Original Article

The impact of serum sodium levels on short and long-term outcomes after lung resection for non-small cell lung cancer: a retrospective cohort study

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Background: Low sodium levels have been associated with worse prognosis in some subgroups of patients with malignancy. However, this phenomenon remains under-explored in patients undergoing lung resection for non-small cell lung cancer (NSCLC). Our aim was to explore the relationship between sodium levels and outcomes after lung resection and determine which variables affected sodium levels.

Methods: All consecutive patients undergoing lung resection between 2016 and 2019 for NSCLC in a single UK centre were included. Patients with missing sodium values were excluded. Sodium levels immediately prior to and after surgery were measured and the difference between these two values was calculated. Hyponatraemia was defined as sodium <135 mmol/L as per the World Health Organisation classification. Primary outcomes were 90-day mortality, post-operative complications, post-operative length of stay (PLOS) and overall survival. Multivariable Cox and logistic regression analyses were performed to identify factors associated with reduced overall survival and low pre-operative serum sodium levels respectively.

Results: The study comprised 1,448 patients. The mean age was 68.9 years (±8.7) and 44.1% (n=638) were male. Overall 90-day mortality was 1.9% (n=28). There was no link between lower pre-operative serum sodium levels and 90-day mortality [low sodium: 2.4% (n=3) *vs.* non-low sodium: 1.9% (n=25), P=0.69], although there was a significantly higher composite rate of post-operative complications [low sodium: 28.0% (n=35) *vs.* non-low sodium: 18.8% (n=249), P=0.01] and prolonged PLOS [low sodium: 6 days (IQR 4–9 days) *vs.* non-low sodium: 5 days (IQR 3–8 days), P=0.002] for patients with pre-operative hyponatraemia. Lower pre-operative serum sodium was independently associated with reduced overall survival (hazard ratio 0.950, 95% confidence intervals: 0.922–0.978, P<0.001). Finally, stage III disease, higher Performance Status score, lower body mass index and lower haemoglobin level were all independently associated with pre-operative hyponatraemia.

Conclusions: Lower pre-operative serum sodium levels may have an impact on short and long-term outcomes after surgery for NSCLC. If additional studies corroborate these findings, sodium levels should be considered for inclusion in models for risk prediction and prognostication after lung resection.

Keywords: Non-small cell lung cancer (NSCLC); 90-day mortality; hyponatraemia

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Introduction

Lung cancer is the most commonly diagnosed malignancy (1) and remains the leading cause of cancer death worldwide (2). Non-small cell lung cancer (NSCLC) is the major histological subtype (3) and accounts for nearly 80% of cases (4). The gold standard treatment for early-stage NSCLC is surgical resection of the tumour (5) and harvesting of lymph nodes (6). However, fewer than 20% of patients with lung cancer receive this treatment. The majority of patients have advanced disease at the time of diagnosis and hence are anatomically unsuitable to undergo lung resection (7). A further subgroup of patients with a significant burden of comorbidities and poor functional status are also precluded from undergoing surgery due to the prohibitive risk of peri-operative death.

Whilst lung cancer is associated with an overall poor prognosis (8), patients with early-stage lung cancer who undergo radical treatment usually experience significantly higher survival rates (9). Multimodality therapy (including surgery, chemoradiotherapy and more recently immunotherapy) is recognised as an appropriate treatment for certain patients with locally advanced lung cancer (10) although long-term survival rates vary widely (11). Multiple risk models have been developed to attempt to provide greater prognostic accuracy for patients with lung cancer and have traditionally included clinical, surgical and pathological components (12,13).

Highlight box

Key findings

- Pre-operative lower serum sodium levels were associated with a significantly higher rate of post-operative complications and significantly reduced overall survival after curative-intent lung resection for non-small cell lung cancer.

What is known and what is new?

- Existing studies have shown a link between lower serum sodium levels and worse prognosis for patients with advanced lung cancer.
- This study has shown a similar phenomenon for patients with early-stage and locally advanced lung cancer undergoing curative-intent surgery even after adjustment for variables associated with advanced malignant disease.

What is the implication and what should change now?

- These findings suggest that lower sodium is an independent marker of adverse short and long-term outcomes in patients with lung cancer undergoing surgery. Its use in risk stratification tools should be considered to improve prognostication.

Contemporary research into gene mutation (14) and the development of immunotherapy (15) has led to an increased focus on the role of targeted therapeutic agents (16). Simultaneously, several studies in recent years have examined the role of serum biochemical markers, serum measures of inflammation and serum tumour markers as indicators of prognosis, (17,18) and have included these variables in newly-developed risk prediction tools (19). Future lung cancer treatment regimens are anticipated to revolve around personalised therapies (20) and hence the role of specific markers detectable in an individual's blood may become increasingly important.

A low serum sodium level (hyponatraemia) is a common electrolyte abnormality and has been associated with increased morbidity and mortality in cancer patients (21). Specifically for lung cancer patients, some studies have shown that hyponatraemia is associated with reduced overall survival (22,23), although this is thought to be primarily due to an association between low serum sodium levels and advanced malignant disease (24). There is limited published data presenting varied results regarding the role of sodium levels on short and long-term outcomes for patients with NSCLC undergoing surgical resection (25,26). Hence, the aim of this study was to utilise a contemporary dataset to examine whether serum sodium levels were associated with short and long-term outcomes in patients undergoing surgical resection of NSCLC. We present this article in accordance with the STROBE reporting checklist (available at https://ccts.amegroups.com/article/view/10.21037/ccts-23-10/rc).

Methods

Patients

All consecutive patients undergoing any form of lung resection (including sublobar wedge resection, segmentectomy, lobectomy and pneumonectomy) at Manchester University NHS Foundation Trust between 2016 and 2019 for primary NSCLC were included. Patients undergoing resection for benign disease (n=105) or for secondary cancer (n=174) were excluded. Patients with missing serum sodium data were also excluded. The diagnosis of primary NSCLC was confirmed via post-operative histopathological analysis and staging was undertaken in accordance with the 8th edition of the Tumour Node Metastasis Classification for Lung Cancer. The survival time was defined as the number of days from the date of surgery to the date of death or the

date of the most recent follow-up.

Data

Our data collection methods have been explained in previous publications (27). Variables were excluded if the rate of missing data exceeded 15%. Missing categorical data were imputed based on an assumption that missingness was equal to absent, whilst missing continuous data were replaced with either the mean or median value, dependent upon the normality of distribution of data for each individual variable. All data were cleaned and stored in the Northwest Clinical Outcomes Research Registry (NCORR) (IRAS 260294). The NCORR database has full ethical approval from the regional Research Ethics Committee of the Health Research Authority. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the NCORR steering committee and individual patient consent was waived due to anonymisation of the data prior to use and the retrospective nature of the project.

Definitions

Pre-operative sodium refers to the most recent serum sodium value prior to surgery whilst post-operative sodium refers to the first recorded serum sodium value immediately after surgery. Patients with pre-operative sodium levels measured more than seven days prior to surgery were excluded. All post-operative sodium values were measured within 24 hours of surgery. Peri-operative change in serum sodium levels was defined as the difference between these two values. In order to adjust for imprecision of medical measurements and natural biological variation of sodium, the reference change value (RCV) was calculated for pre-operative sodium levels. Patients were only deemed to have had a drop in serum sodium levels if the post-operative sodium level was lower than the RCV of the pre-operative serum sodium level. The RCV for serum sodium was calculated using the values provided by McCormack *et al.* (28). Patients with sodium <135 mmol/L were considered to have low sodium, as defined by the National Institute for Clinical Excellence (NICE).

Outcomes

The primary outcomes were 90-day mortality and overall survival. Secondary outcomes included post-operative length of stay (PLOS), peri-operative change in serum sodium levels and post-operative complications. These complications included lower respiratory tract infection (LRTI), prolonged air leak, reintubation, re-operation and atrial fibrillation (AF). Complications were considered separately and as a composite endpoint.

Statistical analysis

Discrete variables are presented as percentages. Continuous variables are presented using the mean and standard deviation (SD) or median and interquartile range (IQR) for normally and non-normally distributed data respectively. Comparison of categorical variables between groups was assessed using the chi-square test, with the *t*-test or Mann-Whitney test used to compare continuous variables depending on the underlying distribution of the data. Normality of distribution was assessed visually using histograms and statistically using the Kolmogorov-Smirnov test.

The association between PLOS and serum sodium levels was assessed using linear regression. The association between variables and low pre-operative serum sodium levels was assessed using multivariable logistic regression. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated. Variables were selected for inclusion based on clinical relevance and were rationalised to maintain an event per variable ratio of at least 10.

Analysis of the difference in overall survival between groups was assessed using the log rank analysis and a survival curve was generated using the Kaplan-Meier method. Multivariable Cox regression analysis was used to identify the impact of sodium levels on overall survival. Hazard ratios (HR) and 95% CI were calculated.

All tests were 2-sided and statistical significance was defined as P value <0.05. All statistical analysis was undertaken using SPSS version 28 (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 1,469 patients underwent surgery during the study period, of whom 1.4% (n=21) were excluded due to missing sodium data. All patients had pre-operative sodium levels within seven days of surgery. This left a total of 1,448 patients for inclusion in the analysis. The mean age was 68.9 years (±8.7 years) and 44.1% (n=638) were male.

The mean pre-operative serum sodium value was

Table 1 Patient characteristics

Variable	Statistic	Missing data
Age (years)	68.9 (±8.7)	0%
Male sex	638 (44.1)	0%
Performance Status	1 [0–1]	1.8%
% Predicted DLCO	73.7 (±16.4)	9.9%
BMI (kg/m^2)	26.8 (±5.2)	9.0%
Creatinine (μmol/L)	72.0 [63.9–83.0]	13.9%
Hb (g/L)	133.8 (±14.5)	13.5%
Diabetes mellitus	207 (14.3)	1.2%
Smoking	1,114 (76.9)	1.2%
IHD	217 (15.0)	1.2%
Thoracotomy	977 (67.5)	0%
Right-sided resection	899 (62.1)	0%
Resected segments	3.9 (±1.0)	0%
TNM stage		0%
Stage I	905 (62.5)	
Stage II	307 (21.2)	
Stage III	236 (16.3)	
Sodium values		0%
Low pre-operative sodium	125 (8.6)	
Pre-operative sodium (mmol/L)	139.2 (±3.3)	
Post-operative sodium (mmol/L)	134.9 (±3.8)	
Peri-operative drop in sodium (%) (unadjusted sodium values)	1,289 (89.0)	
Peri-operative change in sodium (n=1,289) (mmol/L)	−4.9 (±2.8)	
Peri-operative drop in sodium (%) (RCV adjusted sodium values)	850 (58.7)	
Peri-operative change in sodium (n=850) (mmol/L)	−3.4 (±2.4)	

Data are presented as mean ± standard deviation, n (%) and median [interquartile range]. DLCO, diffusion capacity of the lung for carbon monoxide; BMI, body mass index; Hb, haemoglobin; IHD, ischaemic heart disease; TNM, tumour node metastasis classification; RCV, reference change value.

139.2 mmol/L (±3.3 mmol/L) and the mean post-operative serum sodium value was 134.9 mmol/L (±3.8 mmol/L). Overall, 89.0% (n=1,289) of patients had a lower post-operative sodium result compared to the pre-operative result. The mean difference in peri-operative serum sodium levels for this cohort of patients (n=1,289) was –4.9 mmol/L (±2.8 mmol/L). After considering measurement imprecision and natural biological variation (RCV) of pre-operative serum sodium levels, the proportion of patients with a lower post-operative sodium result compared to the pre-operative result was 58.7% (n=850) and the mean difference in peri-operative serum sodium levels for this cohort was –3.4 mmol/L (±2.4 mmol/L). Complete patient characteristics are shown in *Table 1*.

Short-term outcomes

Overall 90-day mortality was 1.9% (n=28). There was no

Table 2 Patient characteristics and outcomes separated by pre-operative serum sodium level

Variable	Sodium <135 mmol/L (n=125)	Sodium ≥135 mmol/L (n=1,323)	P value
Age (years)	69.9 (±7.8)	68.8 (±8.8)	0.18
Male sex	57 (45.6)	581 (43.9)	0.72
Performance Status	1 [0–1]	1 [1–1]	0.005
% predicted DLCO	67.9 (±14.8)	74.2 (±16.4)	<0.001
BMI (kg/m^2)	24.6 (±4.4)	27.0 (±5.3)	<0.001
Creatinine (μmol/L)	68.0 [60.6–78.0]	72.0 [64.0–83.0]	0.002
Hb (g/L)	127.3 (±16.0)	134.4 (±14.3)	<0.001
Diabetes mellitus	18 (14.4)	189 (14.3)	0.97
Smoking	99 (79.2)	1,015 (76.7)	0.53
IHD	20 (16.0)	197 (14.9)	0.74
Thoracotomy	88 (70.4)	889 (67.2)	0.47
Right-sided resection	78 (62.4)	821 (62.1)	0.94
Resected segments	3.9 (±1.0)	3.9 (±1.0)	0.92
Stage III disease	31 (24.8)	205 (15.5)	0.007
Short-term outcomes			
90-day mortality	3 (2.4)	25 (1.9)	0.69
Complications (composite endpoint)	35 (28.0)	249 (18.8)	0.01
PLOS (days)	6 [4–9]	5 [3–8]	0.002

Data are presented as mean ± standard deviation, n (%) and median [interquartile range]. DLCO, diffusion capacity of the lung for carbon monoxide; BMI, body mass index; Hb, haemoglobin; IHD, ischaemic heart disease; PLOS, post-operative length of stay.

difference between the mean pre-operative serum sodium level, post-operative serum sodium level and peri-operative change in serum sodium levels between patients who died within 90 days of surgery and those who survived beyond 90 days (all P values >0.10). Patients with a low pre-operative serum sodium level also did not have a significantly higher rate of 90-day mortality [low: 2.4% (n=3) *vs.* normal: 1.9% (n=25), P=0.69]. On univariable analysis, pre-operative serum sodium level, post-operative serum sodium level and peri-operative change in sodium levels were not significantly associated with 90-day mortality (all P values >0.10).

A total of 19.6% (n=284) of patients suffered a post-operative complication. These included LRTI (11.5%, n=166), AF (7.7%, n=112), prolonged air leak (11.5%, n=167), reintubation (2.5%, n=36) and re-operation (1.5%, n=22). There was no difference between the mean pre-operative serum sodium level, post-operative serum sodium level and peri-operative change in sodium levels between patients suffering a complication (considered as a composite endpoint) and those not experiencing post-operative complications (all P values >0.20). However, patients with a low pre-operative serum sodium level had a significantly higher rate of post-operative composite complications [low: 28.0% (n=35) *vs.* normal: 18.8% (n=249), P=0.01].

The median PLOS was 5 days (IQR 3–8 days). There was no relationship on univariable analysis between PLOS and pre-operative serum sodium level, post-operative serum sodium level or peri-operative change in serum sodium levels (all P values >0.10). However, patients with low pre-operative serum sodium did experience prolonged PLOS [6 days (IQR 4–9 days) *vs.* 5 days (IQR 3–8 days), P=0.002]. Complete patient outcomes are shown in *Table 2*.

Overall survival

Median follow-up for this cohort was 48 months (IQR 34–64 months). On univariable analysis, patients with low pre-operative serum sodium levels had significantly

Table 3 Cox multivariable survival analysis

Variable	Hazard ratio	95% CI	P value
Age	1.033	1.022–1.044	<0.001
Male sex	1.265	1.070–1.497	0.006
BMI	0.992	0.975–1.009	0.37
Hb	0.997	0.991–1.003	0.32
Thoracotomy	1.551	1.261–1.907	<0.001
Number of resected bronchopulmonary segments	1.006	0.926–1.093	0.89
Stage III disease	2.120	1.742–2.579	<0.001
Pre-operative serum sodium levels	0.950	0.922–0.978	<0.001
Post-operative serum sodium levels	1.008	0.982–1.035	0.56

CI, confidence interval; BMI, body mass index; Hb, haemoglobin.

reduced overall survival (log-rank analysis, P<0.001). After performing Cox multivariable regression analysis to adjust for age, gender, body mass index (BMI), pre-operative haemoglobin level, surgical approach, number of resected bronchopulmonary segments and stage III disease; lower pre-operative serum sodium level emerged as independently associated with reduced overall survival (HR 0.950, 95% CI: 0.922–0.978, P<0.001). However, serum post-operative sodium level was not independently associated with reduced overall survival. These results are displayed in *Table 3*. Finally, this effect was retained when pre-operative RCV serum sodium was included instead of unadjusted pre-operative serum sodium levels (HR 0.949, 95% CI: 0.920–0.978, P<0.001).

Predicting pre-operative sodium values

Given that these results identified that lower pre-operative serum sodium values were associated with adverse outcomes, whilst post-operative values did not appear to affect outcomes, we undertook further multivariable regression analysis to determine whether relevant pre-operative variables were independently associated with low pre-operative serum sodium. A total of 8.6% (n=125) of patients had a low pre-operative serum sodium level. Age, gender, lung function, diabetes and ischaemic heart disease did not emerge as independently associated with lower pre-operative serum sodium values. However, higher pre-operative Performance Status (PS) score (OR 1.417, 95% CI: 1.024–1.962, P=0.04), lower pre-operative BMI (OR 0.916, 95% CI: 0.876–0.958, P<0.001), lower pre-operative Hb level (OR 0.975, 95% CI: 0.963–0.988, P<0.001) and the presence of stage III disease (OR 1.635, 95% CI: 1.046–2.557, P=0.03) were all independently associated with low pre-operative serum sodium. This is shown in *Table 4*.

Discussion

In this study, lower pre-operative serum sodium levels were independently associated with reduced overall survival after lung resection for NSCLC, despite adjustment for multiple variables including stage of disease. Whilst 90-day mortality rates were not affected by serum sodium levels, patients in this cohort with pre-operative hyponatraemia experienced significantly higher rates of post-operative complications and prolonged PLOS. Finally, higher PS score, lower BMI, lower Hb and advanced disease were all independently associated with pre-operative hyponatraemia.

Only a very small number of studies on this topic have been previously published. Kobayashi *et al.* undertook a single-centre study of 386 patients undergoing surgery between 2000 and 2009 with a median follow-up time of 41 months (25). Hyponatraemia was defined as sodium <139 mmol/L and was independently associated with significantly reduced overall survival on multivariable analysis. Li *et al.* also undertook a single-centre study of 1,304 patients undergoing surgery between 2007 and 2014 with a median follow-up time of 41 months (26). Hyponatraemia was defined as sodium <141.9 mmol/L and was associated with significantly reduced overall survival on univariable analysis in patients without an anion gap (n=671) but not those with a low (n=221) or high (n=412) anion

Table 4 Multivariable analysis to identify factors associated with low pre-operative serum sodium levels

Variable	Odds ratio	95% CI	P value
Age	1.011	0.989–1.034	0.33
Male sex	1.212	0.826–1.777	0.33
Performance Status	1.417	1.024–1.962	0.04
% predicted DLCO	0.988	0.975–1.000	0.058
Hb	0.975	0.963–0.988	<0.001
BMI	0.916	0.876–0.958	<0.001
Diabetes	0.902	0.516–1.577	0.72
IHD	0.981	0.579–1.661	0.94
Stage III disease	1.635	1.046–2.557	0.03

CI, confidence interval; DLCO, diffusion capacity of the lung for carbon monoxide; Hb, haemoglobin; BMI, body mass index; IHD, ischaemic heart disease.

gap. No multivariable analysis was performed.

Furthermore, a multi-centre study by Jean *et al.* including 6,435 patients undergoing lobectomy identified dysnatraemia (serum sodium <135 or ≥145 mmol/L) as one of the three independent variables that significantly predicted 30-day mortality (29). The study did not analyse long-term outcomes and did not perform a subgroup analysis looking solely at patients with hyponatraemia. These works have a number of inherent drawbacks, including the fact that hyponatraemia has been defined differently in each of the three studies. The reasons for this are not clear. However, Li *et al.* explained that their choice of 141.9 mmol/L was reached by utilising the receiver operating characteristic curve to identify the optimum cut-off (26) This study has the benefit of using an internationally recognised definition as promulgated by NICE.

Several factors may influence serum sodium levels including syndrome of inappropriate anti-diuretic hormone secretion (SIADH), gastrointestinal losses, renal failure, congestive heart failure, nephrotic syndrome and specific medications (30). The emergence of higher PS score and advanced disease in this study as independently associated with pre-operative hyponatraemia correlates with the findings of Kobayashi *et al.* (25). Given that PS score, advanced disease, lower BMI and lower Hb are all associated with an overall increased burden of malignant disease and reduced physiological reserve, it remains unclear as to whether pre-operative hyponatraemia is simply an additional manifestation of the systemic effects of malignancy or whether it is a true independent risk factor.

The significantly increased incidence of complications amongst patients with hyponatraemia in the context of hyponatraemia not affecting 90-day mortality is interesting and not easily explained. Whilst the hyponatraemia group did have a higher proportion of variables associated with adverse outcomes [i.e., higher mean PS score, higher mean % predicted DLCO (diffusion capacity of the lung for carbon monoxide) etc.] which could account for the higher rate of complications, it would perhaps also be expected that the same variables would have a similar effect on 90-day mortality. However, the limited number of deaths within 90 days of surgery amongst the hyponatraemia group (n=3) precludes this analysis from being entirely reliable. Additionally, the prolonged PLOS amongst the hyponatraemia group is likely reflective of clinical practice whereby patients with lower sodium levels are observed in hospital until clinicians are satisfied that the serum sodium has returned to an acceptable level.

The multivariable analysis undertaken in this study highlighted the link between lower pre-operative serum sodium levels and reduced overall survival. In contrast, no link between lower post-operative serum sodium levels or greater peri-operative drop in serum sodium levels and reduced overall survival. Given that we also adjusted for a number of intra-operative variables, such a phenomenon suggests that the primary risk associated with lower serum sodium levels mainly occurs prior to surgery, whilst indicating that peri-operative changes in sodium levels have minimal influence on outcomes. Measurement of post-operative variables over a longer period of time,

particularly for patients undergoing adjuvant therapy would be useful to determine if the impact of baseline pre-operative serum sodium levels either remain important or diminish over time.

This study has a number of limitations. As a retrospective study, issues with missing data and lack of some key clinical variables such as (neo)adjuvant therapy, histological subtype and disease-free survival must be acknowledged. Furthermore, the single-centre nature of the work means that some subgroups lack sufficient power for robust statistical analysis. The relevance of this study to other centres must also be considered with caution.

Conclusions

This study has shown that whilst 90-day mortality was not affected by pre-operative hyponatraemia, the presence of low serum sodium was associated with prolonged PLOS and a higher rate of post-operative complications for patients undergoing lung resection for NSCLC. Higher PS score, lower BMI, lower pre-operative Hb level and advanced stage of disease were all independently associated with pre-operative hyponatraemia. After adjusting for a number of key pre and intra-operative variables (including stage of disease), lower pre-operative serum sodium levels remained independently associated with reduced overall survival. Additional large-scale multi-centre data is required to corroborate these results. If additional studies support these findings, pre-operative sodium should be considered as a useful variable to be included in tools designed for risk-prediction and long-term prognostication for patients with NSCLC undergoing lung resection.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://ccts.amegroups.com/article/view/10.21037/ccts-23-10/rc

Data Sharing Statement: Available at: https://ccts.amegroups.com/article/view/10.21037/ccts-23-10/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://ccts.amegroups.com/article/view/10.21037/ccts-23-10/coif). 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 study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the NCORR steering committee and individual patient consent was waived due to anonymisation of the data prior to use and the retrospective nature of the project.

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