

Hyponatremia in Cancer Patients Hospitalized in a Palliative Care Department: A Cross-Sectional Analysis

Hiponatremia em Doentes com Cancro Internados num Serviço de Cuidados Paliativos: Uma Análise Transversal



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ABSTRACT

Introduction: Hyponatremia is frequent in cancer patients, as many studies carried out in these patients have shown. However, there are only a few studies carried out at the end of life and in palliative care. The aim of this study was to determine the prevalence of hyponatremia in cancer patients in the palliative care department of an oncology center and its association with survival.

Material and Methods: The study included the first 300 patients hospitalized in the palliative care department in 2017. Survival was measured from the day of hospitalization until death.

Results: Serum sodium was measured in 170 (59%) patients. The median serum concentration was 135 mmol/L (109 to 145). Among 91 (54%) patients, serum sodium was within the normal range, 59 (35%) had mild hyponatremia, 13 (8%) had moderate and seven (4%) had profound hyponatremia. The median survival was 13 days (1 to 1020). Serum sodium was not significantly associated with survival ($p = 0.463$). Regarding other variables, the Eastern Cooperative Oncology Group performance status was significantly associated with survival, while gender, age, primary cancer and number of metastatic sites were not.

Conclusion: Hyponatremia is common in cancer patients receiving palliative care but did not seem to influence survival.

Keywords: Hyponatremia; Neoplasms/complications; Palliative Care

RESUMO

Introdução: A hiponatremia é frequente em doentes com cancro, como muito estudos realizados nesses doentes mostraram. Contudo, há poucos estudos no fim da vida e em cuidados paliativos. O objectivo deste trabalho foi estudar a prevalência da hiponatremia em doentes oncológicos num serviço de cuidados paliativos de um centro oncológico e a sua associação com a sobrevivência.

Material e Métodos: O estudo incluiu os primeiros 300 doentes internados no serviço de cuidados paliativos em 2017. A sobrevivência foi medida do dia da hospitalização até à morte.

Resultados: O sódio plasmático foi medido em 170 (59%) doentes. A mediana da concentração de sódio plasmático foi 135 mmol/L (109 a 145). Em 91 (54%) doentes, o sódio plasmático estava dentro dos valores de referência, 59 (35%) tinham hiponatremia ligeira, em 13 (8%) era moderada e sete (4%) tinham hiponatremia profunda. A mediana da sobrevivência foi de 13 dias (1 a 1020). O sódio plasmático não apresentou uma associação estatisticamente significativamente associado com a sobrevivência ($p = 0,463$). Quanto a outras variáveis, o estado de performance do *Eastern Cooperative Oncology Group* associou-se significativamente à sobrevivência, o que não se verificou com o género, a idade, o tumor primário e o número de locais de metástases.

Conclusão: A hiponatremia é comum nos doentes oncológicos em cuidados paliativos, mas não parece influenciar a sobrevivência.

Palavras-chave: Cuidados Paliativos; Hiponatremia; Neoplasias/complicações

INTRODUCTION

Hyponatremia is a water balance disorder which develops when the amount of water is excessive in relation to the existing sodium stores in the body. It is the most frequent hydroelectrolytic imbalance found in clinical practice.¹ Hyponatremia is usually defined as a serum sodium concentration below 135 mEq/L. The clinical symptoms may be very varied, from none to life-threatening, depending on the level of serum sodium concentration, the speed of development and the previous general clinical condition of the patient.

The most common causes of hyponatremia are the

syndrome of inappropriate antidiuretic hormone secretion (SIADH), diuretic use, polydipsia, adrenal insufficiency, hypovolemia, heart failure and liver cirrhosis.² There are other possible causes, such as iatrogenesis from drugs³⁻⁵ and hypotonic intravenous fluids,⁶ and pseudo-hyponatremia due, for example, to hyperlipidemia.⁷

In cancer patients, hyponatremia is often caused by SIADH triggered by the ectopic antidiuretic hormone (ADH) secretion by tumor cells.⁸ Drugs used in cancer treatment, such as vinca alkaloids, vincristine and vinblastine, alkylating agents, such as cyclophosphamide, and targeted

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therapies (monoclonal antibodies, tyrosine kinase inhibitors, immunomodulators and mammalian target of rapamycin inhibitors) may also induce SIADH. Moreover, platinum compounds stimulate ADH secretion, but can also cause hyponatremia by interfering with sodium reabsorption by directly damaging renal tubules and causing renal salt wasting syndrome or acquired nephrogenic diabetes insipidus.³ Opioids, antidepressants, tricyclics and selective serotonin reuptake inhibitors stimulate ADH secretion and nonsteroidal anti-inflammatory drugs potentiate its effects on the renal tubules.^{4,8} Another cause of hyponatremia is cerebral salt wasting, which may result from brain metastases, head trauma, meningitis or central nervous system (CNS) surgery.⁸ In cancer patients, hyponatremia occurs most frequently in small cell lung cancer, but it may occur in many other cancer types, both solid and hematologic. Hyponatremia was identified as an independent negative prognostic factor for survival in cancer patients.⁹⁻¹¹ The non-normalization of hyponatremia with antineoplastic treatment has also been associated with a worse prognosis.⁸

As far as we know from the few studies carried out concerning hyponatremia in palliative care, only two of them looked at the association of hyponatremia with survival.^{9,12} As data on hyponatremia in palliative care are so scarce,

we carried out a study in our palliative care department with the aim of evaluating its prevalence and prognostic value.

MATERIAL AND METHODS

This study was carried out in the palliative care department (PCD) of an oncology center. The first 300 patients that were hospitalized in the PCD in 2017 were included in the study. The sample size was calculated based on 1000 admissions per year (historical data), a 95% confidence interval and assuming a 50% prevalence of hyponatremia (heterogeneous in previous studies). Only patients with a blood sample collected for other reasons within three days of, or during admission, were studied. For ethical reasons, no blood samples were specifically collected from any patient for this study.

Hyponatremia was classified according to the Guideline on Diagnosis and Treatment of Hyponatraemia¹: 'mild' - serum sodium between 130 and 135 mEq/L; 'moderate' - serum sodium between 125 and 129 mEq/L; 'profound' - serum sodium < 125 mEq/L.

This study was approved by the ethics committee of the hospital.

Descriptive methods were used for the statistical analysis and the chi-squared test was used to assess the

Table 1 – Demographic data and comparison of patients tested and not tested

	Total		Patients tested		Patients not tested		p
	n	%	n	%	n	%	
Gender							
Male	167	58	102	60	65	56	0.280
Female	120	42	68	40	52	44	
Age							
≤ 69 years	145	51	81	47	64	55	0.467
> 69 years	142	49	89	53	53	45	
Primary cancer							
Esophageal/ gastric	56	20	33	19	23	20	0.673
Colorectal	43	15	28	17	15	13	
Lung	32	11	18	11	14	12	
Head and neck	30	11	17	10	13	11	
Breast	29	10	17	10	12	10	
Prostate	19	7	15	9	4	3	
Gynecological	14	5	8	5	6	5	
Other	64	21	34	20	30	26	
Total	287	100	170	100	117	100	
Disease extension/ Number of metastatic sites							
1	77	27	40	24	37	32	0.451
2	102	36	62	37	40	35	
3	68	24	44	26	24	21	
≥ 4	36	13	21	13	15	13	
ECOG							
1 and 2	21	7	10	6	11	9	0.222
3	103	36	67	40	36	31	
4	162	56	92	54	70	60	

existence of associations between variables. Survival was defined as the time from admission until death. Survival curves were calculated using the Kaplan–Meier estimator and compared using the log-rank test. The level of significance was deemed to be 0.05 and the software used was IBM SPSS version 25. Missing data were dealt with by list-wise deletion.

RESULTS

From the 300 patients, three had hypernatremia (serum sodium > 145 mEq/L) and 20 had duplicate records from which the 10 oldest records were deleted. Therefore, the records of 287 patients were analyzed.

Of the 287 patients, 167 (58%) were men and the median age was 69 years (range: 19 to 99; 1st quartile 60, 3rd quartile 77). The most frequent primary cancers were in the digestive tract, namely esophageal/gastric and colorectal cancers (Table 1). The most common metastatic sites were lymph nodes and pleura/lungs; many cancers were locally advanced. Most patients had an Eastern Cooperative Oncology Group (ECOG) performance status of four, 162 (56%).

There were no significant differences between the group of patients tested for sodium and the group of patients not tested in terms of gender, age, primary cancer, number of metastatic sites or ECOG performance status (Table 1).

Sodium was measured in 170 (59%) patients. The median serum sodium concentration was 135 mEq/L (109 to 145). In 91 (54%) patients, it was in the normal range, while 59 (35%) had mild hyponatremia, 13 (8%) had moderate hyponatremia and seven (4%) had profound hyponatremia (Fig. 1). There were no significant differences between the

group of patients with and without hyponatremia (Table 2).

Overall, median survival was 13 days (1 to 1020). The median survival of patients who were not tested for serum sodium levels was 10 days (95% CI: 6.21 - 13.79) and the median survival of patients who were tested was 14 days (95% CI: 9.12 - 18.89), with the difference not being statistically significant ($p = 0.131$) (Fig. 2). The level of serum sodium did not significantly influence survival ($p = 0.463$). Gender ($p = 0.372$), age ($p = 0.928$), primary cancer ($p = 0.059$) and number of metastatic sites ($p = 0.185$) were not associated with survival and, of the variables analyzed, only the ECOG performance status had a significant association with survival: patients with ECOG 1 and 2 had a median survival of 54 days, patients with ECOG 3 had a median survival of 23 days and patients with ECOG 4 had a median survival of nine days ($p < 0.001$) (Fig. 3).

DISCUSSION

Hyponatremia is the most frequent body fluid and electrolyte imbalance encountered in clinical practice.¹ In the few studies carried out in palliative care, the prevalence of hyponatremia has been reported differently: 28.8%,¹³ 38.7%¹⁴ and 63.7%.⁹ The latter⁹ was also carried out solely on cancer patients, as was the present study. In the study by Kreimeike *et al*, 92.7% of the patients had cancer¹⁴ and in the study by Nair *et al*, 61.1 % had oncological diseases.¹³ In the present study, the prevalence of hyponatremia was 49%. However, the real prevalence of hyponatremia in palliative care remains unknown because, for ethical reasons, a blood test was not obtained from all patients, but only from those who needed a blood test for reasons other than the prevalence study.

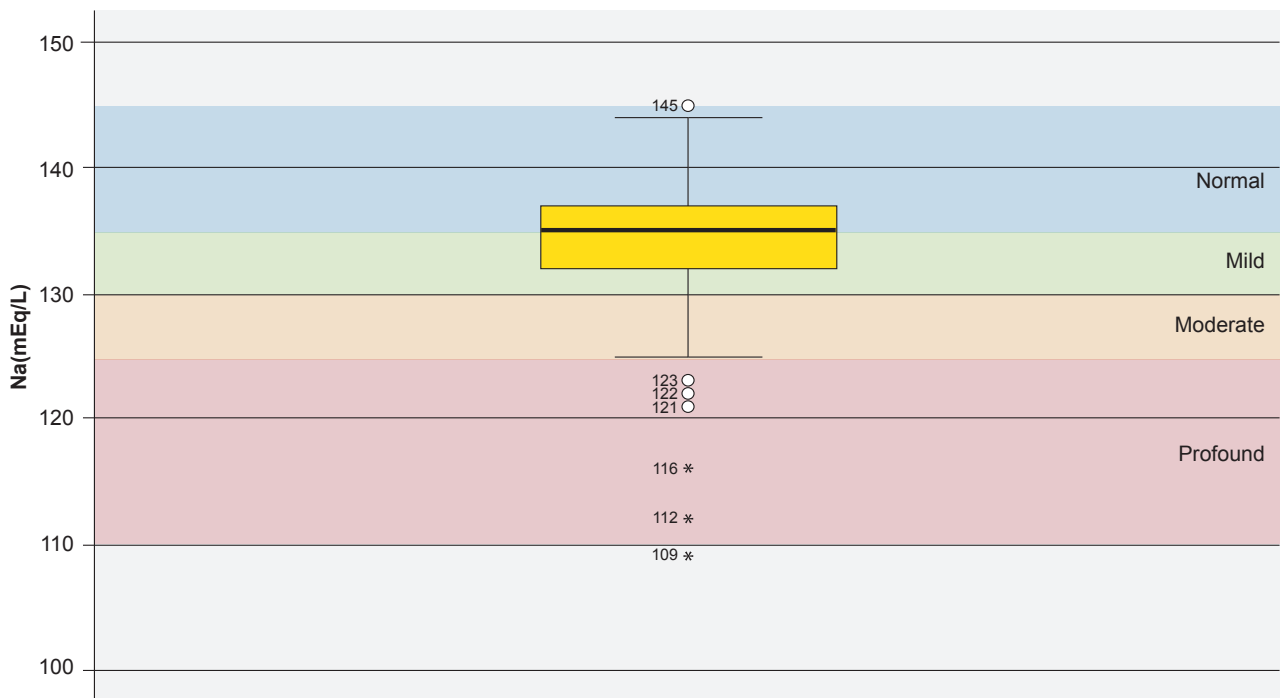


Figure 1 – Distribution of serum sodium levels

Table 2 – Comparison of patients with normal and low sodium

	Total		Normal Na		Low Na		p
	n	%	n	%	n	%	
Gender							
Male	102	60	55	60	47	60	0.900
Female	68	40	36	40	32	40	
Age							
≤ 69 years	81	48	39	43	42	53	0.218
> 69 years	89	52	52	57	37	47	
Primary cancer							
Esophageal/ gastric	33	19	19	21	14	18	0.555
Colorectal	28	17	10	11	18	23	
Lung	18	11	11	12	7	9	
Head and neck	17	10	8	9	9	11	
Breast	17	10	9	10	8	10	
Prostate	15	8	10	11	5	6	
Gynecological	8	5	5	6	3	4	
Other	34	20	19	21	15	19	
Total	170	100	91	100	79	100	
Disease extension/ Number of metastatic sites							
1	40	24	24	26	16	21	0.430
2	62	37	30	33	32	42	
3	44	26	23	25	21	28	
≥ 4	21	13	14	15	7	9	
ECOG							
1 and 2	10	6	6	7	4	5	0.333
3	67	40	31	34	36	46	
4	92	54	53	59	39	49	

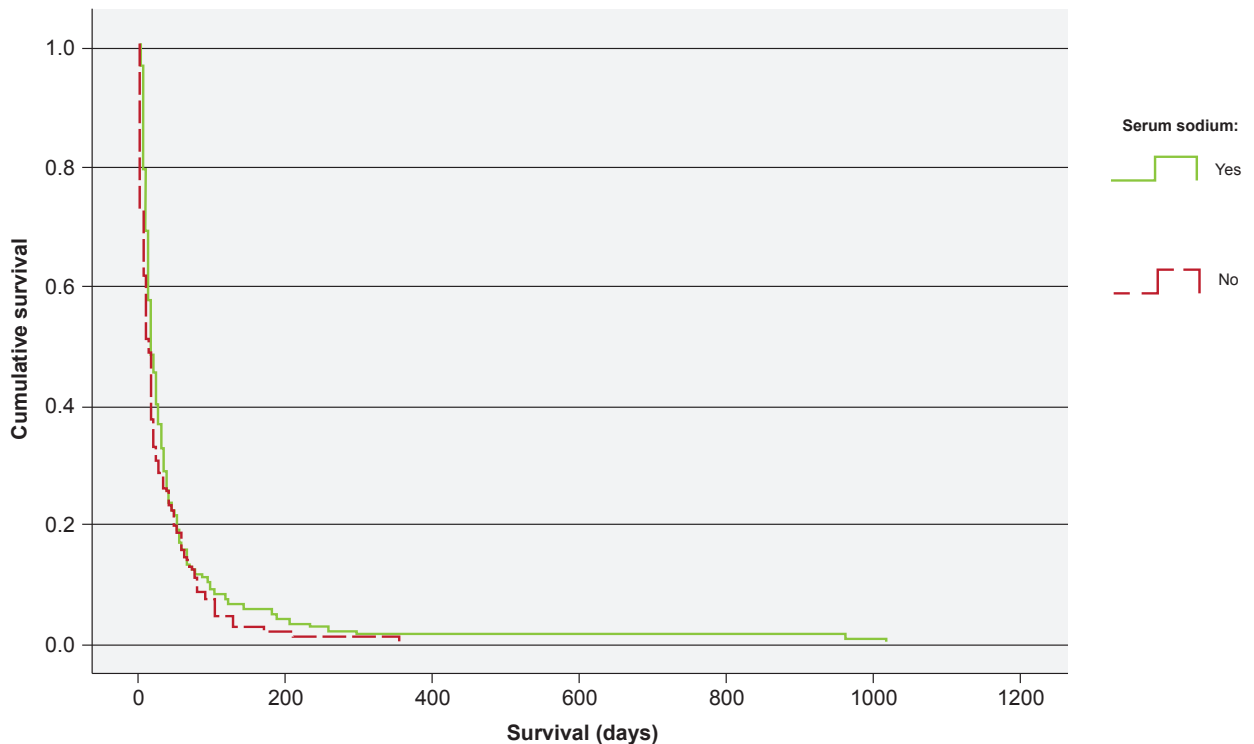


Figure 2 – Survival comparison between patients tested and not tested

In these studies, like in ours, hyponatremia was defined as a serum sodium below 135 mEq/L, except for one which defined hyponatremia as a serum sodium below 136 mEq/L. However, different studies in cancer patients have defined hyponatremia diversely from below 130 mEq/L to below 138 mEq/L.⁸

A recent study reported an association between hyponatremia and symptom burden.¹⁴ Nonetheless, symptoms in advanced cancer may result directly from advanced disease and it may be difficult to distinguish what is due to hyponatremia alone and what is the result of other causes. Given these reasons, we did not try to investigate the symptoms that could perhaps result from hyponatremia itself.

There are several studies reporting hyponatremia as an independent factor of a poorer prognosis in patients with cancer.¹⁵⁻²⁰ But there are divergences in some of them according to the cancer extension, with one identifying hyponatremia as a prognostic factor in extensive disease¹⁹ whereas another only in limited disease.¹⁸ There are also some studies in advanced cancer showing that hyponatremia was independently associated with lower survival,⁹ an increased risk of death among inpatients in palliative care units,¹² longer hospital stays and higher risk of death¹⁰ and costs.¹¹ However, the association of hyponatremia with a poorer prognosis does not imply causality as it may be a marker of general debility in advanced cancer²¹ or in other diseases.²² If this is the case, the correction of hyponatremia would have little impact, if any, on the outcome, but a meta-analysis indicated that the improvement of hyponatremia was associated with a reduction in overall mortality for several diseases.²³ Nevertheless, this remains debatable

and there is a need for randomized controlled trials to evaluate if the correction of hyponatremia improves outcomes.²⁴

In this study, we did not find that hyponatremia was associated with a poorer prognosis. The prognosis for inpatients in this group was, in general, poor, as the median survival for patients who had serum sodium levels available was only 14 days. However, another study with similar median survival found an influence of hyponatremia on survival.⁹ We looked at the survival of patients who had not had a blood test (as patients might not have been tested because they could have appeared worse than the others) and we found that, even though median survival was lower, the difference was not statistically significant.

This study has some weaknesses. It was carried out in a single institution, which may limit its generalizability to other settings. Additionally, patients were in a very advanced stage of disease with a consequently short overall life expectancy that may have masked the influence of hyponatremia on the prognosis. Nevertheless, these data suggest that the correction of hyponatremia may not be a priority, as it does not seem to influence survival in this setting.

CONCLUSION

Around half of the cancer patients hospitalized in the palliative care department had hyponatremia. However, in this end-of-life setting, hyponatremia was not associated with a poorer prognosis.

AUTHORS CONTRIBUTION

JFG: Concept and design of the work and of the protocol, draft of the paper.

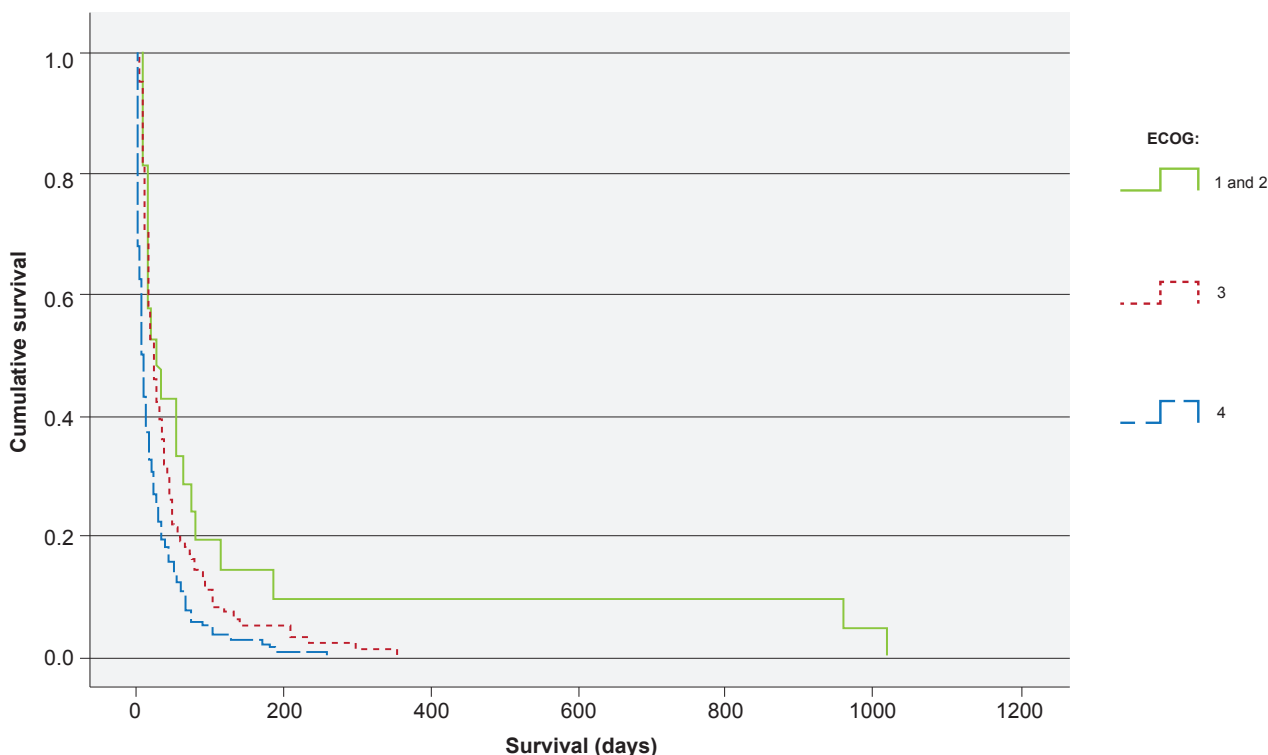


Figure 3 – Survival related with ECOG performance status

MB: Design of the work and of the protocol, critical review of the paper, final approval of the manuscript.

AA, BP, IG, SF, IC, OM, VA: Critical review of the protocol and of the different versions of the paper, data acquisition, final approval of the manuscript.

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PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declara-

tion of the World Medical Association, updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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