Proteinuria: Associated with poor outcome in patients with small cell lung cancer

ABSTRACT

Objective: Although proteinuria has been increasingly reported in lung cancers, especially small cell lung cancer (SCLC), its clinical impact in patients with SCLC remains unknown.

Materials and Methods: We analyzed patients with newly-diagnosed SCLC confirmed by clinical, radiological, and pathological features over a 7-year period. Pretreatment proteinuria was assessed by quantitative analysis of 24-h urine before receiving chemotherapy. The demographic, laboratory characteristics and its impact on survival outcome were evaluated.

Results: There were 140 SCLC patients with the mean age of 70.2 years, extensive stage (89.3%), and male predominance (81.4%). Significant proteinuria (>300 mg/day) occurred in 17.4% (24/140) patients. Patients with proteinuria had significant higher serum blood urea nitrogen, lower total calcium, total protein, albumin levels, and lower creatinine clearance (Ccr) (24-h Ccr). Daily protein excretion was negatively correlated with serum total protein, albumin, and Ccr. Using a multivariable Cox proportional hazard model, proteinuria (hazard ratio, 1.943, 95% confidence interval 1.148–3.259, $P = 0.010$), along with poor performance status and serum albumin, were independent risk factors of all-cause mortality. Proteinuria was also associated with poor survival status (6.08 vs. 11.88 months, $P < 0.001$), especially in those who had severe proteinuria (>2 g/day).

Conclusions: Proteinuria is not uncommon and associated with all-cause mortality in patients with SCLC.

KEY WORDS: Daily protein excretion, outcome, proteinuria, small cell lung cancer

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INTRODUCTION

Lung cancer is the second most common cancer and the leading cause of cancer death worldwide. In patients with lung cancer, acute kidney injury is the most commonly renal complication, such as prerenal volume depletion, nephrotoxic chemotherapeutic agents (cisplatin-based), tumor lysis syndrome, metastatic kidney infiltrations, or postrenal obstruction.[1] In the subgroup of lung cancers, patients with small cell lung cancer (SCLC) frequently manifest paraneoplastic syndromes, such as endocrine, neuromuscular, skeletal, vascular, hematological, and metabolic abnormalities.[2] Paraneoplastic syndrome with renal involvement has been reported and may manifest asymptomatic proteinuria to the severe nephrotic syndrome.[3]

Proteinuria was reported and ranged from 10% to 30% in patients with lung cancers (SCLC and non-SCLC [NSCLC]). Although proteinuria is more frequent in SCLC than other histological types,[4,5] its clinical significance has not yet elucidated.[4,6-8] In this study, we aim to evaluate the incidence of proteinuria and its clinical impact on patients with newly diagnosed SCLC over a 7-year span. Results to be reported indicate that approximately 17.4% of SCLC patients had significant proteinuria, which was associated with poor survival status, especially in those who had severe proteinuria.

MATERIALS AND METHODS

Study subjects

The study was approved by the Ethics Committee on Human Studies at Tri-Service General Hospital, National Defense Medical Center, Taiwan. We investigated patients with newly diagnosed SCLC from January 2004 through December 2011. The selection of the enrolled patients was showed in Figure 1. SCLC was confirmed by clinical, radiological, and pathological features in all cases.

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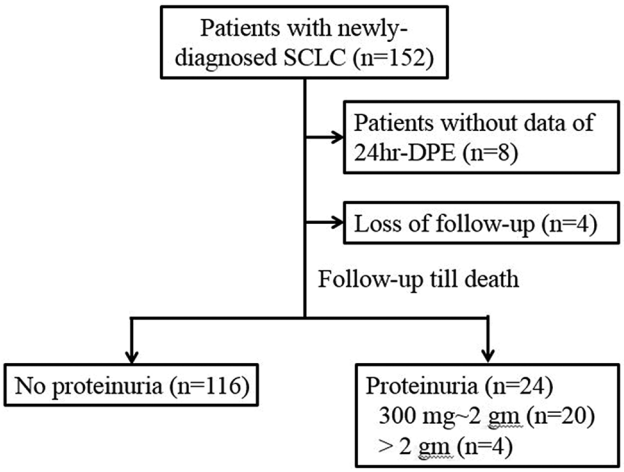

Figure 1: The chart to select small cell lung cancer patients

For treatment purposes, the two-stage system (limited or extensive stage) was used. The stage procedure included a comprehensive laboratory panel, bronchoscopy, the chest and abdominal computed tomography (CT), magnetic resonance imaging, or CT of the brain and bone scan.

Treatment protocol of small cell lung cancer

The first-line chemotherapeutic agent with platinum-based regimen was prescribed.[9-12] Cisplatin was dosed at 75 mg/m^2 intravenously on day 1, or carboplatin at Calvert AUC5 intravenously on the day 1 with etoposide at 140 mg/m^2 intravenously for 3 days. Thoracic radiotherapy was typically given over 5 weeks with cumulative doses ranging from 60 to 70 Gy divided in 30–35 fractions.[13,14] Prophylactic cranial irradiation was administered with 30 Gy divided into 10 fractions.[15,16]

Study measures and data collection

The end-point was all-cause mortality, and survival outcome was calculated as the period from the date of diagnosis to that of death which was defined as any death occurred during the hospitalization or within 1 week after discharge. Baseline demographic features, disease stage, performance status, chemotherapy regimen, accompanying comorbid conditions, smoking history, and survival time were collected.

Assessment of proteinuria

Proteinuria was defined as daily excreting more than 300 mg of protein per 24 h (24-h density polyethylene [DPE] >300 mg) according to The Kidney Disease Outcomes Quality Initiative guidelines.[17] Pretreatment proteinuria was assessed before receiving chemotherapy. All enrolled patients were divided into nonproteinuria (<300 mg/day) and proteinuria group (>300 mg/day).

Statistical analysis

Categorical and continuous variables were presented as numbers or proportion and mean ± standard deviation. The differences in the study variables were tested by unpaired Student's *t*-test or Chi-square test. All variables were assessed using the Cox proportional hazard model. Univariate analysis was first done between groups, and those (confounding factors) with a $P < 0.05$ were included in the final multivariate analysis. For compared with survival status, the Kaplan–Meier curve was used to present their difference, and the log-rank test was used to test. Statistical significance was defined as $P < 0.05$.

RESULTS

Patients' characteristics

As shown in Figure 1, a total of 140 SCLC patients were analyzed. The mean age of all patients was 70.2 years (range 43–90) with male-predominant (male:female = 114:26). Ninety-five (67.9%) patients had the performance status at 0–2 and 45 (33.1%) had the performance status at 3–4. The extensive stage (91.7% vs. 88.8%), history of hypertension (58.3% vs. 37.1%), diabetes (33.3% vs. 19.8%), and smoking prevalence (79.2% vs. 87.1%) and amount (37.3 vs. 38.5 pack-year) were more frequently encountered in patients with proteinuria than without. Totally, there were 64 (45.8%) patients who received cisplatin, whereas 29 (7.3%) received carboplatin as the chemotherapeutic agent. Moreover, there were 47 (33.6) patients who did not receive chemotherapy due to poor health status. Sixteen (11.4%) patients had ever received prophylactic cranial irradiation.

The significance in patients with pretreatment proteinuria

As shown in Table 1, the baseline demographic and laboratory characteristics were compared between patients with ($n = 24$) or without proteinuria ($n = 116$). The significant proteinuria was present in 24 patients (17.14%). The mean age of patients with proteinuria was older than those without proteinuria (72.8 vs. 69.7 years), but no significant difference was found. The significant differences were evident between two groups in terms of 24-h DPE, creatinine clearance (Ccr), serum BUN, total calcium, total protein, and albumin. The median 24-h DPE in proteinuria group was 1547.9 mg (range 315–9176 mg), and there were two cases presenting with nephrotic syndrome. One was diagnosed to have IgM nephropathy, and the other was membranous glomerulonephritis. The mean Ccr in proteinuria group was significantly lower than without proteinuria (55.7 vs. 79.5 ml/min, $P = 0.002$). In addition, serum BUN (30.5 vs. 19.6 mg/dL, $P = 0.002$), total calcium (8.4 vs. 8.9 mg/dL, $P = 0.002$), total protein (5.7 vs. 6.7 g/dL, $P < 0.001$), and albumin (3.3 vs. 3.7 g/dL, $P = 0.009$) revealed significant difference between two groups. Patients who had proteinuria were associated with worsen renal function, and lower levels of serum total calcium, total protein, and albumin. Further analysis indicated a significant negative correlation between 24-h DPE and levels of serum TP ($r = -0.304$, $P = 0.001$), 24-h Ccr ($r = -0.208$, $P = 0.014$), [Figure 2a] and serum albumin ($r = -0.405$, $P < 0.001$), [Figure 2b].

Analysis of factors related to all-cause mortality

Correlations of all-cause mortality with proteinuria were analyzed by univariate analyses. As shown in Table 2, the proteinuria, age, extensive stage, performance status, and chemotherapeutic treatment with cisplatin or carboplatin, 24-h Ccr, serum total protein, and albumin were significantly correlated with all-cause mortality ($P < 0.05$). To identify independent risk factors for survival, all variables that were significantly different were subjected to regression analyses [Table 3]. It showed proteinuria (hazard ratio [HR] 1.943, 95% confidence interval [95% CI] 1.148–3.259, $P = 0.010$), performance status (HR 1.633, 95% CI 1.013–2.632, $P = 0.044$), and serum albumin (HR 0.658, 95% CI 0.452–0.959, $P = 0.029$) were independent risk factors of all-cause mortality.

Table 1: Baseline demographic, clinical and prechemotherapy laboratory characteristics, classified by proteinuria

Variable	Proteinuria on 24hr-DPE		*P* value
	>300 mg/day	<300 mg/day	
	n=24	*n*=116	
Patient characteristics			
Age, years	72.8±12.8	69.6±12.1	NS
Gender			NS
Men, *n* (%)	22 (91.7)	92 (79.3)	
Women, *n* (%)	2 (8.3)	24 (20.7)	
Stage, (%)			NS
Extensive stage	91.7	88.8	
Limited	8.3	11.2	
Performance status			NS
0-2, *n* (%)	14 (58.3)	81 (69.8)	
3-4, *n* (%)	10 (41.7)	35 (30.2)	
First-line therapy			NS
Cisplatin, *n* (%)	5 (20.8)	59 (50.9)	
Carboplatin, *n* (%)	7 (29.2)	22 (19.0)	
No treatment, *n* (%)	12 (50.0)	35 (30.1)	
PCI, *n* (%)	3 (12.5)	13 (11.2)	NS
Smoke status			NS
Never, *n* (%)	5 (20.8)	15 (12.9)	
≦40 page-years, *n* (%)	9 (37.5)	55 (47.4)	
>40 page-years, *n* (%)	10 (41.7)	46 (39.7)	
Hypertension, %	58.3	37.1	NS
Diabetes, %	33.3	19.8	NS
Laboratory data			
24-hr DPE (mg/day)	1547.9±2223.9	115.8±50.1	0.004
Ccr (ml/min)	55.7±18.5	79.5±21.9	0.002
BUN (mg/dL)	30.5±14.8	19.5±10.9	0.002
Cr (mg/dL)	1.4±0.8	1.2±1.1	NS
T Ca (mg/dL)	8.4±0.7	8.9±0.6	0.002
UA (mg/dL)	6.9±3.3	5.6±1.9	NS
TP (g/dL)	5.7±1.0	6.7±0.8	<0.001
Albumin (g/dL)	3.3±0.7	3.7±0.5	0.009
Total cholesterol (mg/dL)	158.3±42.2	172.4±39.9	NS
Triglyceride (mg/dL)	139.2±97.5	109.0±55.1	NS
CRP (mg/dL)	7.6±7.6	8.0±9.9	NS

Note: 1. NS demonstrates no significant difference 2. Data are means±SD or percentages. Abbreviations are: PCI=Prophylactic cranial irradiation, Ccr, 24-hr urine creatinine clearance, 24-hr DPE=24-hr urinary daily protein excretion, T Ca=Serum total calcium, TP=Serum total protein

Table 2: Cox proportional hazard model of factors associated with all-cause mortality in patients with SCLC

Variable	Univariable		*P* value
	HR	95% CI	
Proteinuria on 24hr-DPE			
<300 mg/day	1.000		
>300 mg/day	2.006	1.283-3.136	0.002
Patient characteristics			
Gender			
Men, *n* (%)	1.000		
Women, *n* (%)	1.028	0.669-1.580	NS
Age, years	1.014	1.001-1.028	0.040
Extensive stage, %	1.829	1.022-3.274	0.042
Performance status			
0-2	1.000		
3-4	2.202	1.522-3.184	<0.001
Chemotherapy therapy			
Treatment	0.523	0.365-0.749	<0.001
No treatment	1.000		
PCI			
With	0.949	0.523-1.720	NS
Without	1.000		
Hypertension, %	1.080	0.768-1.520	NS
Diabetes, %	1.184	0.792-1.770	NS
Smoke status			
Never, *n* (%)	1.000		
≦40 page-years, *n* (%)	0.859	0.519-1.421	NS
>40 page-years, *n* (%)	0.982	0.586-1.644	NS
Laboratory data			
Ccr (ml/min)	0.995	0.990-0.999	0.026
BUN (mg/dL)	1.008	0.996-1.021	NS
T Ca (mg/dL)	1.047	0.777-1.411	NS
UA (mg/dL)	1.050	0.965-1.143	NS
TP (g/dL)	0.755	0.601-0.948	0.015
Albumin (g/dL)	0.608	0.440-0.840	0.003
Total cholesterol (mg/dL)	1.002	0.997-1.006	NS
Triglyceride (mg/dL)	1.000	0.997-1.003	NS
CRP (mg/dL)	1.001	0.986-1.017	NS

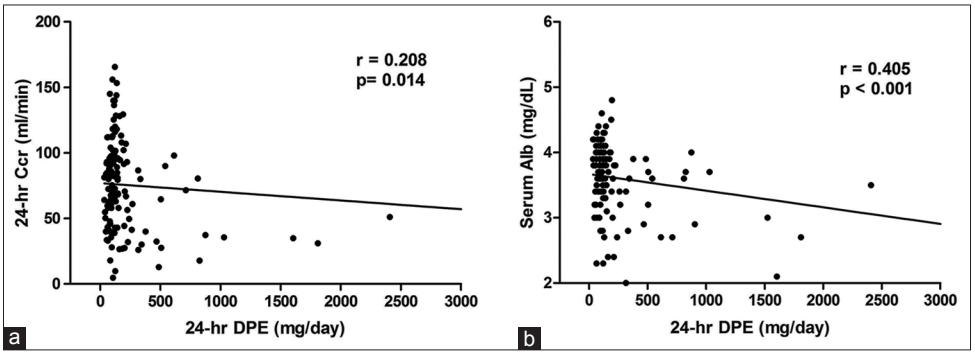

Figure 2: Correlation between 24-h density polyethylene and 24-h creatinine clearance (a) or serum albumin (b)

Groups comparisons of survival outcome

The patients were subgrouped into three groups (<300 mg/day, 300–2 g/day, and >2 g/day) and the survival was compared. The Kaplan–Meier curves revealed a significant difference of survival rate among three groups [Figure 3, $P < 0.001$]. Significant proteinuria was associated with poor survival status (6.08 vs. 11.88 months, $P < 0.001$), especially in those who had severe proteinuria (>2 g/day).

DISCUSSION

In this study, we showed that 17.4% of patients had significant proteinuria which were higher than in the general population (2–4%).[18,19] Importantly, proteinuria was an independent prognostic factor of all-cause mortality after adjusting all confounding factors. Furthermore, more severe proteinuria was associated with poor survival status. This was the first study in Asia countries to investigate the clinical impact of proteinuria in patients with SCLC.

Proteinuria, a marker of kidney disease, is strongly associated with the risk of adverse outcomes. Evidence suggests that proteinuria not only has implications for all-cause mortality and cardiovascular events in general population but also in patients with chronic kidney disease or malignancies.[2,19-22] Despite its evolving role as a major risk factor of all-cause mortality, little is known about the clinical impact of proteinuria in patients with SCLC.

SCLC is the most aggressive histologic type and the median survival without treatment is approximately 2–4 months.[23,24] The identification of poor prognostic factors is the most importance for the treatment of patients with SCLC. Several prognostic parameters have been previously reported including extensive disease, performance status, serum lactate dehydrogenase level and gender. However, the correlation between proteinuria and survival outcome in patients with SCLC has not yet been elucidated. Our results showed that the more severe proteinuria group was associated with poor survival, indicating that proteinuria is an independent prognostic factor for all-cause mortality. The similar result was also observed in the previous study, thus further supported that proteinuria is a poor prognostic factor independent of race. The finding is important because current clinical practice for predicting outcomes in SCLC are solely based on limited or extensive stage without explicit consideration of the concomitant proteinuria.

In accordance with the distribution of paraneoplastic renal syndrome in patients with different histologic types

Table 3: Cox proportional hazard model for multi-factors associated with all-cause mortality in patients with SCLC

Variable	Multivariable		*P* value
	HR	95% CI	
Proteinuria on 24hr-DPE			
<300 mg/day	1.000		
>300 mg/day	1.943	1.148-3.259	0.013
Patient characteristics			
Age, years	0.997	0.981-1.014	NS
Extensive stage, %	1.445	0.784-2.663	NS
Performance status			
0-2	1.000		
3-4	1.633	1.013-2.632	0.044
Chemotherapy therapy			
Treatment	0.629	0.390-1.016	NS
No treatment	1.000		
Laboratory data			
24-hr Ccr (ml/min)	1.000	0.995-1.006	NS
TP (g/dL)	1.021	0.814-1.281	NS
Albumin (g/dL)	0.658	0.452-0.959	0.029

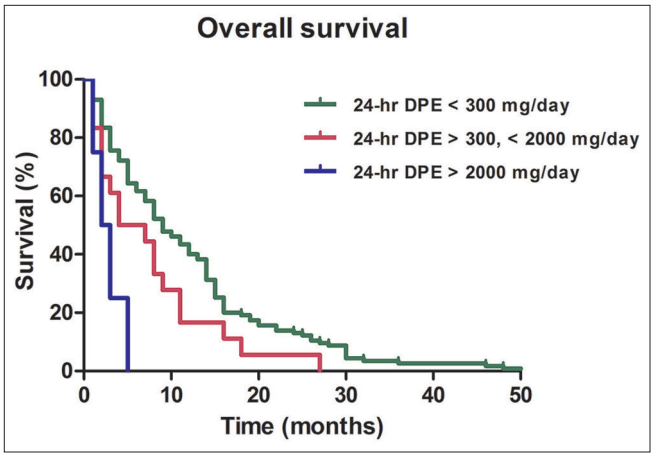

Figure 3: Proportion of free of death, stratified by the severity of proteinuria

Table 4: The prevalence and outcome of albuminuria or proteinuria in patients with lung cancers or SCLC

Study	Case numbers	Cancer type	Assay technique	Definition of albuminuria or proteinuria	Prevalence (%)	Outcome: proteinuria present vs abscent
Sawyer *et al* (1988)[6]	106	Lung	Urinary protein concentrations	>100 mg/L	28	Median survival in months: 1.5 vs 4.5
Puolijoki *et al* (1989)[7]	150	Lung	Daily protein excreation	>100 mg/day	13	-
Pedersen *et al* (1996)[4]	232	SCLC	Urine dipstick testing	Positive for albumin	37.5	Survival rate at 1, 2 and 5 years: 35%, 10%, 3% vs 50%, 26%, 15%
Pedersen *et al* (1998)[8]	102	Lung	Urinary albumin excretion rate	>20 ug/min	32.4	Survival rate at 1 and 3 years: 22%, 4% vs 66%, 16%
Our study (2014)	140	SCLC	24hr-DPE	> 300 mg/day	17.14	Median survival in months: 6.08 vs. 11.88

of lung cancer,[25-28] a European retrospective study using urine dipstick test demonstrated that the proteinuria was significantly higher in patients with SCLC as compared to those with NSCLC (37.5% vs. 28%).[4,5] Our result showed that approximately half of the prevalence [17.4%, Table 4] of proteinuria observed than in the European report.[29-36] The different methodology with an accurate test for quantification of proteinuria and the racial difference may explain the difference between ours and European and the previous reported investigation.[37,38]

In this study, we also found a negative correlation between proteinuria and serum total protein and albumin levels and 24-h Ccr. These observations indicated that SCLC patients with significant proteinuria were associated with poorer nutritional status and more severe renal dysfunction, which might explain why patients with proteinuria have a poorer prognosis.[20,22,39] Smoking is an another well-established risk factor for SCLC, and epidemiologic studies suggest that smokers manifest severe proteinuria and worsen renal function.[40] The precise pathogenesis of the nephrotoxic effect on the kidney is still under investigation, and several potential mechanisms of smoking-induced renal damage have been proposed. Even though these factors may explain the relationship between proteinuria and cancer prognosis, smoking only can partially explain the development of proteinuria in SCLC and no significant difference was found in our study results.

There are some limitations in our study. First, due to the retrospective study, study design and smaller sample size of the study, the prognostic impact of proteinuria needs to be confirmed by large, prospective cohort studies. Second, the prevalence of proteinuria may be underestimated because we only enrolled the cases whose 24-h DPE were available and chart review may raise some selection bias. Third, we did not measure the glomerular and tubular damage biomarkers and did not undergo renal biopsy, which may be helpful to elucidate the source of proteinuria.

CONCLUSIONS

We demonstrated that the prevalence of proteinuria is not uncommon in patients with SCLC. In addition, proteinuria has been proven to be a poor prognostic factor of all-cause mortality. The routine screen of proteinuria in SCLC patients may be helpful for clinicians to provide better patient care. Whether reducing proteinuria improves survival in patients with SCLC needs further investigations.

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Conflicts of interest
There are no conflicts of interest.

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