to day of death. Laboratory testing on day of admission included total white blood cell (WBC) count with differential, hemoglobin, platelet count, serum creatinine, serum albumin, total bilirubin, international normalized ratio (INR), CRP, serum sodium, and potassium. Active infection was determined based on the use of antibiotics.

Statistical analysis

Descriptive data were expressed as medians and numbers of subjects. Kaplan-Meier method and log-rank test were invoked to measure differences in survival times across all patient characteristics, using Cox proportional hazards models to identify independent predictors of survival in univariable and multivariable analyses. Variables showing significance ($p < 0.05$) in univariable analysis served for final multivariable analysis. A two-tailed $p < 0.05$ was deemed significant. All computations were driven by standard software (Stata SE v9.2; StataCorp, College Station, TX, USA).

Results

A total of 487 patients (men: 268, 55%; women: 219, 45%) with terminal cancer qualified for study participation. Baseline clinical characteristics of the study population are shown in **Table 1**. Median age was 70 years. The most common type of malignancy was cancer of the gastrointestinal tract (127 patients, 26.1%), followed by hepatopancreatobiliary cancer (118 patients, 24.2%). ECOG-PS scores 3 and

4 were recorded in 38.8% and 37.6% of patients, respectively. Median values of abnormal laboratory parameters were as follows: hemoglobin 10.1 g/dL, CRP 5.2 mg/dL, and sodium 134 mEq/L. The median survival time overall was 26 days.

Table 2 shows the survival time according to characteristics of participants. Advanced age (>70 years), male sex, lung cancer, poor performance status, leukocytosis, neutrophilia, lymphopenia, thrombocytopenia, azotemia, hypoalbuminemia, hyperbilirubinemia, prolonged prothrombin time (PT)-INR, elevated CRP, and hypernatremia were factors associated with significantly shorter median survival time than the counterparts.

Kaplan-Meier survival curves plotted by serum sodium level are depicted in **Figure 1**. Hypernatremia patients survived shorter than those with eunatremia or hyponatremia ($p<0.001$), whereas difference in survival time between eunatremic and hyponatremic patients were not significant.

Table 3 presents independent prognostic factors identified from the Cox proportional hazards models. Multivariable analysis revealed that various parameters, including male sex (HR=1.53; $p=0.004$), poor ECOG-PS (HR=1.45, $p=0.011$), leukocytosis (HR=1.98, $p<0.001$), hypoalbuminemia (HR=2.06, $p<0.001$), and hypernatremia (HR=1.55, $p=0.002$), were significantly associated with poor survival.

Discussion

Findings of the present study indicate that in terminally ill cancer patients with hypernatremia (vs. eunatremia or hyponatremia), the prognosis is demonstrably poor. These results are aligned with outcomes of previous studies, offering added support. Based on a group of 259 cancer patients referred for palliative care, Alsirafy et al. encountered shorter median survival (8 days) and higher mortality (68%) in those with hypernatremia than in hyponatremic or eunatremic counterparts [10]. However, multivariable analysis of well-known prognostic factors in terminal cancer patients was not done. Our data indicate that the association between hypernatremia and poor survival remains robust after controlling for other predictors of survival.

Salahudeen et al. have also reported poor clinical outcomes involving higher mortality, longer hospitalization, and greater hospital expense in patients with hypernatremia [9]. There were some differences from our cohort of terminal patients whose life expectancies were roughly 6 months. They examined subjects admitted to a comprehensive cancer center with any stage of disease; and their focus was on iatrogenic hypernatremia, because baseline hypernatremia contributed so few patients. In our investigation, laboratory testing took place on day of admission, aimed at existing rather than acquired hypernatremia. Hence, this is perhaps the first effort to explore the prognostic utility of spontaneous hypernatremia in terminally ill cancer patients.

The prevalence of hypernatremia in patients with terminal cancer is unclear. Salahudeen and colleagues found that hypernatremia in cancer patients increased from 0.2% on admission to 2.6% during the course of hospitalization [9]. Another study has also indicated that 8.5% of adult cancer patients referred for

palliative care are hypernatremic [10]. Similar to prior studies, we recorded a 3% prevalence of hypernatremia.

Little is known of the specific mechanism by which hypernatremia worsens survival, but there is at least one plausible explanation. Hypernatremia is generally induced by the loss of electrolyte-free water. Physiologic feedback mechanisms, such as thirst and antidiuretic hormone (ADH) release, are then promptly activated to increase water intake and minimizing additional free water loss. In a healthy population, elevated serum sodium levels return to normal range accordingly [12]. However, feedback dysfunction in patients with terminal cancer may impede or prevent normalization of serum sodium concentrations, and many patients with terminal cancer are faced with non-replenishment of water lost through excessive sweating, vomiting, diarrhea, and nasogastric drainage [15]. Impaired response to thirst due to diminished mental faculties or poor oral intake and subsequent dehydration may induce hypernatremia in such patients outside hospital environments. Still, there is virtually no research on hypernatremia in cancer patients. Retrospective studies of older adult patients and critically ill patients admitted to intensive care units would be helpful to understand this problem in the context of terminal cancer [16, 17]. Mental debilitation and poor oral intake create rapid declines in their general conditions [18]. Although causality between hypernatremia and deteriorating general conditions remain in question, hypernatremic patients are extremely ill and less inclined to survive.

Certain prognostic factors, namely poor functional status, leukocytosis, and hypoalbuminemia, are well documented in past reports, but the data on effects of hyponatremia have been inconsistent. Several earlier endeavors have shown the negative prognostic aspect of hyponatremia in a variety of cancers [19, 20]. Yoon et al. have also demonstrated a relation between hyponatremia and shorter survival time in terminally ill cancer patients [21]. However, another study has failed to support this relation in Korean patients with terminal cancer entering a hospice unit, although hampered by a relatively short median survival time (9.5 days) [22]. To our knowledge, the present analysis offers the most fully controlled results in a comparable setting, adjusted for potential confounders. Also, our subjects survived longer than those in previous studies. Even so, we did not find hyponatremia predictive of poor survival under these conditions. Further prospective studies to explore the prognostic significance of hyponatremia are nevertheless warranted.

At present, evidence of the prognostic value of potassium disorders is sparse. Cui et al. have observed an association between serum potassium level and survival time, but significance was not reached in multivariable analysis [23]. In our study, hyperkalemia similarly did not emerge from multivariable analysis as a significant predictor of poor prognosis. One retrospective study conducted in Taiwan cites a serum potassium level $>5\text{mg/dL}$ as an objective index of short-term survival (7 days) in patients with advanced cancer [11]. Still other researchers have found no prognostic significance attached to potassium imbalance [2,22].

There are acknowledged limitations to interpreting the results of our study. First, the cohort is representative of a single center only, and the number of hypernatremic patients was small. Given the

prevalence of hypernatremia in terminal cancer patients, large-scale multicenter investigations would be helpful to determine the actual prognostic import of hypernatremia under such circumstances. Another drawback is the lack of sequential or interventional data on serum sodium levels. A previous study does indicate that hyponatremia normalization is prognostically beneficial in patients with advanced non-small cell lung cancers [24]. One may thus infer that without normalization, patients with persistent hypernatremia will fare worse. Finally, we did not consider potential confounders related with symptoms such as anorexia-cachexia, delirium, dyspnea, and edema.

Conclusion

We have shown that hypernatremia on admission for palliative care of terminal cancer is predictive of shorter patient survival. Despite its low prevalence (3%), greater clinical attention to the prognostic utility of hypernatremia is needed.

Abbreviations

CRP: C-Reactive Protein

LDH: Lactate DeHydrogenase

INR: International Normalized Ratio

ECOG-PS: Eastern Cooperative Oncology Group Performance Status

WBC: White Blood Cell

ADH: AntiDiuretic Hormone

Declarations

-Ethics approval and consent to participate: The institutional review board of Gachon University Gil Medical Center approved this study (GCIRB2019-149), waiving the need for informed patient consent as designed.

Consent for publication: Not applicable.

-Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. Characteristics of study participants (N=487)

	Median (IQR) or n (%)	Reference range
Age, yrs	70 (59-79)	
Female sex	219 (45.0)	
Cancer site		
Gastrointestinal tract	127 (26.1)	
Hepatobiliary/pancreatic	118 (24.2)	
Lung	108 (22.2)	
Urogenital tract	57 (11.7)	
Others	77 (15.8)	
ECOG-PS		
≤ 2	115 (23.6)	
3	189 (38.8)	
4	183 (37.6)	
Active infection ^a	164 (33.7)	
Laboratory parameter		
White blood cells, 10 ³ /mm ³	9.1 (6.3-12.7)	3.8-10
Neutrophils, %	78.9 (72.0-85.7)	50-75
Lymphocytes, %	11.2 (6.8-17.4)	20-44
Hemoglobin, g/dL	10.1 (8.8-11.7)	13-17
Platelets, 10 ³ /mm ³	227 (154-323)	150-400
Creatinine, mg/dL	0.8 (0.5-1.2)	0.5-1.2
Albumin, g/dL	3.2 (2.8-3.7)	3.5-5.2
Total bilirubin, mg/dL	0.7 (0.5-1.4)	0.2-1.2
PT/INR	1.2 (1.1-1.3)	0.8-1.2
C-reactive protein, mg/dL	5.2 (2.3-12.9)	0-0.5
Sodium, mEq/L	134 (130-137)	135-145
Potassium, mEq/L	4.2 (3.8-4.6)	3.5-5.5
Censored ^b	19 (3.9)	
Survival time, days	26 (14-45)	

ECOG-PS, Eastern Cooperative Oncology Group performance status; PT/INR, prothrombin time/international normalized ratio; IQR, interquartile range

^aDetermined by the use of antibiotics

^bNo available information for survival by discharge or transfer.

Table 2. Survival time in relation to patient characteristics

	N	Median survival, days (95% CI)	<i>p</i> ^b
Age, years			
<70	232	29 (13-52)	0.003
≥70	255	24 (14-40)	
Sex			
Female	219	29 (13-48)	0.035
Male	268	24 (14-40)	
Cancer site			
Gastrointestinal tract	127	29 (14-47)	0.012
Hepatobiliary/pancreatic	118	24 (13-33)	
Lung	108	22 (12-41)	
Urogenital tract	57	27 (13-55)	
Others	77	35 (19-47)	
ECOG-PS			
≤2	115	30 (18-50)	0.012
3	189	27 (14-48)	
4	183	23 (11-40)	
Active infection			
No	322	27 (12-46)	0.558
Yes	164	25 (14-38)	
Leukocytosis			
No	279	31 (15-52)	<0.001
Yes	208	22 (11-34)	
Neutrophilia			
No	173	31 (18-55)	<0.001
Yes	314	24 (12-39)	
Lymphopenia			
No	90	36 (19-60)	<0.001
Yes	397	25 (13-41)	
Anemia			
No	56	25 (13-45)	0.707
Yes	431	26 (14-45)	
Thrombocytopenia			
No	371	28 (14-47)	0.020
Yes	116	20 (11-36)	
Azotemia			
No	367	28 (14-46)	0.011
Yes	120	20 (12-38)	
Hypoalbuminemia			
No	176	35 (20-60)	<0.001
Yes	311	20 (11-37)	
Hyperbilirubinemia			
No	341	29 (15-48)	<0.001
Yes	145	19 (10-32)	
PT/INR prolongation			
No	259	29 (16-51)	<0.001
Yes	200	20 (10-34)	
C-reactive protein ^a			
Low	239	29 (14-52)	0.007
High	233	22 (12-38)	
Sodium level			
Within normal range	219	28 (14-49)	<0.001
Hyponatremia	253	25 (13-43)	
Hypernatremia	15	6 (3-28)	
Potassium level			
Within normal range	394	27 (14-46)	0.118
Hypokalemia	65	26 (13-43)	
Hyperkalemia	28	19 (10-27)	

^aMedian value applied

^bLog-rank test

ECOG-PS, Eastern Cooperative Oncology Group performance status; PT/INR, prothrombin time/international normalized ratio; CI, confidence interval

Table 3. Independent prognostic indices of survival (Cox proportional hazards model)

	Univariable analysis		Multivariable analysis ^a	
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Advanced age (>70 years)	1.31 (1.09–1.58)	0.004		
Male sex	1.21 (1.01–1.46)	0.038	1.53 (1.15–2.04)	0.004
Poor functional score (ECOG=4)	1.30 (1.08–1.57)	0.005	1.45 (1.09–1.94)	0.011
Lung cancer	1.20 (0.96–1.50)	0.108		
Active infection	1.06 (0.87–1.28)	0.564		
Leukocytosis	1.56 (1.29–1.87)	<0.001	1.98 (1.47–2.66)	<0.001
Neutrophilia	1.45 (1.19–1.75)	<0.001		
Lymphopenia	1.53 (1.20–1.94)	0.001		
Anemia	0.95 (0.71–1.26)	0.711		
Thrombocytopenia	1.28 (1.04–1.59)	0.022		
Azotemia	1.30 (1.06–1.61)	0.013		
Hypoalbuminemia	1.88 (1.54–2.28)	<0.001	2.06 (1.49–2.73)	<0.001
Hyperbilirubinemia	1.47 (1.21–1.80)	<0.001		
PT/INR prolongation	1.46 (1.21–1.77)	<0.001		
CRP elevation	1.28 (1.07–1.54)	0.008		
Hypokalemia	1.01 (0.77–1.32)	0.958		
Hyperkalemia	1.22 (1.01–1.48)	0.044		
Hyponatremia	1.24 (1.03–1.49)	0.025		
Hypernatremia	1.59 (1.22–2.07)	0.001	1.55 (1.18–2.03)	0.002

^aBased on variables of significance ($p < 0.05$) in univariable analysis

PT/INR, prothrombin time/international normalized ratio; CRP, C-reactive protein

Figures

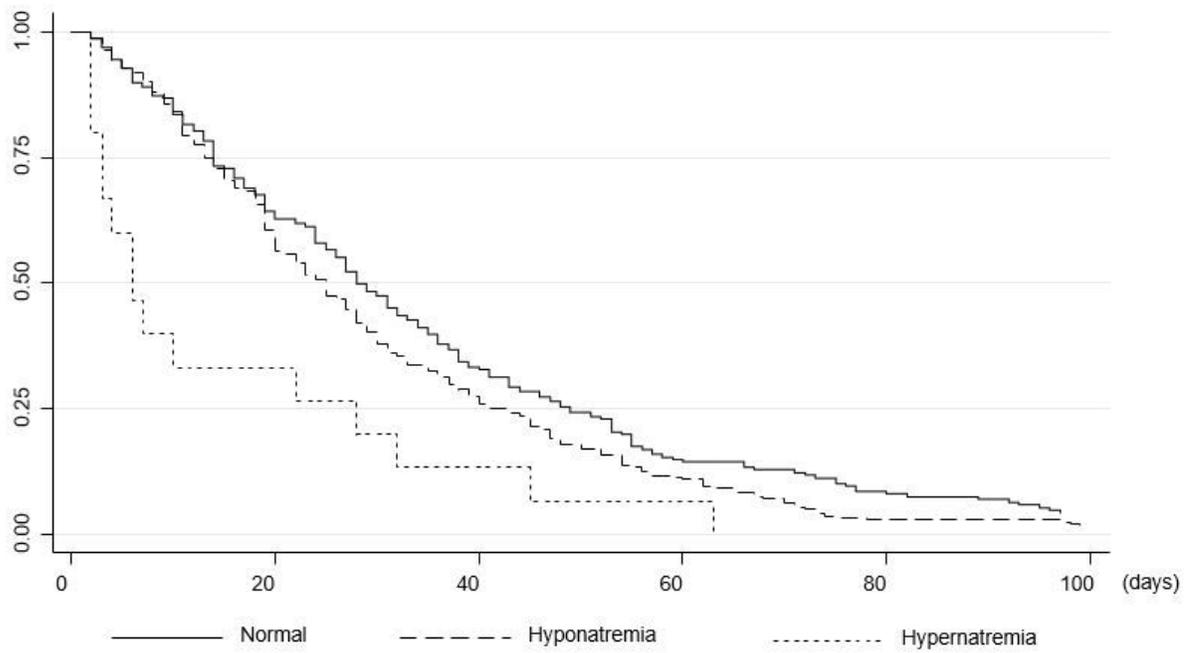


Figure 1

Kaplan-Meier survival curves of terminal cancer patients plotted by sodium level (note significantly shorter survival in patients with hypernatremia).