Mild Hyponatremia as an Early Marker for Intrathoracic Cancer: A Cohort Study

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ABSTRACT **Background:** Intrathoracic cancer can cause hyponatremia, but it is uncertain whether mild hyponatremia in the outpatient setting should be regarded as an early sign of intrathoracic cancer.
Objectives: To evaluate the risk of undiagnosed intrathoracic cancer in patients with new persistent mild hyponatremia.
Methods: We conducted a retrospective cohort study using the electronic health record database of a large healthcare organization. The hyponatremia group included patients with sodium concentration of 130–134 mmol/L twice, after a previous normal value and without previous history of cancer or diseases related to hyponatremia. A control group with normal sodium concentration was matched by sex, age, and year of testing. We measured specific intrathoracic cancer incidence during 3 years of follow-up after sodium concentration test date. A logistic regression was used to adjust for further clinical information including smoking history, symptoms, and medications.
Results: The study comprised 1539 participants with mild hyponatremia and 7624 matched controls. New intrathoracic cancer diagnosis was more common in the hyponatremia group during a 3-year follow-up; 1.49% in the hyponatremia group and 0.39% in the control group, crude odds ratio (OR) 3.84, 95% confidence interval (95%CI) 2.22–6.63. After adjustment, hyponatremia remained a significant risk factor for the diagnosis of intrathoracic cancer; adjusted OR 3.61, 95%CI 2.08–6.28.
Conclusions: New mild persistent hyponatremia might be a significant predictive marker to a yet undiagnosed intrathoracic cancer.

IMAJ 2023; 25: 303–307

KEY WORDS: cohort studies, diagnosis, early detection of cancer, hyponatremia, lung neoplasms

Lung cancer is the leading cause of cancer death worldwide, with 1.80 million deaths in 2020 [1]. The incidence of lung cancer in Israel is rising [2]. Smokers are at high risk, and early symptoms include cough, shortness of breath, and chest pain. Most lung cancers are diagnosed at an advanced stage, and their prognosis is poor [3]. Early detection of lung cancer can be achieved by screening [4,5] or by symptom awareness [6]. Apart from symptoms, laboratory results such as thrombocytosis [7] have been suggested as early markers. One such laboratory marker is hyponatremia.

HYPONATREMIA IN LUNG CANCER

Lung cancer of any histologic type can cause hyponatremia [8,9], mostly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [10,11]. Prevalence of hyponatremia in lung cancer patients at any stage is 16% for non-small cell lung cancer and 26% for small cell lung cancer [9]. A meta-analysis demonstrated a wide variance in prevalence of hyponatremia in lung cancer patients and a correlation with worse outcomes [12]. In small cell lung cancer, hyponatremia appears irrespectively to tumor stage [13] and is sometimes the only sign of cancer [14]. Hyponatremia is a common laboratory finding in the community [15], and intrathoracic cancer should be considered as a possible etiology [16,17].

Two large population-based studies have suggested a correlation between hyponatremia and an increased incidence of subsequent lung cancer diagnosis [18,19]. Holland-Bill and colleagues [18] found that a diagnosis of hyponatremia was a predictor of lung cancer diagnosis later.

Selmer and co-authors [19] assessed the first sodium results in the medical record. Compared to patients with normal sodium levels, those with mild hyponatremia had an increased incidence of subsequent lung cancer diagnosis.

Nevertheless, mild hyponatremia might cause a dilemma for a general practitioner. As with any condition where diagnostic tests are considered, the need for early diagnosis of a disease must be balanced with the burden [20] and harm [21] of the diagnostic process. This problem is especially true for investigation of laboratory abnormalities with mild deviations from the norm.

The aim of this study was to test whether new mild hyponatremia was associated with an intrathoracic cancer that was not yet diagnosed, controlling for possible confounders.

PATIENTS AND METHODS

STUDY DESIGN AND SETTING

This retrospective cohort study was based on the electronic health records of Maccabi Healthcare Services, the second largest health maintenance organization in Israel, serving 2.6 million members. Maccabi's fully computerized database captures information on all patient interactions with the medical system and includes demographics, doctor visits, diagnoses, imaging results, medications dispensed, procedures performed, and laboratory measurements. Blood tests in this database were obtained in the ambulatory setting and often ordered by general practitioners. We followed patients with mild hyponatremia (130–134 mmol/L) and a matched group with normal sodium levels for 3 years and searched for a diagnosis of intrathoracic cancer. The long follow-up time was chosen due to the natural history of lung cancer [22]. Follow-up data ended on 31 December 2019. The Maccabi institutional review board approved this study (ID 0024-19-BBL-MHS).

PARTICIPANTS

The hyponatremia group inclusion criteria represent the specific clinical scenario. In this scenario, a patient presents with new mild hyponatremia with no clear cause and without a past diagnosis of cancer. Many physicians would repeat mildly abnormal blood tests so this scenario included a repeated test. Thus, the hyponatremia group included all adults (older than 18 years) with mild hyponatremia, that was new (after a previous normal test), and that persisted in a subsequent test. Mild hyponatremia was defined as sodium concentration between 130–134 mmol/L as measured at Maccabi using the indirect selective electrode method.

The control group included patients with normal sodium concentration, matched by age, sex, and year of testing. Up to five control patients were matched to each patient in the hyponatremia group. For both groups, the exclusion criteria were any cancer diagnosis at baseline or a record of any of the following conditions: Addison's disease, hypothyroidism, heart failure, nephrotic syndrome, and chronic liver disease.

VARIABLES

The main outcome was the incidence of intrathoracic cancer, defined as a diagnosis of any cancer in the lung, pleura, or mediastinum after the index date and within 3 years. The diagnoses were retrieved from both patient files and the Israeli cancer registry. The exposure variable was the presence of mild hyponatremia (130–134 mmol/L) versus normal sodium level. The index date in the hyponatremia group was the date of the first abnormal sodium concentration test. We also collected data about age, sex, smoking status, drug use 4 months prior to the index date, and symptoms related to intrathoracic cancer. Smoking status was measured by Maccabi in clinical encounters using prompts to the clinician and was defined as current, past, or never. Drug use was defined by any purchase of a specific medication within the 4 months preceding the index date. Medications related to hyponatremia included amiodarone, amitriptyline, bromocriptine, carbamazepine, chlorpropamide, ciprofloxacin, desmopressin, duloxetine, furosemide, haloperidol, hydrochlorothiazide, methotrexate, nonsteroidal anti-inflammatory agents, oxycodone, proton pump inhibitors, selective serotonin reuptake inhibitors, and sodium valproate. Systemic steroid use was defined similarly by purchase history and was included in the analysis as a separate variable.

We obtained documentation regarding four symptoms related to intrathoracic cancer: cough, chest pain, dyspnea, and weight loss. Symptoms were defined as positive if they were documented as a visit symptom at least twice during the year preceding the index date.

STATISTICAL ANALYSIS

Baseline characteristics were presented as percentage or average, with chi-square test or Student's *t*-test, respectively, for group comparisons. In the main logistic regression analysis, we included pre-defined confounders that could explain both hyponatremia and intrathoracic cancer. Our assumption was that cancer that causes hyponatremia already existed at the time of testing and so the proportional hazard of diagnosis between groups would not be constant over time. Therefore, we did not use Cox regression. Age and sex were dealt by matching. The main outcome was the adjusted odds ratio (OR) of intrathoracic cancer diagnosis with mild hyponatremia versus normal sodium concentration. We adjusted for smoking status, systemic steroid use, use of drugs that are known to cause hyponatremia, and the existence of any specific symptom. In addition to the adjusted OR from the logistic regression, we also calculated the crude odds with its confidence interval. A different predefined model was used to test whether age, sex, and smoking status could predict intrathoracic cancer in the hyponatremia group. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 27 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

PARTICIPANTS

The study comprised 1539 patients in the new mild hyponatremia group and 7624 patients in the control group. Due to matching, groups had the same mean age, 68 ± 18 years, and 60.8% in both groups were women [Table 1]. The average so-

Table 1. Baseline characteristics, comparison between groups

Baseline characteristics		Control group	Hyponatremia group	*P*-value
Patients, n		7624	1539	
Age in years, mean ± SD		68 ± 18	68 ± 18	0.29
Sodium level, mean ± SD		140.1 ± 2.3	132.0 ± 1.8	0.002
Sex, n (%)	Male	2985 (39.2)	603 (39.2)	0.98
	Female	4639 (60.8)	936 (60.8)	
Medication use, n (%)*	Steroids	543 (7.1)	149 (9.7)	0.001
	Drugs related to hyponatremia	1305 (17.1)	363 (23.6)	< 0.001
Symptoms, n (%) (12 months pre-index date)	Dyspnea	122 (1.6)	62 (4.0)	< 0.001
	Cough	248 (3.3)	67 (4.4)	0.031
	Chest pain	286 (3.8)	69 (4.5)	0.17
	Weight Loss	46 (0.6)	27 (1.8)	< 0.001
At least one symptom (%)**		649 (8.5)	202 (13.1%)	< 0.001
Smoking, n (%)	Never	6580 (86.3)	1210 (78.6)	< 0.001
	Ever	676 (8.9)	187 (12.2)	
	Missing	386 (4.8)	142 (9.2)	
Chronic obstructive pulmonary disease, n (%)		438 (5.7)	92 (6.0)	0.72
Laboratory tests, mean ± SD	Urea; mg/dl	39.8 ± 17.5	40.7 ± 21.9	< 0.001
	Protein, g/dl	7.2 ± 0.4	7.1 ± 0.8	< 0.001
	Albumin, g/dl	4.2 ± 0.3	3.8 ± 0.6	< 0.001

*At least one purchase during the 4 months preceding index date
**In two medical visits during the year preceding index date
SD = standard deviation

dium concentrations in the hyponatremia and the control group at index date were 132.0 mmol/L and 140.1 mmol/L, respectively. Patients in the hyponatremia group were more likely to be smokers; to use medications known to cause hyponatremia; and to experience cough, dyspnea, or weight loss in the year before the index date. The average albumin level in this group was lower. The average interval between the index date and the second test in the hyponatremia group was 148 days and the median was 46 days.

CANCER INCIDENCE AT FOLLOW-UP

During the 3-year follow-up period, 23 participants (1.49%) in the hyponatremia group and 30 (0.39%) in the control group experienced a new diagnosis of intrathoracic cancer. Crude OR was 3.84, 95% confidence interval (95%CI) 2.22–6.63. The median time between the index date (first test) and cancer diagnosis was 855 days, interquartile range (IQR) (702–1058) in the hyponatremia group and 381.50 (IQR 210–843) in the control group.

Specific diagnoses in the medical records were *bronchus and lung primary malignancy*, *small cell carcinoma of the lung*, *non-small cell lung carcinoma*, and for one patient (in the hyponatremia group) *malignant neoplasm of the pleura.*

MULTIVARIATE ANALYSIS

Hyponatremia was significantly associated with intrathoracic cancer, adjusted OR 3.61 (95%CI 2.08–6.28) [Table 2]. Among the other variables, smoking was a significant predictor (adjusted OR 3.72, 95%CI 1.10–12.50) in the model, whereas drug use, steroid use, and symptoms were not. We performed two post-hoc sensitivity analysis. Hyponatremia was still a significant predictor in a similar regression model after adding age and sex as variables (adjusted OR 3.60 ,95%CI 2.07–6.26) and in a more restricted model with hyponatremia, age, sex, and smoking status as the only variables (adjusted OR 3.68, 95%CI 2.12–6.37).

Table 2. Logistic regression for lung cancer diagnosis during 3 years after index date, (n=9163, *P* < 0.001 for the model)

	Odds ratio (95% confidence interval)	*P*-value
Hyponatremia	3.61 (2.08–6.28)	< 0.001
Smoking ever	3.72 (1.10–12.50)	0.034
Medication use	1.09 (0.57–2.11)	0.79
Steroid use	1.92 (0.89–4.14)	0.094
At least one symptom	0.96 (0.40–2.29)	0.92

Table 3. Logistic regression results for lung cancer diagnosis during 3 years post-index in the hyponatremia group only (n=1539, *P* = 0.004 for the model)

			Odds ratio (95% confidence interval)	*P*-value
Logistic regression variable	Age		1.00 (0.98–1.03)	0.74
	Sex (female)		0.69 (0.29–1.64)	0.40
	Smoking history	Never: reference		
		Ever	5.71 (2.28–14.30)	< 0.001
		Missing	1.46 (0.31–6.77)	0.63

FACTORS ASSOCIATED WITH CANCER IN PATIENTS WITH MILD HYPONATREMIA

The logistic regression in the hyponatremia group included age, sex, and smoking status as possible predictor variables [Table 3]. Smoking history (past or current) was a significant predictor in this group (OR 5.71, 95%CI 2.28–14.30). Age and sex were not statistically significant predictors.

DISCUSSION

MAIN RESULTS

The results of this study showed a threefold risk for the diagnosis of intrathoracic cancer in patients with new mild hyponatremia compared to a matched control group. This finding persisted after adjusting for additional risk factors and after adding lung cancer symptoms at baseline. This elevated risk was robust and persisted with sensitivity analyses. In the hyponatremia group, smoking was a strong risk factor for the development of intrathoracic cancer.

INTERPRETATION

Our findings support the evidence that mild hyponatremia may be an early marker for an undiagnosed intrathoracic cancer. A competitive hypothesis is that hyponatremia is not a marker but represents other risk factors (confounders) that would later cause cancer, such as age, other diseases, and drug treatment for smoking-related conditions. There are two main arguments supporting the early-marker hypothesis: the previous evidence that intrathoracic cancer causes hyponatremia and controlling for confounders by matching and adjustment in the main analysis.

This study adds additional information to previous studies that identified hyponatremia as an early marker. The study by Holland and co-authors [18] included participants with a diagnosis of hyponatremia in their medical file, and thus included patients with moderate or severe hyponatremia. Selmer and colleagues [19] did examined the group of mild hyponatremia but used the first sodium test in the medical record, thus not representing the clinical scenario of new hyponatremia. In addition, despite adjusting for age and sex, findings were not controlled for smoking, which is the major cause of lung cancer, and drugs that might represent unmeasured confounders. Selmer et al. [19] used a Poisson regression model and calculated the incidence rate ratio (IRR) for lung cancer comparing mild hyponatremia to normal sodium concentration. The adjusted IRR was 1.87, compared to adjusted odds ratio of 3.61 in our study. The different inclusion criteria might explain this difference. We excluded participants with hyponatremia-causing diseases to prevent dilution of the study population by patients with congestive heart failure, for example, that would cause hyponatremia unrelated to lung cancer.

The yield of intrathoracic cancer diagnosis in our study, at 1.5%, is low compared to the 3% threshold for initiating cancer investigation as suggested by the National Institute for Health and Care Excellence (NICE) guidelines [23]. Despite this seemingly low yield, early diagnosis and treatment of lung cancer have a large effect on survival [24], and 1.5% yield is higher than that of a single computed tomography (CT) scan in the National Lung Screening Trial (NLST) trial [4], where among 26,309 patients in the CT arm, 270 had confirmed CT-detected cancer in the first screening round (giving a yield of 1.02%).

STRENGTHS AND LIMITATIONS

This study was planned to simulate a clinical scenario in which the general practitioner has a dilemma whether an investigation of lung cancer is indicated. To represent this dilemma, very specific inclusion criteria were used. Our large database allowed for enough patients in this study despite these inclusion criteria and with enough power to demonstrate a significant and clinically relevant elevated risk in hyponatremic patients. A much higher number of patients could be reached if only one test of hyponatremia would be required for inclusion, but this method would not represent the typical physician who orders a repeated test when mild deviations from the norm appear.

This study used most risk factors that can be tracked in the electronic health records including age, sex, smoking status, and drugs that might cause hyponatremia. Other risk factors that include occupational exposure and family history of lung cancer could not be obtained. The length of follow-up (3 years) was planned to increase sensitivity for an undiagnosed cancer at baseline, allowing also for late diagnosis. The time to cancer diagnosis

was longer in the hyponatremia group, which might result from time-immortality bias. This bias could also cause a false correlation between the hyponatremia group, which was defined by an additional test thus prolonging surveillance time, and cancer. Long follow-up can also bias the results toward the null effect if some cancer diagnoses represent the new appearance of diseases rather than a late diagnosis of cancer that existed at baseline. The results of this study should be interpreted with caution due to possible biases and the possibility of residual confounding.

CONCLUSIONS

A threefold risk exists for intrathoracic cancer diagnosis in patients with new mild, persistent hyponatremia compared to a matched control group. This result suggests that mild hyponatremia might be an early marker for intrathoracic cancer, mainly primary lung cancer.

ACKNOWLEDGEMENTS

This study was funded by Maccabi Healthcare Services Marom Research Program and by the Israeli Association of Family Physicians.

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Too often we underestimate the power of a touch, a smile, a kind word, a listening ear, an honest compliment, or the smallest act of caring, all of which have the potential to turn a life around.
Leo Buscaglia (1924–1998), American author and motivational speaker

The higher up you go, the more mistakes you are allowed. Right at the top, if you make enough of them, it's considered to be your style.
Fred Astaire (1899–1987), dancer, actor, singer, musician, and choreographer