

Hyponatremia in Cancer

Subjects: [Oncology](#)

Contributor: Benedetta Fibbi , Giada Marroncini , Laura Naldi , Cecilia Anceschi , Alice Errico , Dario Norello , Alessandro Peri

Hyponatremia is the most common electrolyte disorder encountered in hospitalized patients. This applies also to cancer patients. Multiple causes can lead to hyponatremia, but most frequently this electrolyte disorder is due to the syndrome of inappropriate antidiuresis. In cancer patients, this syndrome is mostly secondary to ectopic secretion of arginine vasopressin by tumoral cells.

hyponatremia

arginine vasopressin

cancer

1. Introduction

Hyponatremia is the most common electrolyte disorder among hospitalized patients, with a prevalence of about 30% ^{[1][2]}. The aetiology of hyponatremia is multifaceted, but the most frequent cause is the syndrome of inappropriate antidiuresis (SIAD), which accounts for 40–50% of cases ^[3]. Severe, acute hyponatremia is associated to neurological symptoms, due to brain oedema, which may lead to brain stem herniation, respiratory arrest and death ^[2]. However, it is now well known that also chronic and mild hyponatremia may cause neurological as well as non-neurological alterations, such as gait disturbances, risk of fall, cognitive impairment and bone demineralization ^{[4][5]}. Moreover, it has been demonstrated that hyponatremia, if prolonged over time, can lead to an increased risk of death ^{[6][7][8][9]}.

Hyponatraemia is the most frequent electrolyte alteration occurring also in cancer patients. In this subgroup of patients hyponatremia is present in up to 40% of cases at the time of hospital admission ^{[10][11]}. Furthermore, about 50% of cancer patients with hyponatremia, have one or more episode of hyponatremia during the course of the disease, with a peak of 75% in patients with small cell (SCLC) or non-small cell lung cancer (NSCLC) ^[12]. Moreover, in this clinical setting, SIAD is the most frequent cause of hyponatremia ^[13]. However, other factors may determine hyponatremia in cancer patients, including associated comorbidities. Notably, hyponatremia has been associated to a significantly decreased progression-free and overall survival in these patients ^[10] and serum $[Na^+]$ has been proposed as a possible biomarker to identify high-risk cancer patients ^[14].

2. Aetiology of Hyponatremia in Cancer Patients

As already mentioned, hyponatremia in cancer patients can be determined by multiple causes.

Hyponatremia can be secondary to SIAD in patients with cancer of the lung (most frequently), nasopharynx, oropharynx, stomach, duodenum, colon, pancreas, prostate, uterus, ureter, bladder, breast or with lymphomas, leukaemias, sarcomas, brain tumours, mesotheliomas and thymomas [15][16][17]. In these cases, the pathogenesis is due to ectopic secretion of arginine vasopressin (AVP) [18]. Overall, the probability that hyponatremia in a cancer patient is due to tumoral AVP secretion is >30% [15].

Another cause of SIAD in these patients can be related to pharmacological treatments, which can induce hyponatremia by stimulating the release of AVP, or by potentiating the effect of AVP on the arginine vasopressin receptor (AVPR) type 2 or by a mixed action [17][19]. Among these, chemotherapeutic drugs [e.g., cyclophosphamide, vincristine, vinblastine, cisplatin (although more frequently induces a salt losing nephropathy), and melphalan], morphine and other narcotic painkillers, immunomodulators (immunoglobulins, interferon, interleukin-2, levamisole) [20], antiepileptic drugs (mostly carbamazepine and oxcarbazepine, but also eslicarbazepine, sodium valproate, lamotrigine, levetiracetam and gabapentin), antidepressants (e.g., selective serotonin reuptake inhibitors and tricyclics), phenothiazines that are used as antiemetic agents, and non-steroidal anti-inflammatory drugs deserve a mention. Recent therapeutic strategies, such as targeted therapies and treatment with immune-check points inhibitors, should also be included among the anticancer drugs responsible for hyponatremia, since they can cause corticotropin deficiency and consequently hypocortisolism [21][22].

Furthermore, in cancer patients, other conditions can induce or aggravate hyponatremia, such as nausea, vomiting, pain, physical and emotional stress, hydration in patients subjected to chemotherapy, diarrhoea, and heart or kidney failure [20].

3. Hyponatremia in Cancer: Does It Affect Patient Outcome?

In the oncology setting, the prevalence of chronic hyponatremia is even higher than in patients hospitalized for all causes and it affects nearly half of cancer patients [10]. Although it is well established that hyponatremia can affect health care costs, primarily due to the need of hospitalizations and a doubled length of hospital stay compared to normonatremic cancer subjects, and quality of life [23][24], the correlation between low serum $[Na^+]$ and cancer progression-free and overall survival unexpectedly emerged only in the last decade. Hyponatremia was reported as an independent, negative prognostic factor in different solid and blood tumours, such as NSCLC [12], and SCLC [25][26], gastrointestinal cancers [27][28], lymphoma [29], hepatocellular carcinoma [30][31], renal cell carcinoma [32][33], prostatic and pancreatic carcinoma [34][35], biliary tract cancer [36], mesothelioma [36], multiregional upper tract urothelial carcinoma [37], and epithelial ovarian cancer [38].

Reduced serum $[Na^+]$ has an impact on survival at all cancer stages [26][39], with the highest rate of in-hospital mortality (OR = 2.05, 95%CI 1.67–2.53) in metastatic patients [40] and a hazard ratio for death almost three fold higher than in normonatremic oncologic subjects [10].

Another important aspect in the relationship between hyponatremia and life expectancy is the influence of low serum $[Na^+]$ on the response to cancer therapy. In a cohort of NSCLC patients treated with pemetrexed-platinum

doublet chemotherapy, the presence of hyponatremia significantly reduced median progression-free survival of patients compared to the normonatremic group (6 months vs. 7 months; $p < 0.05$), even after adjusting for confounding factors. Hence, the authors concluded that pre-treatment serum $[\text{Na}^+]$ is a determinant prognostic marker in stage IIIb/IV patients, able to predict a differential response to treatment [41]. Similar results were obtained in metastatic renal cell carcinoma treated with targeted therapy (sunitinib, sorafenib) [42] or everolimus [43], in neuroendocrine neoplasms treated with peptide receptor radionuclide therapy [44], and in hepatocellular carcinoma treated with sorafenib [45]. Interestingly, in NSCLC patients treated with the EGFR inhibitor erlotinib a multivariate analysis revealed that hyponatremia was an independent predictive factor of non-response to therapy, in the same way as a poor performance status and the absence of EGFR mutations in the tumoral tissue [46].

Two large retrospective studies conducted on the Danish population not only confirmed that low serum $[\text{Na}^+]$ negatively correlated with all-cause mortality, but also with a higher risk to develop a neoplasm [9][47]. In other words, hyponatremic subjects seem to be more likely to get cancer, and if this electrolyte disorder is not properly treated, they have a higher risk of death.

These data may suggest that the correction of hyponatremia has a favourable role in the outcome of cancer patients. As a matter of fact, the normalization of reduced serum $[\text{Na}^+]$ was shown to increase overall and progression-free survival in 15 pre-treatment hyponatremic patients that underwent carboplatinum/etoposide regimen for SCLC compared to uncorrected ones [48]. Accordingly, in a group of 69 patients affected by NSCLC and hyponatremia, both overall and progression-free survival were significantly lower in those who had been maintained hyponatremic compared to those with normalized serum $[\text{Na}^+]$ (respectively 4.7 vs. 11.6 months and 3.3 vs. 6.7 months) [49]. These results were confirmed also in a small cohort of patients with different but extensive and terminal cancers (overall survival 13.6 months vs. 16 days, corrected vs. uncorrected hyponatremia), thus determining the option of receiving multiple lines of antineoplastic treatment [50]. Based on these data, hyponatremia has been proposed as a reliable biomarker of high-risk subjects with lung cancer [14].

Overall, these data indicate that hyponatremia should be promptly recognized and corrected also in an oncological setting, in view of the well demonstrated effect of patients' outcome.

References

1. Adrogué, H.J.; Madias, N.E. Hyponatremia. *N. Engl. J. Med.* 2000, 342, 1581–1589.
2. Rondon-Berrios, H.; Agaba, E.I.; Tzamaloukas, A.H. Hyponatremia: Pathophysiology, Classification, Manifestations and Management. *Int. Urol. Nephrol.* 2014, 46, 2153–2165.
3. Cuesta, M.; Thompson, C.J. The Syndrome of Inappropriate Antidiuresis (SIAD). *Best Pract. Res. Clin. Endocrinol. Metab.* 2016, 30, 175–187.

4. Renneboog, B.; Musch, W.; Vandemergel, X.; Manto, M.U.; Decaux, G. Mild Chronic Hyponatremia Is Associated with Falls, Unsteadiness, and Attention Deficits. *Am. J. Med.* 2006, 119, 71.e1–71.e8.
5. Suárez, V.; Norello, D.; Sen, E.; Todorova, P.; Hackl, M.J.; Hüser, C.; Grundmann, F.; Kubacki, T.; Becker, I.; Peri, A.; et al. Impairment of Neurocognitive Functioning, Motor Performance, and Mood Stability in Hospitalized Patients with Euvolemic Moderate and Profound Hyponatremia. *Am. J. Med.* 2020, 133, 986–993.e5.
6. Wald, R.; Jaber, B.L.; Price, L.L.; Upadhyay, A.; Madias, N.E. Impact of Hospital-Associated Hyponatremia on Selected Outcomes. *Arch. Intern. Med.* 2010, 170, 294–302.
7. Corona, G.; Giuliani, C.; Parenti, G.; Norello, D.; Verbalis, J.G.; Forti, G.; Maggi, M.; Peri, A. Moderate Hyponatremia Is Associated with Increased Risk of Mortality: Evidence from a Meta-Analysis. *PLoS ONE* 2013, 8, e80451.
8. Mohan, S.; Gu, S.; Parikh, A.; Radhakrishnan, J. Prevalence of Hyponatremia and Association with Mortality: Results from NHANES. *Am. J. Med.* 2013, 126, 1127–1137.e1.
9. Holland-Bill, L.; Christiansen, C.F.; Heide-Jørgensen, U.; Ulrichsen, S.P.; Ring, T.; Jørgensen, J.O.L.; Sørensen, H.T. Hyponatremia and Mortality Risk: A Danish Cohort Study of 279508 Acutely Hospitalized Patients. *Eur. J. Endocrinol.* 2015, 173, 71–81.
10. Doshi, S.M.; Shah, P.; Lei, X.; Lahoti, A.; Salahudeen, A.K. Hyponatremia in Hospitalized Cancer Patients and Its Impact on Clinical Outcomes. *Am. J. Kidney Dis. Off. J. Natl. Kidney Found.* 2012, 59, 222–228.
11. Berardi, R.; Rinaldi, S.; Caramanti, M.; Grohè, C.; Santoni, M.; Morgese, F.; Torniai, M.; Savini, A.; Fiordoliva, I.; Cascinu, S. Hyponatremia in Cancer Patients: Time for a New Approach. *Crit. Rev. Oncol. Hematol.* 2016, 102, 15–25.
12. Castillo, J.J.; Glezerman, I.G.; Boklage, S.H.; Chiodo, J., 3rd; Tidwell, B.A.; Lamerato, L.E.; Schulman, K.L. The Occurrence of Hyponatremia and Its Importance as a Prognostic Factor in a Cross-Section of Cancer Patients. *BMC Cancer* 2016, 16, 564.
13. Grohé, C. Hyponatremia in Oncology Patients. *Front. Horm. Res.* 2019, 52, 161–166.
14. Kasi, P.M. Proposing the Use of Hyponatremia as a Marker to Help Identify High Risk Individuals for Lung Cancer. *Med. Hypotheses* 2012, 79, 327–328.
15. Berghmans, T.; Paesmans, M.; Body, J.J. A Prospective Study on Hyponatraemia in Medical Cancer Patients: Epidemiology, Aetiology and Differential Diagnosis. *Support. Care Cancer Off. J. Multinat. Assoc. Support. Care Cancer* 2000, 8, 192–197.
16. Ellison, D.H.; Berl, T. Clinical Practice. The Syndrome of Inappropriate Antidiuresis. *N. Engl. J. Med.* 2007, 356, 2064–2072.

17. Verbalis, J.G.; Goldsmith, S.R.; Greenberg, A.; Korzelius, C.; Schrier, R.W.; Sterns, R.H.; Thompson, C.J. Diagnosis, Evaluation, and Treatment of Hyponatremia: Expert Panel Recommendations. *Am. J. Med.* 2013, 126, S1–S42.
18. Sørensen, J.B.; Andersen, M.K.; Hansen, H.H. Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH) in Malignant Disease. *J. Intern. Med.* 1995, 238, 97–110.
19. Liamis, G.; Milionis, H.; Elisaf, M. A Review of Drug-Induced Hyponatremia. *Am. J. Kidney Dis. Off. J. Natl. Kidney Found.* 2008, 52, 144–153.
20. Raftopoulos, H. Diagnosis and Management of Hyponatremia in Cancer Patients. *Support. Care Cancer Off. J. Multinatl. Assoc. Support. Care Cancer* 2007, 15, 1341–1347.
21. Berardi, R.; Santoni, M.; Rinaldi, S.; Nunzi, E.; Smerilli, A.; Caramanti, M.; Morgese, F.; Torniai, M.; Savini, A.; Fiordoliva, I.; et al. Risk of Hyponatraemia in Cancer Patients Treated with Targeted Therapies: A Systematic Review and Meta-Analysis of Clinical Trials. *PLoS ONE* 2016, 11, e0152079.
22. Cho, K.Y.; Miyoshi, H.; Nakamura, A.; Kurita, T.; Atsumi, T. Hyponatremia Can Be a Powerful Predictor of the Development of Isolated ACTH Deficiency Associated with Nivolumab Treatment. *Endocr. J.* 2017, 64, 235–236.
23. Boscoe, A.; Paramore, C.; Verbalis, J.G. Cost of Illness of Hyponatremia in the United States. *Cost Eff. Resour. Alloc.* 2006, 4, 10.
24. Berardi, R.; Caramanti, M.; Fiordoliva, I.; Morgese, F.; Savini, A.; Rinaldi, S.; Torniai, M.; Tiberi, M.; Ferrini, C.; Castagnani, M.; et al. Hyponatraemia Is a Predictor of Clinical Outcome for Malignant Pleural Mesothelioma. *Support. Care Cancer Off. J. Multinatl. Assoc. Support. Care Cancer* 2015, 23, 621–626.
25. Gandhi, L.; Johnson, B.E. Paraneoplastic Syndromes Associated with Small Cell Lung Cancer. *J. Natl. Compr. Canc. Netw.* 2006, 4, 631–638.
26. Rawson, N.S.; Peto, J. An Overview of Prognostic Factors in Small Cell Lung Cancer. A Report from the Subcommittee for the Management of Lung Cancer of the United Kingdom Coordinating Committee on Cancer Research. *Br. J. Cancer* 1990, 61, 597–604.
27. Zhou, M.H.; Wang, Z.H.; Zhou, H.W.; Liu, M.; Gu, Y.J.; Sun, J.Z. Clinical Outcome of 30 Patients with Bone Marrow Metastases. *J. Cancer Res. Ther.* 2018, 14, S512–S515.
28. Choi, J.S.; Bae, E.H.; Ma, S.K.; Kweon, S.S.; Kim, S.W. Prognostic Impact of Hyponatraemia in Patients with Colorectal Cancer. *Color. Dis. Off. J. Assoc. Coloproctology Gt. Br. Irel.* 2015, 17, 409–416.
29. Dhaliwal, H.S.; Rohatiner, A.Z.; Gregory, W.; Richards, M.A.; Johnson, P.W.; Whelan, J.S.; Gallagher, C.J.; Matthews, J.; Ganesan, T.S.; Barnett, M.J. Combination Chemotherapy for

- Intermediate and High Grade Non-Hodgkin's Lymphoma. *Br. J. Cancer* 1993, 68, 767–774.
30. Ginès, P.; Guevara, M. Hyponatremia in Cirrhosis: Pathogenesis, Clinical Significance, and Management. *Hepatology* 2008, 48, 1002–1010.
 31. Cescon, M.; Cucchetti, A.; Grazi, G.L.; Ferrero, A.; Viganò, L.; Ercolani, G.; Zanello, M.; Ravaioli, M.; Capussotti, L.; Pinna, A.D. Indication of the Extent of Hepatectomy for Hepatocellular Carcinoma on Cirrhosis by a Simple Algorithm Based on Preoperative Variables. *Arch. Surg.* 2009, 144, 57–63; discussion 63.
 32. Vasudev, N.S.; Brown, J.E.; Brown, S.R.; Rafiq, R.; Morgan, R.; Patel, P.M.; O'Donnell, D.; Harnden, P.; Rogers, M.; Cocks, K.; et al. Prognostic Factors in Renal Cell Carcinoma: Association of Preoperative Sodium Concentration with Survival. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* 2008, 14, 1775–1781.
 33. Schutz, F.A.B.; Xie, W.; Donskov, F.; Sircar, M.; McDermott, D.F.; Rini, B.I.; Agarwal, N.; Pal, S.K.; Srinivas, S.; Kollmannsberger, C.; et al. The Impact of Low Serum Sodium on Treatment Outcome of Targeted Therapy in Metastatic Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Cancer Database Consortium. *Eur. Urol.* 2014, 65, 723–730.
 34. Abu Zeinah, G.F.; Al-Kindi, S.G.; Hassan, A.A.; Allam, A. Hyponatraemia in Cancer: Association with Type of Cancer and Mortality. *Eur. J. Cancer Care* 2015, 24, 224–231.
 35. Berardi, R.; Rinaldi, S.; Belfiori, G.; Partelli, S.; Crippa, S.; Torniai, M.; Falconi, M. The Role of Hyponatraemia Before Surgery in Patients with Radical Resected Pancreatic Cancer. *Clin. Med. Insights Oncol.* 2020, 14, 1179554920936605.
 36. Berardi, R.; Mocchegiani, F.; Rinaldi, S.; Fiordoliva, I.; Rovinelli, F.; Caramanti, M.; Federici, A.; Burattini, M.; Morgese, F.; Torniai, M.; et al. Hyponatremia Is a Predictor of Clinical Outcome for Resected Biliary Tract Cancers: A Retrospective Single-Center Study. *Oncol. Ther.* 2020, 8, 115–124.
 37. Yeh, H.-C.; Li, C.-C.; Wen, S.-C.; Singla, N.; Woldu, S.L.; Robyak, H.; Huang, C.-N.; Ke, H.-L.; Li, W.-M.; Lee, H.-Y.; et al. Validation of Hyponatremia as a Prognostic Predictor in Multiregional Upper Tract Urothelial Carcinoma. *J. Clin. Med.* 2020, 9, 1218.
 38. Guo, J.-Y.; Gong, T.-T.; Yang, Z.; Liu, Y.; Wang, L.; Wang, Y.-N.; Wu, Q.-J. Prognostic Value of Preoperative Hyponatremia in Patients with Epithelial Ovarian Cancer. *J. Cancer* 2019, 10, 836–842.
 39. Osterlind, K.; Andersen, P.K. Prognostic Factors in Small Cell Lung Cancer: Multivariate Model Based on 778 Patients Treated with Chemotherapy with or without Irradiation. *Cancer Res.* 1986, 46, 4189–4194.
 40. Waikar, S.S.; Mount, D.B.; Curhan, G.C. Mortality after Hospitalization with Mild, Moderate, and Severe Hyponatremia. *Am. J. Med.* 2009, 122, 857–865.

41. Doshi, K.H.; Shriyan, B.; Nookala, M.K.; Kannan, S.; Joshi, A.; Noronha, V.; Gota, V.; Prabhash, K. Prognostic Significance of Pretreatment Sodium Levels in Patients of Nonsmall Cell Lung Cancer Treated with Pemetrexed-Platinum Doublet Chemotherapy. *J. Cancer Res. Ther.* 2018, 14, 1049–1053.
42. Kawashima, A.; Tsujimura, A.; Takayama, H.; Arai, Y.; Nin, M.; Tanigawa, G.; Uemura, M.; Nakai, Y.; Nishimura, K.; Nonomura, N. Impact of Hyponatremia on Survival of Patients with Metastatic Renal Cell Carcinoma Treated with Molecular Targeted Therapy. *Int. J. Urol. Off. J. Jpn. Urol. Assoc.* 2012, 19, 1050–1057.
43. Penttilä, P.; Bono, P.; Peltola, K.; Donskov, F. Hyponatremia Associates with Poor Outcome in Metastatic Renal Cell Carcinoma Patients Treated with Everolimus: Prognostic Impact. *Acta Oncol.* 2018, 57, 1580–1585.
44. Refardt, J.; Brabander, T.; Minczeles, N.S.; Feelders, R.A.; de Herder, W.W.; Hofland, J. Prognostic Value of Dysnatremia for Survival in Neuroendocrine Neoplasm Patients. *Eur. J. Endocrinol.* 2022, 187, 209–217.
45. Kegasawa, T.; Sakamori, R.; Maesaka, K.; Yamada, R.; Tahata, Y.; Urabe, A.; Kodama, T.; Hikita, H.; Imanaka, K.; Ohkawa, K.; et al. Lower Serum Sodium Levels Are Associated with the Therapeutic Effect of Sorafenib on Hepatocellular Carcinoma. *Dig. Dis. Sci.* 2021, 66, 1720–1729.
46. Svaton, M.; Fiala, O.; Pesek, M.; Bruha, F.; Mukensnabl, P.; Racek, J.; Minarik, M.; Bortlicek, Z. Predictive and Prognostic Significance of Sodium Levels in Patients with NSCLC Treated by Erlotinib. *Anticancer Res.* 2014, 34, 7461–7465.
47. Selmer, C.; Madsen, J.C.; Torp-Pedersen, C.; Gislason, G.H.; Faber, J. Hyponatremia, All-Cause Mortality, and Risk of Cancer Diagnoses in the Primary Care Setting: A Large Population Study. *Eur. J. Intern. Med.* 2016, 36, 36–43.
48. Hansen, O.; Sørensen, P.; Hansen, K.H. The Occurrence of Hyponatremia in SCLC and the Influence on Prognosis: A Retrospective Study of 453 Patients Treated in a Single Institution in a 10-Year Period. *Lung Cancer* 2010, 68, 111–114.
49. Berardi, R.; Santoni, M.; Newsom-Davis, T.; Caramanti, M.; Rinaldi, S.; Tiberi, M.; Morgese, F.; Torniai, M.; Pistelli, M.; Onofri, A.; et al. Hyponatremia Normalization as an Independent Prognostic Factor in Patients with Advanced Non-Small Cell Lung Cancer Treated with First-Line Therapy. *Oncotarget* 2017, 8, 23871–23879.
50. Balachandran, K.; Okines, A.; Gunapala, R.; Morganstein, D.; Popat, S. Resolution of Severe Hyponatraemia Is Associated with Improved Survival in Patients with Cancer. *BMC Cancer* 2015, 15, 163.

Retrieved from <https://encyclopedia.pub/entry/history/show/95166>