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Hyponatremia as a Prognostic Factor in Advanced Stage Ovarian Cancer Patients

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Rezumat

Hiponatremia ca factor de prognostic la pacienții cu neoplasm ovarian în stadiu avansat

Introducere: hiponatremia reprezintă una din cele mai importante modificări de labotrator întâlnite la pacienții internați, fiind cauzată prin multiple mecanisme, neoplaziile fiind o cauză importantă. Scopul acestui studiu este de a analiza prezența şi influența asupra prognosticului pe termen scurt dar şi la distanță a hiponatremiei în cazul pacientelor diagnosticate cu neoplasme de ovar avansate supuse intervenției chirurgicale.

Metodă: 57 paciente au fost diagnosticate cu neoplasme de ovar avansate şi au fost supuse intervenției chirurgicale în perioada 2014-2020. Pacientele au fost ulterior clasificate în funcție de concentrația sodiului seric preoperator.

Rezultate: 21 din cele 57 cazuri au prezentat valori normale ale sodiului preoperator]n timp ce restul de 36 cazuri au prezentat hiponatremie. Pacientele cu hiponatremie preoperatorie au asociat o rată semnificativ mai mare a complicațiilor postoperatorii şi respectiv un prognostic semnificativ mai prost la distanță. Astfel, cazurile cu hiponatremie preoperatorie a raportat o supraviețuire liberă de boală medie de 10,8 luni şi respective o supraviețuire medie globală de 31,4 luni în timp ce în cazurile cu valori normale ale sodiului preoperator perioada liberă de boală a fost în medie de 18,5 luni iar supraviețuirea medie globală a fost de 49,7 luni (p=0,0001 respectiv <0,001).
Concluzii: pacientele cu nivele scăzute ale sodiului preoperator au un risc crescut de a dezvolta complicații postoperatorii şi un prognostic la distanță semnificativ mai nefavorabil comparativ cu cele la care nivelul sodiului preoperator a fost normal.

Cuvinte cheie: hiponatremie, neoplasm ovarian, morbiditate, prognostic pe termen lung

Abstract
Background: hyponatremia represents one of the most commonly encountered conditions in hospitalized patients, multiple mechanisms being cited so far, neoplastic syndromes being an important cause. The aim of the current paper is to analyse the presence and influence of the short- and long-term outcomes of hyponatremia on ovarian cancer patients submitted to surgery for advanced stage ovarian cancer.
Method: 57 patients diagnosed with advanced stage ovarian cancer were submitted to surgery between 2014-2020. The patients were further classified according to the preoperative value of sodium into two groups.
Results: there were 21 cases with preoperative normal values of sodium and respectively 36 cases with hyponatremia. Patients with preoperative hyponatremia associated a significantly higher rate of early postoperative complications and a significantly poorer long-term outcome. Therefore, cases with hyponatremia reported a mean disease-free survival of 10.8 months and respectively a mean overall survival of 18.5 months while cases with normal natrium levels reported a mean disease-free survival of 31.4 months and respectively a mean overall survival of 49.7 months (p=0.0001 and p<0.001).
Conclusions: patients with lower preoperative values of sodium have a higher risk of developing postoperative complications and a significantly poorer outcome when compared to cases presenting normal levels of sodium preoperatively.

Key words: hyponatremia, ovarian cancer, morbidity, long term outcomes

Introduction

Once debulking surgery became the gold standard in treating advanced stage ovarian cancer, cytoreduction to no residual disease has been widely tempting in these cases. However, in certain cases this desiderate cannot be achieved and incomplete debulking surgery is performed. In such cases although adjuvant chemotherapy is performed the overall prognostic remains scarce and the overall survival is impaired (1-3). Therefore, attention was focused on identifying prognostic factors which could suggest the presence of a more advanced disease which could further guide the patient to neoadjuvant chemotherapy followed by interval debulking surgery than for per primam resection (4-6).

Although initially it was considered that the preoperative value of cancer antigen 125 (CA 125) was the best prognostic value, studies published so far have come to demonstrate that this marker has a scarce value in identifying cases in which maximal debulking surgery can be performed (7-9). Therefore, attention was focused on establishing other correlations between different serum parameters and the intraoperative and postoperative outcomes of ovarian cancer patients (9-11).

An interesting parameter which has been widely studied in the last decade is represented by natremia, a routinely measured electrolyte before any surgical procedure. Therefore, it has been widely observed that among hospitalized patients, hyponatremia is present in up to 20% of hospitalized patients, being usually related to certain conditions such as cardiac or renal disfunction, diabetes, excessive diuretic therapies or as a paraneoplastic syndrome (12-14).

As far as the correlation between hyponatremia and gynecological cancers is concerned, it has been demonstrated that 4 to 8% of patients diagnosed with such neoplastic processes present a certain degree of natrium depletion (15). The main causes of hyponatremia in advanced stage ovarian cancer have been reported to be related to tumoral burden, the presence of ascites, malnutrition or other associated comorbidities (15,16). The aim of the current paper is to investigate the presence of hyponatremia on a study group of 57 patients submitted to surgery for advanced stage ovarian cancer and to study the possible correlations between this parameter and the perioperative and long-term outcomes.

Material and Methods

After receiving the Ethics Committee approval no 88/2023, data of patients submitted to surgery for advanced stage ovarian cancer between 2014-2020 were retrospectively reviewed. Inclusion criteria were represented by patients age over 18 years with histologically confirmed stage IIIC-IV ovarian cancer, with no antecedents of neoadjuvant therapy. Exclusion criteria were age under 18 years, infirmed histopathological diagnosis, any history of neoadjuvant therapy, association of other neoplasia or other comorbidities which could influence the serum levels of natrium such as diabetes mellitus, chronic administration of diuretics, renal or cardiac disfunction. Based on the intraoperative findings, a number of 65 cases was obtained; however, after studying the histopathological reports, eight patients were excluded from the study due to the fact that the final staging was lower than FIGO IIIC. In all 57 cases preoperative blood count, ionograms and CA 125 levels were retrospectively reviewed. Cytoreductive surgery to no residual disease was attempted in all cases. The patients were further classified into two groups according to the preoperative level of natrium, hyponatremia being defined as a serum level lower than 135 mEq/l. The early postoperative complications were classified according to Clavien Dindo scale (17). Progression free survival was defined as the interval between the first surgical procedure and the diagnosis of the first recurrence while the overall survival was defined as the interval between the first surgical procedure and the time when cancer related death occurred.

Statistical Analysis

Cox proportional hazard model was used in order to identify factors showing statistical significance, which were further entered into the multivariate analysis. Statistical significance was considered if p values lower than 0.05 were obtained. Survival curves were obtained and compared by using the Kaplan-Meier analysis and respectively the Log Rank test. Version 18.0 of SPSS statistical software (SPSS Inc. Chicago, IL, USA) was used in order to analyze data.

Results

The mean age of patients in the current study was 56 years (range 25-83 years) while the mean value of preoperative natremia was 133

mEq/l (range 124-143 mEq/l); using a cut-off value of 135 mEq/l, we divided the study group in two subgroups: the first one with normal serum values of natrium – 21 cases and respectively with hyponatremia – 36 cases. The mean age among patients with normal levels of preoperative natrium levels was of 52.85 years (range 25-73 years) while the mean age among cases with preoperative hyponatremia was of 58.47 years (range 35-83 years) (p=0.001).

Details regarding clinco-pathological characteristics of the study group are presented in *Table 1* while data regarding the early perioperative outcomes are presented in *Table 2*.

Interestingly, there was not a significantly statistic difference between the presence of comorbidities among patients with normal natrium values and respectively patients with hyponatremia; therefore, there, severe comorbidities were encountered in nine out of the 21 cases with normal serum values of sodium and respectively in 13 of the 36 cases with preoperative hyponatremia (p=0.7786). However, a statistically significant correlation was observed between the preoperative levels of sodium and the levels of proteins, of albumin and of CA125; moreover, when studying the relationship between the preoperative complete blood count and natrium levels, we demonstrated that hyponatremia was significantly associated with higher numbers of circulating platelets, monocytes, and neutrophils and with lower numbers of lymphocytes. As expected, hyponatremia was also statistically significant associated with a higher value of platelet to lymphocyte ratio, of neutrophil to lymphocyte ratio and respectively with a lower level of lymphocyte to monocyte ratio. Interestingly, a positive correlation between the presence of a lower hemoglobin level and hyponatremia could not be demonstrated. When analyzing the possible correlation between hyponatremia and the presence of ascites, another positive correlation was observed; therefore, patients presenting a lower than 135 mEq/l level of preoperative natremia presented a significantly higher volume of ascites (4252 ml versus 490 ml in patients with normal preoperative sodium values, p<0.0001).

Table 1. Clinco-pathological characteristics of the study group

	Hyponatremia	Normal natrium values	Total 2
Stage of disease:			
- IIIC	34	20	54
- IV	2	1	3
Histology:			
- Serous ADK	25	14	39
- Mucinous ADK	0	2	2
- Endometroid ADK	1	3	4
- Clear cell carcinoma	7	0	7
- Other histological subtypes	3	2	5
Degree of differentiation:			
- G1	2	4	6
- G2	7	8	15
- G3	27	9	36
Type of resection:			
- Complete debulking	26	20	46
- Incomplete debulking	10	1	11
Mean blood loss (ml)	890	1100	-
Mean duration of the surgical procedure (min)	320	380	-

Data regarding the correlation between preoperative natrium levels and clinical and laboratory features are presented in *Table 3*.

When analyzing the histopathological findings, there were 36 cases of serous ovarian cancer, six cases of endometroid ovarian cancer, and five cases each with mucinous, clear cell carcinoma and other histological types; however, there was no statistically significance between the preoperative natrium levels according to the histological subtype (p=0.512). As for the degree of differentiation, although poorly differentiated tumors trended to associate a lower level of preoperative

Table 2. Details of early postoperative outcomes related to preoperative sadium levels

	Hyponatremia	Normal natrium values	Total
Intraoperative complications	3	0	3
Postoperative complications:			
- Grade 1	1	0	1
- Grade 2	7	1	8
- Grade 3	3	0	3
- Grade 4	3	0	3
- Grade 5	3	0	3
Length of hospital in stay	13.48	7.5	-

Table 3. The corelation ship between preoperative natrium levels and clinical and laboratory features

	Hyponatremia (36 cases)	Normal natrium values (21 cases)	p value
Age (years)	58.47	52.85	P=0.001
Albumin levels (g/dl)	3.6	4.09	P<0.001
Protein levels (g/dl)	5.4	7.06	P<0.0001
CA 125 (U/l)	4252	557	P<0.0001
Ascites (ml)	1633	490	P<0.0001
Hb levels (g/dl)	11.4	12.7	P=0.057
Platelet number (/microl)	415582	285411	P<0.0001
Lymphocytes	1193	1947	P<0.0001
Monocytes	782	403	P<0.0001
Neutrophiles	5990	3780	P=0.001
Platelet to lymphocyte ratio	408	162	P=0.002
Neutrophil to lymphocyte ratio	5.5	2.05	P<0.0001
Lymphocyte to monocyte ratio	1.85	5.31	P<0.0001

natrium concentration, the difference was not statistically significant (p=0.064).

Regarding the intraoperative and early postoperative outcomes, patients with hyponatremia were more likely to achieve an incomplete cytoreduction; therefore, complete Debulking surgery was achieved in 20 out of the 21 cases with preoperative normal natrium values and respectively 26 out of the 36 cases with preoperative hyponatremia (p=0.0047). When discussing about the short-term outcomes, postoperative complications were encountered in a single patient with preoperative normal values of natrium and in 15 out of the 36 cases with preoperative hyponatremia, p= 0.0025. During the first 30 days postoperatively there were three deaths, all of them occurring among patients with preoperative hyponatremia. As expected, patients with preoperative hyponatremia necessitated a longer hospital in stay (13.48 days versus 7.5 days, p=0.03). On univariate analysis, preoperative hyponatremia was significantly associated with a higher hospital in stay, with a higher rate of severe complications (defined as Clavien Dindo 3-4 complications) and with a higher rate of early postoperative mortality.

When investigating the long-term outcomes, we observed that patients with preoperative hyponatremia reported a mean disease-free survival of 10.8 months and respectively a mean overall survival of 18.5 months while cases with normal natrium levels reported a mean disease free survival of 31.4 months and respectively a mean overall survival of 49.7 months (p<0.0001 and respectively p=0.0001).

When performing the univariate analysis by using the Cox proportional hazard model, a significant correlation was established between the preoperative levels of natrium and overall survival (p=0.033, HR=1.9, 95% CI= 1.7-2.4). When analyzing the influence of the preoperative sodium values on the disease-free survival by using the same statistical tool, a p value of 0.039 was obtained, HR=1.6, CI=1.3-1.9.

The Kaplan-Meier curves of survival for patients with normal versus low levels of preoperative natrium concentration are presented in *Fig. 1* and *Fig. 2*. As expected, patients with preoperative hypernatremia experienced a significantly lower overall survival when compared to cases with normal preoperative serum values of natrium (p=0.001) as well as a lower disease free survival. Meanwhile, when investigating the impact of hyponatremia on the disease free survival, a similar correlation-ship was observed; therefore, patients diagnosed with preoperative hyponatremia reported a significantly shorter disease free survival when compared to those in which normal serum values of sodium was encouneterd preoperatively.

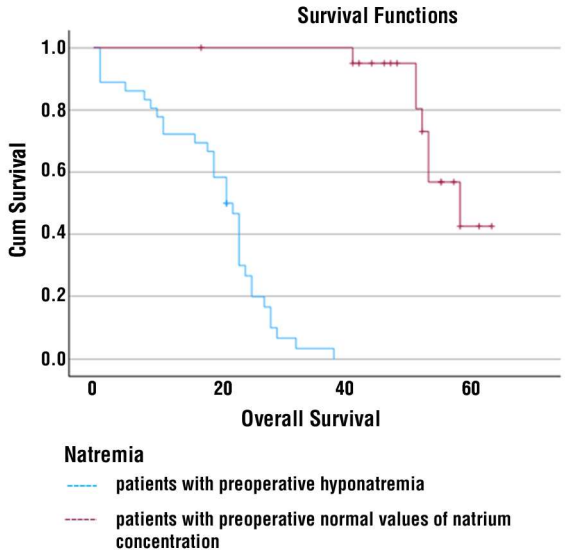

Figure 1. Kaplan Meyer analysis curve demonstrating a significant impact on survival of preoperative hyponatremia

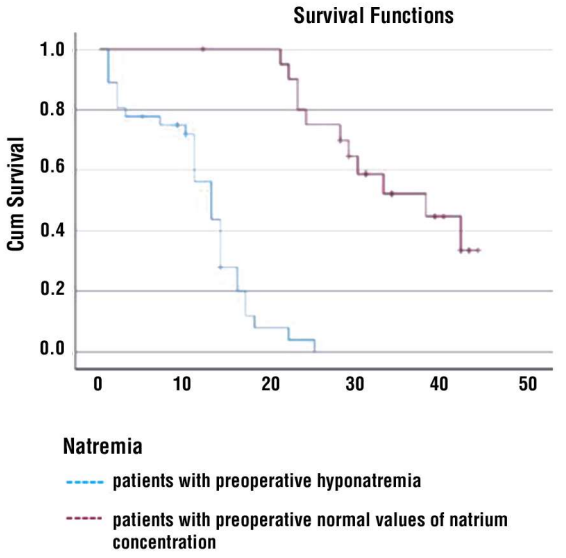

Figure 2. the impact of hyponatremia on the disease free survival

Discussions

Hyponatremia represents a common finding among patients necessitating hospital admission, certain authors demonstrating that in up to 15% of cases hyponatremia represents a tumor-related condition (18); moreover, it seems that up to half of patients hospitalized in oncology services are hyponatremic at the time of admission (19). However, the exact percentage of hypontramic cases is hard to be established due to the fact that the cut off values defining normal natrium concentration and respectively hyponatremia can widely vary between different studies between 130 and 134mEq/l (14).

In ovarian cancer patients the mechanisms leading to hyponatremia are multiple and consist of low oral intake, cachexia, malnutrition, the presence of high tumoral burden and ascites, vomiting or diarrhea (14). Moreover, in certain cases hyponatremia is caused by the synthesis of high amounts of antidiuretic hormone (the syndrome of inappropriate antidiuretic hormone – SIADH), this phenomenon being initially observed in lung cancer patients and further incriminated in breast, colorectal, and more recently, in ovarian cancer patients (20).

Due to the fact that, theoretically, a lower amount of sodium is expected to be associated with a higher tumoral burden, certain authors went further and analyzed whether this association can be also demonstrated in terms of outcomes; in this respect Martin et al. conducted a study on patients diagnosed with ovarian, fallopian tube, and peritoneal cancer and demonstrated that hyponatremia was present in 10% of cases, its presence being positively corelated with a higher postoperative hospital in stay, a higher 30-day postoperative morbidity and mortality (14). Reagrding the impact of hyponatremia on the long term outcomes, Guo et al. conducted a study on 607 patients diagnosed with epithelial ovarian cancer and demonstrated that preoperative hyponatremia was associated with a significantly poorer progression free and overall survival; therefore, after adjustment for potential confounders preoperative hyponatremia proved to induce a 51% reduction in progression free survival and 47% reduction in overall survival when compared to normal patients (21).

Due to all these aspects, we consider that hyponatremia should be taken into account as a preoperative marker in order to exclude patients from per primam debulking surgery

and to decide for the administration of neoadjuvant chemotherapy followed by interval debulking surgery in order to minimize the risk of postoperative complications and to maximize the benefits in terms of survival.

However, the main limitation of our study is represented in our opinion by the limited number of cases introduced in the study group; the preliminary results and the significant impact which seems to be induced by the low level of natrium on the short term and long term outcomes of advanced stage ovarian cancer needs to be validated by larger monocentric and even multicentric studies in order to become one of the preoperative parameters which will further decide the therapeutic strategy in such cases. Once this subject will be studied on greater study groups and will become a key factor in adjusting new classes of neoadjuvant or adjuvant therapies an improvement in both short and long term outcomes is to be expected. Therefore, a potential new direction of study in such cases might be represented by the utility of adding monoclonal or immunological therapies in cases diagnosed with preoperative hyponatremia in order to improve survival.

When discussing about the possibility of adding new therapeutic lines in treating advanced stage ovarian cancer in which complete, per primam debulking is not feasible, immunotherapy has been cited as an important tool in the last decade. However, we should not omit the fact that certain immunological therapies induce themselves a higher risk of developing severe post-therapeutic conditions such as leukoencephalopathy, pulmonary embolism, anaphylactic shock, tumor lysis syndrome or even hyponatremia (22-25). One such product is represented by volociximab, an anti-angiogenic monoclonal antibody (26). This immunological agent proved to be an efficient tool in the armamentarium against platinum resistant ovarian cancer, a population subgroup with scarce therapeutic options; weekly administration of Volociximab was reported to induce stability of the disease (27). However, one of the most severe complications which were cited after administration of this product was represented of hyponatremia; therefore, these data come to demonstrate that the administration of this product in cases in which pretreatment hyponatremia is already present is rather contraindicated (28).

Another interesting issue which should be discussed is related to the possible corelation ship between hyponatremia and extent of the disease at the time of relapse. As mentioned before, independently to the completeness of cytoreduction, a significant number of patients will develop recurrent ovarian cancer and will need performing a new cytoreductove process (29,30). In such cases preoperative assessment of the resecability of the disease is even harder to be estimated due to the fact that the anatomical structures are modified by the previous administrated therapies, including surgery and due to the fact that tumoral markers might present only a slight increase (31,32). In this respect, attention was focused on determining wether other prognostic markers identified at the time of the initial diagnosis might also have a prognostic value (33). As shown in this article, the preoperative serum value of sodium has a significant predictive potential in regard to the postoperative outcomes after primary cytoreduction. However, when it comes to relapse a significant number of patients will develop the syndrome of inappropriate secretion of antidiuretic hormone as a side effect of the administration of adjuvant chemotherapy; therefore, these cases will also present a certain degree of hyponatremia which cannot be associated with the extent of the disease but with the administration of adjuvant chemotherapy (34,35). In this respect, we are enabled to consider that at the time of relapse hyponatremia itself cannot be propoed as a prognostic, marker, other biological parameters needing to be further investigated.

Conclusions

Hyponatremia represents a significant prognostic marker in regard to the development of early postoperative complications; meanwhile,

according to the findings of our study, a lower preoperative value of sodium is associated with a significantly poorer overall survival. Therefore, we suggest that preoperative hyponatremia should be considered as a prognostic factor on the long-term outcomes in advanced stage ovarian cancer; patients presenting this preoperative particularity should be also considered for neoadjuvant therapy followed by interval debulking surgery in order to maximize the chances to achieve a long-term survival rate.

Authors' Contributions

Conceptualization: Irina Balescu, Nicolae Bacalbasa. Project administration: Ciprian Bolca. Data curation: Irina Balescu, Victor Cauni, Sorin Petrea, Camelia Diaconu, Bogdan Gaspar. Software: Irina Balescu. Investigation: Adriana Ciuvica, Cristina Martac Resources: Irina Balescu, Claudiu Eduard Nistor. Supervision: Sorin Petrea, Nicolae Bacalbasa. Validation: Claudiu Eduard Nistor. Visualization: Irina Balescu, Adrian Ciuche, Adrian Hasegan.
Writing original draft: Irina Balescu, Valentin Varlas. Writing - review & editing: Irina Balescu, Nicolae Bacalbasa.

Conflicts of Interest

The authors have no conflicts of interest to declare and received no grants or funding for this study.

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Ethical Statement

Ethical approval no 88/2023 of the Ion Cantacuzino clinical hospital was obtained before beginning the study.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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