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Hyponatraemia — evaluation of prevalence in patients hospitalized in the Pulmonary Department and prognostic significance in lung cancer patients

Hiponatremia — ocena częstości występowania u chorych hospitalizowanych na oddziale chorób płuc i wpływu na rokowanie u chorych na raka płuca

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Abstract

Introduction: It is known from clinical practice that data concerning plasma sodium concentration and its influence on patient prognosis are underestimated. The aim of this study was the evaluation of the prevalence and influence of hyponatraemia on prognosis in patients with lung diseases, particularly with lung cancer.

Material and methods: Retrospective analysis of data obtained from a single Pulmonary Department was performed. A total of 449 patients divided in two groups, were analysed. The first group consisted of all lung cancer patients (n = 290) hospitalized in the analysed period. The second group included patients with hyponatraemia but without diagnosed lung cancer (n = 159). The prevalence of hyponatraemia, including severity (mild, moderate or severe), was evaluated. Histological types of lung cancer as well as comorbidities were taken into account.

Results: Hyponatraemia was found in 46.9% of patients with lung cancer, including mild (serum sodium 135–130 mEq/L), moderate (129–125 mEq/L) and severe hyponatraemia (< 125 mEq/L) in 66.9%, 25% and 8.1, respectively. In patients without lung cancer and with recognized hyponatraemia, mild, moderate and severe hyponatraemia were found in 81.8%, 13.2% and 5%, respectively (mainly in obstructive and interstitial lung diseases). Hyponatraemia was observed in 52.6% of patients with non-small cell lung cancer (NSCLC) and in 45.2% of patients with small cell lung cancer (SCLC). There was no statistical significance in prevalence of hyponatraemia between histological types of lung cancer. In patients with lung cancer and hyponatraemia compared to patients with lung cancer but without hyponatraemia, a significant increase of in-hospital mortality was found (28.7% vs. 7.8%, respectively) $p < 0.001$.

Conclusions: Hyponatraemia was a common abnormality found in approximately 50% of lung cancer patients. Hyponatraemia was a significant prognostic factor associated with poor prognosis.

Key words: hyponatraemia, lung diseases, lung cancer, prognosis

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Streszczenie

Wstęp: Z doświadczeń klinicznych wynika, że danym o obniżonym stężeniu sodu we krwi przypisuje się niewielką rolę. Celem niniejszej pracy jest ocena częstości występowania hiponatremii u pacjentów pulmonologicznych oraz jej wpływu na rokowanie u chorych na raka płuca.

Materiał i metody: Badanie miało charakter retrospektywny i dotyczyło chorych diagnozowanych i/lub leczonych w Klinice Chorób Płuc. Badana grupa liczyła 449 chorych. Wyodrębniono dwie grupy pacjentów: chorych z rozpoznanym rakiem płuca (n-290) oraz pacjentów z hiponatremią wolnych od tego rozpoznania (n-159). Obliczono częstość występowania hiponatremii poszczegól-

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nych stopni w obu grupach pacjentów, w tym w przypadkach raka z podziałem na typy i podtypy histologiczne. W opracowaniu uwzględniono występowanie chorób współistniejących oraz stosowaną terapię.

Wyniki: Hiponatremię stwierdzono u 46,9% chorych na raka płuca, w tym hiponatremię łagodną (Na 135–130 mmol/l), umiarkowaną (Na 129–125 mmol/l) i ciężką (Na < 125 mmol/l) odpowiednio u 66,9%, 25%, 8,1% pacjentów. W grupie 159 chorych bez raka hiponatremię łagodną stwierdzono u 81,8%, umiarkowaną u 13,2%, a ciężką u 5% chorych (głównie wśród pacjentów z rozpoznaniem chorób śródmiąższowych i obturacyjnych). Hiponatremię rozpoznano u 52,6% chorych z rakiem drobnokomórkowym, u 45,2% chorych z rakiem niedrobnokomórkowym . Nie stwierdzono statystycznie istotnych różnic w częstości występowania hiponatremii w poszczególnych podtypach raka niedrobnokomórkowego. W grupie chorych z rakiem stwierdzono znamiennie statystycznie większą częstość zgonów wewnątrzszpitalnych u pacjentów z hiponatremią tj. 28,7% *v.* 7,8% (p < 0,001).

Wnioski: Hiponatremia jest zaburzeniem stwierdzanym w różnych chorobach płuc, najczęściej bo u około 50% chorych z rozpoznanym rakiem płuca. Wystąpienie hiponatremii istotnie wpływa na gorsze rokowanie w tej grupie chorych.

Słowa kluczowe: hiponatremia, choroby płuc, rak płuca, rokowanie

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Introduction

Tests measuring electrolyte concentration in the blood are the most frequently performed laboratory examinations. They are carried out mainly to determine potassium concentration. Our clinical observations and the analysis of patients' discharge reports have shown that sodium deficiencies are often ignored and seldom treated. The aim of the present study was to evaluate the prevalence and prognostic significance of hyponatraemia in pulmonological patients, including lung cancer patients, hospitalized in the Pulmonary Department.

Material and methods

The study group included 449 patients (M = 296/F = 153) hospitalized in the Department of Lung Diseases and Tuberculosis at the Medical University of Silesia in Zabrze from November 2010 until March 2012. The study was retrospective and it concerned diagnosed and/or treated patients. Two groups of patients were distinguished: all patients with diagnosed lung cancer (n = 290, M = 205/F = 85) (III, IV TNM stages) and all patients with hyponatraemia without lung cancer (n = 159, M = 91/F = 68). Patients with lung cancer were treated with drug doublets: in non-small cell lung cancer (NSCLC) — with platinum preparations and third generation drugs (vinorelbine, gemcitabine, pemetrexed, docetaxel, paclitaxel), in small cell lung cancer (SCLC) — with platinum preparations plus etoposide. In order to evaluate the prognostic significance of hyponatraemia in lung cancer, the data of patients with lung cancer, with or without hyponatraemia, were compared.

In the group of 290 patients with lung cancer, in 57 patients SCLC was diagnosed, in 217 — NSCLC (in 80 — squamous cell carcinoma, in 85 — adenocarcinoma, in 45 — unspecified NSCLC, in 4 — large cell carcinoma, in 2 — carcinoma male differentiatum, in 1 — pleomorphic carcinoma); and 16 patients were not given histopathological diagnosis (this group included patients with an undoubted neoplastic process in the lungs, who due to various reasons did not undergo histopathological diagnosis). Based on routinely performed laboratory examinations, the degree of hyponatraemia was determined and patients were classified to one of three groups: mild hyponatraemia (Na = 135–130 mmoL/L), moderate (Na = 129–125 mmoL/L) and severe (Na < 125 mmoL/L). The prevalence of various degrees of hyponatraemia in the two groups of patients was calculated. The occurrence of comorbid diseases and the applied therapy were taken into account. In-hospital mortality was evaluated in the two groups of patients. Statistical analysis was made for independent variables by using t-student and chi-square tests[2].

Results

The mean age of patients in the cancer group was 63.8 ± 9.2 years, and in the group without cancer it was 59.2 ± 14.1 years; p < 0.001. The mean age of patients with cancer and hyponatraemia was 63.6 ± 8.6 years, and it did not differ from that of patients with cancer and normonatraemia, at 64.1 ± 9.8 years; p < 0.66.

Hyponatraemia was diagnosed in 136 (46.9%) patients with lung cancer. Mild, moderate and severe hyponatraemia were diagnosed in 91 (66.9%), 34 (25%) and 11 (8.1%) patients, respectively. In the group of 159 patients without cancer, mild hyponatraemia was diagnosed in 130 (81.8%) patients, moderate — in 21 (13.2%) and severe — in 8 (5%) patients. Although mild hyponatraemia predominated in the two groups,

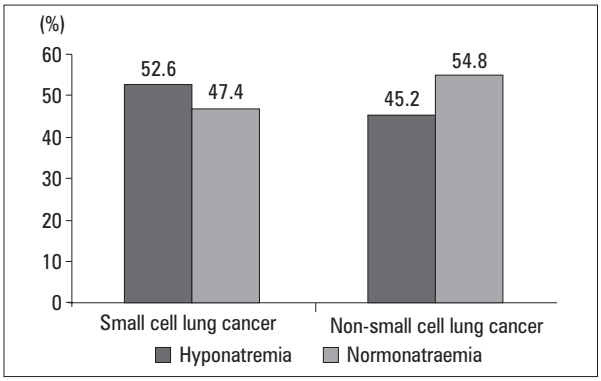

Figure 1. Percentage of diagnosed hyponatraemia according to lung cancer type

Rycina 1. Odsetek rozpoznanych przypadków hiponatremii w zależności od typu raka płuca

moderate hyponatraemia occurred statistically more often in the group of cancer patients ($p < 0.03$). In order to eliminate the potential influence of prior therapy, the prevalence of hyponatraemia in patients with a newly diagnosed lung cancer was also analysed. Hyponatraemia was diagnosed in 47/136 patients (34.5%) (in 63.8% — mild, in 21.3% — moderate, in 14.9% — severe).

Taking into account histological types, hyponatraemia was diagnosed in 30 (52.6%) patients with SCLC, in 98 (45.2%) patients with NSCLC, and in 8 (50%) patients without histopathological diagnosis (Fig. 1). After taking into consideration histological subtypes of NSCLC, no statistically significant differences were found in the prevalence of hyponatraemia in separate subtypes, $p = 0.505$. In all histological subtypes mild hyponatraemia predominated (statistical significance was not found either, $p = 0.75$) (Table 1). Among patients with cancer not treated to date, hyponatraemia was diagnosed in 12 (42.8%) patients with SCLC, in 29 (31%) patients with NSCLC and in 6 (46.2%) patients without histopathological diagnosis.

In the cancer group, a higher frequency of in-hospital deaths was found in patients with hyponatraemia, i.e. 28.7% vs. 7.8% (Fig. 2). The difference was characterized by a high statistical significance $p = 0.0001$. The highest frequency of deaths occurred in patients with severe hyponatraemia (36.4%), then moderate (29.4%) and mild (27.5%), but no statistical significance was found for this dependence, $p = 0.82$ (Fig. 3). Among cancer patients with hyponatraemia not treated to date, in-hospital mortality was estimated at 38.3%, whereas in the group of patients with hyponatraemia without lung cancer it was estimated at 8.2% ($p = 0.08$).

Table 1. The number and the mean age of patients with lung cancer in the study

Tabela 1. Liczba i średni wiek pacjentów z rakiem płuca objętych badaniem

Diagnosis Cancer in total	n-290	A mean age 63.8 years
Small cell lung cancer	n-57	62.8
Adenocarcinoma	n-85	63.4
Squamous cell carcinoma	n-80	64.9
Non-small cell lung cancer	n-45	63.7
Giant cell carcinoma	n-4	56.5
Carcinoma male differentiatum	n-2	60.5
Pleomorphic carcinoma	n-1	48.0
Lung cancer without histopathological diagnosis	n-16	71.1

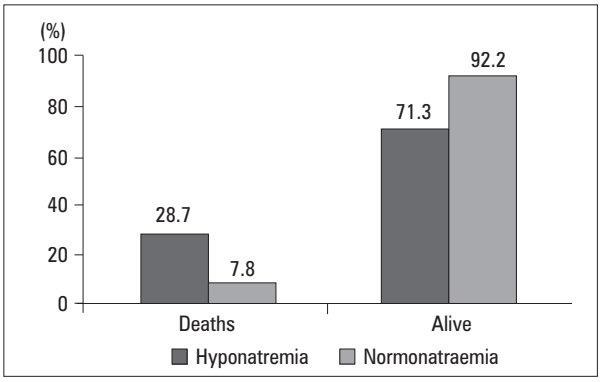

Figure 2. Mortality rate among patients with diagnosed lung cancer

Rycina 2. Odsetek zgonów wśród pacjentów z rozpoznanym rakiem płuca

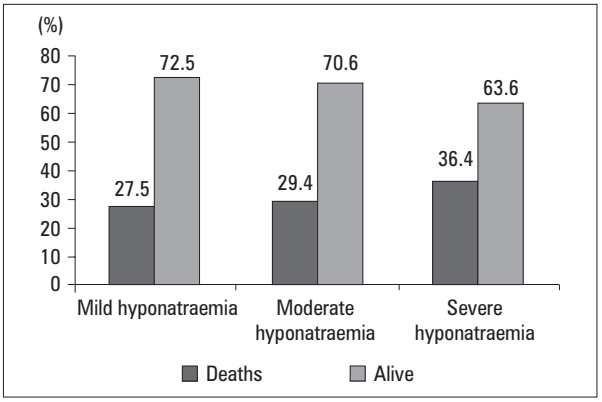

Figure 3. Mortality rate among patients with diagnosed lung cancer according to hyponatraemia severity

Rycina 3. Odsetek zgonów wśród pacjentów z rozpoznanym rakiem płuca w zależności od stopnia hiponatremii

The frequency of comorbid diseases that might lead to hyponatraemia in the group of cancer

Table 2. The frequency of hyponatraemia in different subtypes of NSCLC according to hyponatraemia severity

Tabela 2. Częstość występowania hiponatremii w podtypach raka niedrobnokomórkowego z uwzględnieniem stopni ciężkości

Types of non-small cell lung cancer (NSCLC)	Number of patients	Hyponatraemia	Mild	Moderate	Severe
Squamous cell carcinoma	31	38.7%	61.2%	32.2%	6.45%
Adenocarcinoma	41	48.2%	68.3%	29.3%	2.4%
Undifferentiated cell carcinoma	21	46.67%	61.9%	23.8%	14.2%
Others	5	71.0%	100%	0	0
Total	98	45.2%	66.3%	27.5%	6.1%

patients with hyponatraemia was also evaluated. Renal failure (GFR < 60 mL/min according to MDRD pattern) occurred in 30/136 (22.1%) patients, hepatic failure — in 16/136 (11.8%); and heart failure — in 11/136 (8.1%). In 1 patient adrenal hypofunction was diagnosed, and in 6 — hypothyroidism. 19.8% of cancer patients with hyponatraemia were also diagnosed with COPD, in 6.61% of patients bacteriologically confirmed inflammation of the airways occurred and in 5.1% — tuberculosis. Metastases to the CNS occurred in 21/136, i.e. in 15.4% of patients. Respiratory failure was diagnosed in 30.2% of all patients with hyponatraemia (among cancer patients it was 22.1%), whereas no statistically significant difference was found in the frequency of deaths in these patients compared to patients without hyponatraemia. Nearly 60% (58.8%) of cancer patients with hyponatraemia were undergoing therapy with platinum derivatives (cisplatin, carboplatin), 38.97% of patients had been using diuretics before cytotoxic treatment, 36.8% — various analgesics and 4.4% — carbamazepine.

Taking into account diagnoses in accordance with ICD-10, among the group with hyponatraemia and without lung cancer, diagnosis of interstitial lung diseases predominated (47/159 patients, including 17 patients with sarcoidosis). The remaining diseases according to their prevalence were: obstructive diseases (31/159; 28 — COPD, 3 — asthma), fluid in the pleural cavity (14/159), pneumonia (10/159), mesothelioma of the pleura (9/159) and metastases to the lungs (5/159), obstructive sleep apnoea and haemoptysis (4/159 each), burns to the airways (3/159), emphysema, Wegener's granuloma, pulmonary obstruction (2/159 each), lung abscess and mediastinal lymphadenopathy (1/159 each). Tuberculosis or mycobacteriosis was diagnosed in 10 patients, whereas the general prevalence of tuberculosis in patients with hyponatraemia was 7.1%.

In none of the 295 hyponatraemia patients (in the two groups with and without cancer) were symptoms of severe hyponatraemia observed. Hyponatraemia was not a direct cause of any death. The disorder was included in diagnoses according to ICD-10 barely in 8 patients.

Discussion

Hyponatraemia is one of the most frequent electrolyte disorders encountered in clinical practice, also in lung cancer patients. Hyponatraemia defined as lowered (< 136 mmoL/L serum sodium concentration) is in the majority of cases a mild, chronic and asymptomatic disorder. The frequency of hyponatraemia in patients hospitalized for various reasons is estimated at 1–40% [1], and it depends on the characteristics of the studied population, and on criteria used to decrease sodium values. In the study conducted by Berghmans et al. on a small group of cancer patients (n = 106, including 20 patients with lung cancer) the frequency of hyponatraemia < 135 mmol/l found at the time of diagnosis was 3.7% [1]. In another study including a significantly bigger group of patients with cancer metastases (4,702 admissions, in 3,357 patients) Doshi et al. found hyponatraemia in 47% of hospitalized patients (in 22% — hyponatraemia was diagnosed during admission, in 24% — it was acquired in hospital) — in 36% of cases mild hyponatraemia 134–130 mmoL/L, in 10% — moderate 129–120 mmoL/L and in 1% — severe < 120 mmoL/L was observed [2]. The frequency of hyponatraemia in lung cancer patients included in the present study was also high, amounting to 46.9% (66% — mild hyponatraemia, 25% — moderate, 8.1% — severe). It should be emphasized that we were estimating the frequency of hyponatraemia in all patients with lung cancer hospitalized during the study period, in both diagnosed and treated patients. 34.5% of these patients had hyponatraemia discovered at the time of diagnosis (in 63.8% — mild hyponatraemia, in 21.3% — moderate, in 14.9% — severe).

In the study group, the mean age of patients with hyponatraemia without cancer was lower than in the group with cancer (59.2 ± 14.1 vs. 68.8 ± 9.2 years $p < 0.001$). According to the literature, hyponatraemia patients are older than those with a normal serum sodium concentration, which is connected, among others, with more frequent comorbid diseases that result in hyponatraemia, e.g. renal and heart failure, thyroid dysfunction and many others [3]. No statistically significant difference was found in the age of cancer patients with or without hyponatraemia (63.6 ± 8.6 vs. 64.1 ± 9.8 years; $p < 0.66$) in the study group. We did not find a statistically significant difference in the age of patients depending on degree of hyponatraemia either.

Hyponatraemia in cancer patients is usually diagnosed in the case of SCLC [4]. In 9 studies including in total 1,684 patients with SCLC, summarised by Lassen et al. [5], hyponatraemia < 136 mmoL/L was found in 24.6%. In smaller groups, values from 25% to 44% were found [6–8], and in studies that excluded patients with mild hyponatraemia (Na 130–135 mmoL/L), this frequency amounted to 15% [9].

There are only a few reports on the prevalence of hyponatraemia in NSCLC. In the study conducted by Jacot et al. on a group of 301 patients with NSCLC this prevalence was estimated at 8% [10].

In our group of 270 patients with lung cancer, hyponatraemia was diagnosed in 52.6% of patients with SCLC, and in 45.2% of NSCLC patients, without statistically significant differences in the prevalence of hyponatraemia in its separate subtypes. Taking into account the subgroup of patients receiving no treatment, hyponatraemia was diagnosed in 42.8% of patients with SCLC, in 31% of patients with NSCLC and in 46.2% of patients without histopathological diagnosis.

It has been shown that although the prevalence of hyponatraemia in cancer patients and patients from the general population is similar, its causes are different [11]. The most crucial causes of hyponatraemia in cancer patients are excessive secretion of vasopressin by tumour cells, which clinically manifests itself as the syndrome of inappropriate antidiuretic hormone secretion (SIADH) — the most frequent cause of normovolemic hyponatraemia — and sodium loss through various ways (mainly through the alimentary tract and the kidneys) in the course of primary disease or due to the conducted therapy. The above causes in equal parts account for 2/3 of all hyponatraemia cases connected with cancer [12].

SIADH is responsible for 30% of hyponatraemia cases in cancer patients [1]. It is estimated that SIADH occurs in 15% of patients with SCLC and in 0.7% of patients with NSCLC. Other neoplasms that coexist with hyponatraemia are first of all carcinomas of the head and neck (3%), primary and metastatic tumours of the CNS, breast carcinoma, haematological malignancies (lymphomas, chronic lymphocytic leukaemia, multiple myeloma) and many others [13]. SIADH is also diagnosed in the course of many non-neoplastic diseases: in CNS diseases (traumas, meningitis, encephalitis, postoperative states), psychoses and benign diseases of the lung and pleura — in pleuritis, pneumonia, tuberculosis, empyema and asthma.

In the present study we were not assessing the prevalence of SIADH but only hyponatraemia *per se*. However, we have taken into account many clinical situations that could potentially influence the results of the present study.

In the study by Jacot et al. it has been shown that in 231 patients with NSCLC and metastases to the CNS, hyponatraemia < 132 mmoL/L was an indicator of poor prognosis, both in univariate and multivariate analysis [14]. In the present study, metastases to the CNS were diagnosed in 15.1% of hyponatraemia patients, which is very important in the prognosis for these patients.

Increased ADH secretion also occurs in the course of respiratory failure, especially chronic. Respiratory failure was diagnosed in 30.1% of hyponatraemia patients in the study population; however, a statistically significant difference in the frequency of deaths was not found. Almost 20% of cancer patients with hyponatraemia were also diagnosed with COPD, 6.6% with inflammation of the upper airways and 5.1% with tuberculosis, which are potential causes of SIADH. It is also known that SIADH may be caused by numerous drugs used in oncological practice, among others cisplatin, narcotic analgesics, carbamazepine and antidepressants [4]. We noticed that almost 60% of cancer patients with hyponatraemia were treated with cisplatin, 36.8% were administered analgesics, and 4.4% — carbamazepine. Therefore, the impact of this factor on the general prevalence of hyponatraemia has to be taken into account. On the other hand, for the patients with cancer-related SIADH syndrome, cytotoxic treatment is able to reduce the degree of hyponatraemia. It has been shown that lack of initial normalization of hyponatraemia in patients with SCLC, after two or more chemotherapy cycles based on cisplatin, results in worse survival in 75% of cases [8].

The next frequent cause of hyponatraemia in cancer patients (1/3 of all cases) is sodium depletion. In the case of lung cancer it happens mainly through the alimentary tract (vomiting and diarrhoea, usually drug-induced) and through the kidneys (usually dehydration, cisplatin preparations, diuretics). In the presented group, renal failure was diagnosed in 22.1% of patients with cancer and hyponatraemia, statistically more often than in the group with hyponatraemia without cancer. 39% of patients with cancer and hyponatraemia were using diuretics. Therefore, these factors might have a significant impact on the results.

While looking for other causes of hyponatraemia in cancer patients it should be remembered that stress and pain may be important contributing factors [13].

Apart from the two main, already mentioned causes of hyponatraemia in cancer patients, there may coexist conditions that lead to hyponatraemia irrespective of the primary disease. In the present study hepatic failure was diagnosed in the cancer group in 11.8% of patients (vs. 9.4% in the group without cancer), heart failure — in 8.1% (vs. 18.2% in the group without cancer), hypothyroidism — in 5% (the same frequency was observed in the group without cancer) and adrenocortical hypofunction occurred in 1 patient. Thus, these conditions did not occur more frequently in lung cancer patients than in others, despite the older age of cancer patients.

It was noticed that hyponatraemia, regardless of cause, might be the factor that increases in-hospital and post-hospital mortality and prolongs hospitalization [2, 4, 12]. Even mild hyponatraemia influences the higher risk of in-hospital deaths [11]. It has been proven that in-hospital mortality increases together with the degree of hyponatraemia [2]. These research projects concern mainly patients from the general population. Only a few of them estimate that such a phenomenon occurs in cancer patients. In the previously mentioned study by Doshi et al., it was shown that hyponatraemia was connected with worse 90-day survival, and HR amounted to 2.04 (95% CI 1.42–2.91), 4.74 (95% CI 3.21–7.01) and 3.46 (95% CI 1.05–11.44) for mild, moderate and severe hyponatraemia, respectively [2]. In another previously mentioned study on patients with cancer metastases, Waikar et al. showed an increased probability of death, which was significantly higher compared to patients without hyponatraemia, and which was increasing together with its severity [11].

In the present study we have shown that the frequency of in-hospital deaths in patients with lung cancer and hyponatraemia was higher than in the lung cancer group without hyponatraemia (28.7% vs. 7.8%); the difference was highly significant. Conversely, no significant differences concerning in-hospital mortality were found between the groups with various degrees of hyponatraemia. In-hospital mortality was highest in the group with newly diagnosed lung cancer (38.3%). Therefore, it may be presumed that hyponatraemia negatively influences the prognosis in these patients.

For the last three decades many researchers have been trying to estimate the role of hyponatraemia as a survival predictor in lung cancer. The majority of them (16 research projects conducted between 1982 and 2010) concerned SCLC. Hyponatraemia was combined with a significantly shorter survival time in univariate analysis (7/13 research projects) and in multivariate analysis (6/13 research projects). However, it was impossible to formulate meta-analysis based on the data from these research projects due to a lack of HR value for survival in the majority of them [4]. In the study carried out by Hermes et al. on a group of 395 patients with newly diagnosed SCLC (the study was not included in the above-mentioned analysis) it was also shown that hyponatraemia is a negative predictor in both uni-and multivariate survival analysis [15].

Only in 3 research projects were similar dependencies for NSCLC analysed. In 2 out of 3 projects, hyponatraemia turned out to be a bad prognostic indicator both in univariate and in multivariate analysis [4].

In the present study we noticed a high prevalence of hyponatraemia in patients with interstitial lung diseases - they accounted for nearly 30% of patients with hyponatraemia without diagnosis of cancer. Almost one in five patients from the group with hyponatraemia had COPD or asthma. In 6.2% of patients pneumonia was diagnosed.

The majority of reports on the frequency of hyponatraemia in lung diseases and its impact on prognosis concern pneumonia. In the study by Zilberberg et al., the frequency of hyponatraemia that accompanies community acquired pneumonia was estimated at 8.1%. They observed longer hospital stays in these patients, higher frequency of hospitalization in intensive care units, and mechanical ventilation [16]. However, no statistically significant difference was found (similarly as in the previously mentioned studies by Waikar et al. [11]) in the frequency of in-hospital deaths in these patients.

It should be also emphasized that although the frequency of hyponatraemia in hospitalized patients is high, barely 2% of cases with sodium concentration < 135mmoL/L was mentioned during discharge from hospital. The disorder was more frequently diagnosed in the case of severe forms of hyponatraemia, but still barely 30% of hyponatraemia with < 115 mmoL/L were reported and coded in accordance with ICD requirements [17]. This observation has also been confirmed by the present study.

Conclusions

Despite many years of research, it has not been finally determined whether hyponatraemia is a significant negative predictor of survival or just a marker that indicates poor general condition of the patient. The symptoms of chronic hyponatraemia are indistinct and difficult to distinguish from symptoms found in cancer patients, connected with both the disease itself and the conducted treatment (strength reduction, apathy, cognitive function disorders, headache and vertigo). Elimination of electrolyte disorder by the use of fluid restriction, infusion of iso- and hypertonic NaCl solutions, and possibly the use of V2 receptor inhibitors for vasopressin (vaptans) may possibly improve not only general condition but also prognosis in these patients. Taking into account the high prevalence of hyponatraemia in lung cancer patients and, as shown in the present study, the 28.7% in-hospital mortality in this group of patients, correct diagnosis and treatment of the disorder seems to be mandatory.

Conflict of interest

The authors declare no conflict of interest.

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