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Original Article

Hyponatremia and hypercalcemia: a study of a large cohort of patients with lung cancer

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Background: Hyponatremia and hypercalcemia are reported to be associated with poorer prognosis in lung cancer. Our study assessed the incidence of hyponatremia and hypercalcemia in a recent large cohort of patients diagnosed with lung cancer in an academic institution and correlated incidence with patient and tumour parameters.

Methods: All patients presented at our regional lung cancer multidisciplinary team meeting between January 2011 and December 2016 were included. The incidence of hyponatremia (serum sodium ≤135 mEq/L) and hypercalcemia (serum calcium >2.62 mmol/L), including severity (mild, moderate or severe) was evaluated and stratified by tumour subtype and stage, and correlated with patient parameters.

Results: A total of 624 patients (mean age, 67.4 years; 59.3% male) diagnosed with tissue-proven lung cancer were included. Hyponatremia and hypercalcemia were present in 31.6% (n=197) and 7.1% (n=44) at time of diagnosis. Hyponatremia occurred most commonly in patients with small cell lung carcinoma (SCLC) (n=42; 41.2%; P=0.001). Hypercalcemia occurred most commonly in patients with non-small cell lung carcinoma (NSCLC) squamous subtype (n=27; 12.2%; P=0.003). The incidence of hyponatremia and hypercalcemia were significantly higher in the advanced stages (P<0.041), except in SCLC where no difference in hypercalcemia incidence across the stages was observed (P=0.573). The Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score was positively correlated with severity of hyponatremia at the early stage of NSCLC (Spearman correlation coefficient =0.325; P=0.003).

Conclusions: Hyponatremia is a common association in lung cancer, especially in SCLC. Hypercalcemia is an uncommon but significant association in the NSCLC squamous subtype. Hyponatremia might contribute to poorer ECOG-PS scores at the early stage of NSCLC.

Keywords: Epidemiology; hyponatremia; hypercalcemia; small cell lung cancer; non-small cell lung cancer

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Introduction

Lung cancer is the commonest cause of cancer-related death in men and women in Ireland, with 5-year average survival rate post-diagnosis of 17.9% (1). Electrolyte imbalance has been associated with poor survival in lung cancer patients (2-4). Hyponatremia and hypercalcemia are most commonly associated with lung cancer among other cancer types (5-7).

Hyponatremia in lung cancer is most commonly related to the syndrome of inappropriate anti-diuretic hormone secretion (SIADH) (4,8-11). Paraneoplastic syndromes and bone metastasis are two main causes of lung cancer-related hypercalcemia (7,10,12). Prior reports suggest patients with hyponatremia and hypercalcemia are asymptomatic in early stages but can become symptomatic if untreated. This could affect treatment efficacy and decrease quality of life

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(6,12-14). Early recognition and prompt correction of electrolyte imbalance may prevent clinical complications and potentially improve lung cancer morbidity and mortality (10,13).

Our center, like other centers globally, is seeing a change in the demographics of patients presenting with lung cancer, including more females and more non-squamous tumours (1). Thus, there now is a paucity of information regarding the incidence of hyponatremia and hypercalcemia in lung cancer patients in Ireland, making it difficult to determine the extent to which the presence of electrolyte imbalance contributes to the high mortality rate of lung cancer. It is also unknown if correcting this electrolyte imbalance would be of prognostic significance in these patients. This study aimed to assess the incidence of hyponatremia and hypercalcemia in lung cancer patients in a local regional cancer centre, and further analyzed the role of such electrolyte imbalance in these patients by evaluating the associations with tumour histological subtype, ECOG-PS and stage.

Methods

Data source and study population

Ethical approval for this study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals [No. ECM6(b)5/12/17], in accordance with principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. Data was derived from the National Cancer Control Programme (NCCP) Regional Cancer Centre (RCC) in Cork University Hospital (CUH) (15). Patients with tissue-proven lung cancer who were presented at our regional lung cancer MDT between January 2011 and December 2016 were retrospectively identified. This includes all patients with lung cancer presenting through our national healthcare service in Cork and Kerry. Patients were included if they had ≥1 post-cancer-diagnosis serum sodium and serum calcium laboratory test result available on the same day or week, and had no history of diagnosed hyponatremia (serum sodium ≤135 mEq/L) or hypercalcemia (serum calcium >2.62 mmol/L) (16), recorded >30 days prior to lung cancer diagnosis. Patients who were on diuretics or lithium were excluded. Our study population is representative of the age and sex distribution of the entire lung cancer population in Cork and Kerry.

Study measures

Hyponatremia and hypercalcemia were defined according to the Common Terminology Criteria for Adverse Events (CTCAE) Grading Scale (16). Hyponatremia was defined as a serum sodium ≤135 mEq/L, and further classified as mild (130–135 mEq/L), moderate (125–129 mEq/L), or severe (<125 mEq/L). Cases of true hyponatremia were identified as serum osmolality <275 mOsm/kg within 48 hours of the serum sodium result with no evidence of hyperglycemia (9). Hypercalcemia was defined as serum calcium >2.62 mmol/L, and further classified as moderate (2.63–2.99 mmol/L), or severe (≥3.00 mmol/L). In cases of hypoalbuminemia (serum albumin <35 g/L), corrected serum calcium (CSC) was calculated as CSC (mmol/L) = 0.025 × (40 – serum albumin) + serum calcium (17).

The classification of lung cancer was made in accordance with the American College of Chest Physicians (ACCP) guidelines (18). All lung cancer patients were histologically classified into three groups: (I) small cell lung carcinoma (SCLC); (II) NSCLC, which was further classified into NSCLC squamous and NSCLC non-squamous carcinoma; and (III) carcinoid carcinoma. The SCLC tumours were staged as limited (limited to one hemithorax, including mediastinal and supraclavicular lymphadenopathy) or extensive stage. Other lung tumours were staged using the TNM 7 classification (18).

The following relevant patient clinical characteristics were recorded as of the date of cancer diagnosis: age of diagnosis, sex, smoking status, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), lung function test results (FEV_1, FVC, FEV_1/FVC ratio, TLCO and DLCO), comorbidities, tumour subtype and stage.

Statistical analysis

Categorical variables were reported as frequencies and percentages, while continuous variables were expressed as mean ± standard deviation (SD). Pearson's Chi-Square test, Fisher's Exact Test, One-way Analysis of Variance (ANOVA) or *t*-test were used where appropriate to assess the differences between groups with and without electrolyte imbalance. Spearman's rho was used to measure the correlation between ordinal variables (ECOG-PS scores and severity of hyponatremia). All tests were two-tailed, with a significance level of P<0.05. All statistical analysis was performed using IBM SPSS, v24 software.

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Results

Patients

A total of 624 patients met all study requirements. 505 (80.9%) patients had serum sodium and calcium values measured >30 days prior to time of diagnosis of lung cancer. Relevant characteristics of the study cohort recorded at time of diagnosis are shown in *Table 1*. Of 624 patients, there were 370 (59.3%) males and 254 (40.7%) females. The mean age at diagnosis was 67.4±10.0 years. The majority were current or former smokers at time of diagnosis (565 patients, 90.5%). Diagnosis of lung cancer was made at an advanced stage (extensive stage in SCLC and stages IIIB/IB in TNM staging) in 338 (54.2%) patients. The subtypes included were SCLC (102 patients), NSCLC squamous (222 patients), NSCLC non-squamous (282 patients) and carcinoid carcinoma (18 patients). There were no differences in gender, age at diagnosis, smoking status, lung function and co-morbidities between the hyponatremic and non-hyponatremic groups, or between the hypercalcemic and non-hypercalcemic groups.

Incidence of hyponatremia

Hyponatremia was found in 197 (31.6%) patients (*Table 1*), of which: 151 (76.6%) were mild, 31 (15.7%) were moderate and 15 (7.6%) were severe hyponatremia (*Table 2*). The mean serum sodium of hyponatremic patients (n=197) was 131±4.5 mEq/L. The minimum serum sodium was 108 mEq/L and the maximum value was 145 mEq/L.

Hyponatremic patients were stratified by histological subtype in *Table 2*. Hyponatremia was most common (P=0.001) in SCLC (42/102, 41.2%) compared to NSCLC squamous (81/222, 36.5%), NSCLC non-squamous (73/282, 25.9%), and carcinoid (1/18, 5.6%) subtypes (*Table 2*). Patients with SCLC (135±6.0 mEq/L) had significantly lower mean serum sodium values than patients with NSCLC non-squamous (137±3.9 mEq/L; P=0.001) and carcinoid (139±2.7 mEq/L; P=0.006) subtypes. The mean was also significantly lower in the NSCLC squamous (136±5.0 mEq/L) than NSCLC non-squamous subtype (P=0.008).

Hyponatremic and hypercalcemic cases were stratified by tumour stage in *Table 3*. Hyponatremia was identified in 35/74 (47.3%) with extensive stage SCLC, and in 95/264 (36.0%) with stages IIIB/IV (*Table 3*), both percentages significantly higher than in patients with early stages of lung cancer (P<0.041). The mean serum sodium for extensive stage SCLC (134±6.48 mEq/L) was significantly lower than for limited stage SCLC (137±3.56 mEq/L; P=0.003). The mean serum sodium was also significantly lower in Stage IIIB/IV cancer (136±4.52 mEq/L) than all other stages (138±4.22 mEq/L in stages I/II, and 137±3.90 mEq/L in stage IIIA; P<0.001).

Incidence of hypercalcemia

Hypercalcemia was found in 44 (7.1%) patients (*Table 1*), of which: 38 (86.4%) were moderate and 6 (13.6%) were severe hypercalcemia (*Table 4*). The mean serum calcium of hypercalcemic patients (n=44) was 2.79±0.20 mmol/L. The minimum serum calcium was 1.93 mmol/L and the maximum value was 3.47 mmol/L.

Hypercalcemic cases were stratified by histological subtype in *Table 4*. Hypercalcemia was most common (P=0.003) in NSCLC squamous (27/222, 12.2%) compared to SCLC (4/102, 3.92%), NSCLC non-squamous (12/282, 4.26%), and carcinoid (1/18, 5.6%) subtypes (*Table 4*). The mean serum calcium values of patients with NSCLC squamous subtype (2.45±0.18 mmol/L) was significantly higher than in patients with SCLC (2.40±0.13 mmol/L; P=0.045) and NSCLC non-squamous (2.40±0.13 mmol/L; P=0.001) subtypes.

When stratified by tumour stage (*Table 3*), no patients with limited stage SCLC had hypercalcemia compared to 4/74 (5.4%) patients with extensive stage SCLC tumours, but this difference was insignificant (P=0.573) (*Table 1*). For the TNM Classification, hypercalcemia was significantly more common (P=0.016) in stages IIIB/IV (24/264, 9.1%) and stage IIIA (9/67, 13.4%) than in early stage (7/191, 3.7%) (*Table 3*). The mean serum calcium for extensive SCLC (2.42±0.13 mmol/L) was significantly higher than for limited SCLC (2.35±0.10 mmol/L; P=0.007). The mean serum calcium was also significantly higher in patients with stage IIIA (2.43±0.17 mmol/L) and IIIB/IV (2.44±0.17 mmol/L) compared to stages I/II (2.38±0.12 mmol/L; P<0.037). The difference in mean serum calcium of stages IIIA and IIIB/IV was insignificant (P=0.688).

ECOG-PS

Patients with hyponatremia showed poorer ECOG-PS scores than those without hyponatremia (P=0.012) (*Table 1*). When stratified by stage, hyponatremia was associated with poorer ECOG-PS scores only at the early (stages I/II) stage of NSCLC (P=0.039) while the presence of hyponatremia

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Table 1 Baseline characteristics of 624 patients diagnosed with lung cancer in Cork University Hospital (CUH)

Patients	Overall	Serum sodium			Serum calcium		
		≤135 mEq/L	≥136 mEq/L	P	≤2.62 mmol/L	≥2.63 mmol/L	P
Total number	624	197 (31.6)	427 (68.4)		580 (92.9)	44 (7.1)	
Gender				0.576			0.053
Male	370 (59.3)	120 (60.9)	250 (58.5)		350 (60.3)	20 (45.5)	
Female	254 (40.7)	77 (39.1)	177 (41.5)		230 (39.7)	24 (54.5)	
Mean age at diagnosis	67.4±10.0	68.1±9.4	67.0±10.3	0.195	67.4±10.0	66.6±10.6	0.606
Smoking history				0.632			0.326
Former/current smoker	565 (90.5)	180 (91.4)	385 (90.2)		527 (90.9)	38 (86.4)	
Never smoker (<100 cigarettes)	59 (9.5)	17 (8.6)	42 (9.8)		53 (9.1)	6 (13.6)	
ECOG-PS				0.012			0.333
0 to 1 or unknown	586 (93.9)	178 (90.4)	408 (95.6)		546 (94.1)	40 (90.9)	
2 to 4	38 (6.1)	19 (9.6)	19 (4.4)		34 (5.9)	4 (9.1)	
Lung function tests				0.251			0.257
FEV_1 predicted, % reference	71.8±20.0	69.0±20.6	73.0±19.7	0.574	72.4±19.7	66.2±22.6	0.967
DLCO, % reference	52.1±16.8	49.8±15.1	52.9±17.5		52.1±17.3	51.8±11.7	
Lung cancer subtype				0.001			0.003
Small cell	102 (16.3)	60 (14.2)	42 (20.8)		98 (16.9)	4 (9.1)	
Non-small cell	504 (80.8)	346 (82.0)	158 (78.2)		465 (80.2)	39 (88.6)	
Squamous cell	222 (35.6)	139 (32.9)	83 (41.1)		196 (33.8)	26 (59.1)	
Non-squamous	282 (45.2)	207 (49.1)	75 (37.1)		269 (46.4)	13 (29.5)	
Carcinoid	18 (2.9)	16 (3.8)	2 (1.0)		17 (2.9)	1 (2.3)	
Lung cancer stage							
SCLC staging	102 (16.3)	42 (21.3)	60 (14.1)	0.041	98 (16.9)	4 (9.1)	0.573
Limited stage	28 (4.5)	7 (3.6)	21 (4.9)		28 (4.8)	0	
Extensive stage	74 (11.9)	35 (17.8)	39 (9.1)		70 (12.1)	4 (9.1)	
TNM staging	522 (83.7)	155 (78.7)	367 (85.9)	0.004	482 (83.1)	40 (90.9)	0.016

Table 1 (*continued*)

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Table 1 (*continued*)

Patients	Overall	Serum sodium			Serum calcium		
		≤135 mEq/L	≥136 mEq/L	P	≤2.62 mmol/L	≥2.63 mmol/L	P
I/II	191 (30.6)	41 (20.8)	150 (35.1)		184 (31.7)	7 (15.9)	
IIIA	67 (10.7)	19 (9.6)	48 (11.2)		58 (10.0)	9 (20.5)	
IIIB/IV	264 (42.3)	95 (48.2)	169 (39.6)		240 (41.4)	24 (54.5)	
Co-morbidities				0.432			0.696
None	50 (8.0)	14 (7.1)	36 (8.4)		43 (7.4)	7 (15.9)	
Potential electrolyte disturbance							
Congestive heart failure	92 (14.7)	31 (15.7)	61 (14.3)		84 (14.5)	8 (18.2)	
Chronic kidney disease	16 (2.6)	4 (2.0)	12 (2.8)		15 (2.6)	1 (2.3)	
Liver cirrhosis	13 (2.1)	5 (2.5)	8 (1.9)		13 (2.4)	0	
Thyrotoxicosis	2 (0.3)	0	2 (0.5)		2 (0.3)	0	
Multiple myeloma	3 (0.5)	1 (0.5)	2 (0.5)		3 (0.5)	0	
Sarcoidosis	1 (0.2)	0	1 (0.2)		1 (0.1)	0	
Other	459 (73.6)	144 (73.1)	315 (73.8)		431 (74.3)	28 (63.6)	

Data are shown as mean ± SD or number (percentage).

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Table 2 Stratification of serum sodium according to histological subtype

Histological subtype	Serum sodium (mEq/L)					Total cases
	Mild hyponatremia (130 to 135)	Moderate hyponatremia (125 to 129)	Severe hyponatremia (≤124)	Total hyponatremia	Serum sodium ≥136	
SCLC	30	5	7	42	60	102
NSCLC (squamous)	63	12	6	81	141	222
NSCLC (non-squamous)	57	14	2	73	209	282
Adenocarcinoma	56	14	2	72	200	272
Large cell carcinoma	1	0	0	1	9	10
Carcinoid	1	0	0	1	17	18
Total cases (%) (n=624)	151 (24.2)	31 (5.0)	15 (2.4)	197 (31.6)	427 (68.4)	624

Table 3 Severity of hyponatremia and hypercalcemia cases according to tumour stage

Staging [n]	Serum sodium (mEq/L)				CSC (mmol/L)		
	Mild hyponatremia (130 to 135)	Moderate hyponatremia (125 to 129)	Severe hyponatremia (≤124)	Total (% of n)	Moderate hypercalcemia (2.63–2.99)	Severe hypercalcemia (≥3.00)	Total (% of n)
SCLC [102]							
Limited stage [28]	6	1	0	7 (25.0)	0	0	0 (0)
Extensive stage [74]	24	4	7	35 (47.3)	4	0	4 (5.4)
TNM staging [522]							
Stage I/II [191]	32	5	4	41 (21.5)	6	1	7 (3.7)
Stage IIIA [67]	16	3	0	19 (28.4)	8	1	9 (13.4)
Stage IIIB/IV [264]	73	18	4	95 (36.0)	20	4	24 (9.1)

Table 4 Stratification of corrected serum calcium (CSC) according to histological subtype

Histological subtype	Corrected serum calcium (mmol/L)					Total cases
	Moderate hypercalcemia (2.63–2.99)	Severe hypercalcemia (≥3.00)	Total hypercalcemia	Normal serum calcium (2.12–2.62)	Hypocalcemia (≤2.11)	
SCLC	4	0	4	98	0	102
NSCLC (squamous)	23	4	27	193	2	222
NSCLC (non-squamous)	10	2	12	269	1	282
Adenocarcinoma	10	2	12	259	1	272
Large cell carcinoma	0	0	0	10	0	10
Carcinoid	1	0	1	17	0	18
Total cases (%) (n=624)	38 (6.1)	6 (0.96)	44 (7.1)	577 (92.5)	3 (0.48)	624

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had no effect on ECOG-PS scores at the advanced (stages III/IV) stage of NSCLC (P=0.148), or at the limited and extensive stages of SCLC (P<0.562). The ECOG-PS score was positively correlated with severity of hyponatremia at the early stage of NSCLC (Spearman correlation coefficient =0.325; P=0.003). There was no difference in ECOG-PS scores of patients with and without hypercalcemia (P=0.333) (*Table 1*). Further comparison by stage was not possible due to the small number of hypercalcemic patients.

Discussion

In this study, we demonstrated that (I) hyponatremia is a common occurrence at time of diagnosis of lung cancer while hypercalcemia is uncommon; (II) characteristics of lung cancer patients with hyponatremia or hypercalcemia differed significantly in subtype and stage from those without either electrolyte imbalance; and (III) ECOG-PS was positively correlated with severity of hyponatremia at the early stage of NSCLC.

The incidence of hyponatremia in our study was similar to reported incidence rates of 34.5% in Poland (4) and 44.8% in India (11), that used the same serum sodium cutoff value measured at time of diagnosis of lung cancer.

The incidence of hyponatremia was significantly highest in the SCLC subtype, and this was consistent with previous studies (8,19). This observation can be explained by the occurrence of paraneoplastic SIADH (4,8,10,11). SIADH is more common in SCLC, occurring in 15% of patients with SCLC compared to 0.7% of patients with NSCLC (20). Our study accounted for various causes of hyponatremia by excluding all patients with previously diagnosed hyponatremia, and known to be on diuretics. However, 119 (19.1%) patients did not have serum sodium measurements >30 days before lung cancer diagnosis, of which 28 patients had hyponatremia at time of cancer diagnosis. It is possible that these patients could have had chronic hyponatremia. Anti-cancer therapies were not a contributing factor as measurements were recorded at time of diagnosis of lung cancer. In patients (n=21) with measurements of serum osmolality and urine osmolality available, all had serum osmolality <275 mOsm/kg, and urine osmolality >100 mOsm/kg. However, diagnosing SIADH requires further knowledge of the patient's volume status and urinary sodium. Most previously published studies focus only on SCLC tumours (9,21), while studies on NSCLC attribute hyponatremia to anti-cancer therapies (6). However, our study shows pre-treatment hyponatremia is also common in the NSCLC subtypes, hence an NSCLC subtype-specific explanation should be explored.

The advanced stages of lung cancer were associated with lower mean serum sodium values than early stages. The incidence of hyponatremia was significantly highest in the advanced stages of lung cancer. This finding was consistent with previous studies (21,22). However, other studies, conducted on patients with SCLC, have reported hyponatremia occurs independently of stage (9,10). Hyponatremia in the advanced stage has been hypothesized to be caused by more severe paraneoplastic syndromes secondary to increased tumour burden, resulting in elevated ectopic hormone production (11,21,22). Further measurement of association between the onset of hyponatremia with the presence and number of metastatic sites could determine if hyponatremia would be useful as a measure of tumour burden or as a predictor of recurrence.

Unlike hyponatremia, lung cancer-related hypercalcemia has been less extensively studied. Our incidence of hypercalcemia was higher than the reported incidence rate of 4.32% in the United Kingdom (7) using the same cutoff values measured at time of diagnosis of lung cancer. This could be due to systematic differences in geographical location of our study population.

Consistent with previous studies (5,10), hypercalcemia occurred most commonly in the NSCLC squamous subtype, compared to the SCLC and NSCLC non-squamous subtypes. This finding can be may be explained by ectopic parathyroid hormone-related protein (PTHrP) production by the NSCLC squamous tumour (2,7,10,12). In our study, it was not possible to confirm ectopic PTHrP production in these patients as PTH and PTHrP levels were not routinely measured. However, the statistically significant higher incidence of hypercalcemia in patients with NSCLC squamous subtype indicates a systematic difference exists between this group and patients with other histological subtypes. The occurrence of paraneoplastic syndromes would be the most likely explanation for this difference. Early recognition of hypercalcemia may allow for early diagnosis of paraneoplastic syndromes and contribute to detection of the tumour at an earlier, treatable stage.

Our study finding of significantly higher mean calcium values in the advanced stages of all subtypes of lung cancer than early stages is consistent with previous studies, which reported increased hypercalcemia incidence as lung cancer progresses to more advanced stages (2,3,7,12). Hypercalcemia in the advanced stage has been attributed

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to the presence of bone metastasis, estimated to cause 20% of hypercalcemia of malignancy (2,12). Although the site of metastasis was not recorded, patients with advanced stage of lung cancer often have distant metastasis, and severe hypercalcemia in our study population presented mostly in stages IIIB/IV. Hence, the higher incidence of hypercalcemia could potentially be an indicator of tumour burden. Further measurement of the number of metastatic sites could confirm this hypothesis.

The mechanism of hypercalcemia in SCLC is still not understood beyond the rare occurrence of PTHrP and PTH-mediated hypercalcemia (23). In our study, although the extensive stage of SCLC showed higher mean calcium values than the limited stage, there was no difference in incidence of hypercalcemia between both stages. While this could mean hypercalcemia plays a less significant role in SCLC tumour burden than other subtypes, our study was limited by the small number of hypercalcemic SCLC patients. Nonetheless, as bone metastasis occurs in all histological subtypes, this finding indicates exploration of other reasons besides bone metastasis causing increased hypercalcemia incidence in advanced stages of NSCLC.

Another important finding of our study is that hyponatremic patients had statistically significantly poorer ECOG-PS scores than non-hyponatremic patients. This association was also reported in a prospective study of 116 lung cancer patients (11). Performance status is a significant independent prognostic factor for survival in lung cancer (24,25). Poor ECOG-PS scores could be influenced by several factors such as advanced age, advanced clinical stage of lung cancer, smoking status and presence of comorbidities (26). Our study accounted for the clinical stage of lung cancer by comparing ECOG-PS scores with serum sodium status by stage. Hyponatremia significantly worsened the ECOG-PS of patients only in the early stage of NSCLC, whereas in advanced stages, hyponatremic patients had the same ECOG-PS scores as non-hyponatremic patients. This indicates that hyponatremia may be a potential prognostic factor in early stages, whereas poor ECOG-PS scores in advanced NSCLC is more likely due to increased tumour burden than low serum sodium. However, the retrospective methodology of our study may lead to unidentified confounders which can influence presumed associations.

Notably, hypercalcemic patients had the same ECOG-PS scores as non-hypercalcemic patients. Hypercalcemia may not have been sufficiently severe to cause symptoms and influence their ECOG-PS scores. Our study was also limited by the small number of hypercalcemic patients. Further study of the association of severity of hypercalcemia with ECOG-PS scores would be worthwhile.

There are a number of study limitations principally related to our retrospective study design. Not all confounding factors may have been identified. 119 (19.1%) patients had no serum sodium and calcium measurement >30 days before lung cancer diagnosis, of which 28 patients had hyponatremia and 2 patients had hypercalcemia at time of diagnosis. It is possible that these patients may have unrecorded chronic hyponatremia or hypercalcemia. Not all patients on diuretics may have been identified and excluded. Unfortunately, we have no data on patient survival, but it would be interesting to determine the speed of onset and timeline of progression of electrolyte imbalance, which could influence the survival time of patients.

Conclusions

In summary, we have shown for the first time the incidence of hyponatremia and hypercalcemia in a modern cohort of lung cancer patients in Ireland. Our results confirm hyponatremia is a common association in lung cancer, especially in SCLC. Hypercalcemia is an uncommon but significant association in the NSCLC squamous subtype. Hyponatremia might contribute to poorer ECOG-PS scores at early stage of NSCLC and should be further investigated.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The authors state that ethical approval for this study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, in accordance with principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

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