Original Article

Prognostic significance of procalcitonin in small cell lung cancer

Kosuke Ichikawa[1], Satoshi Watanabe[1], Satoru Miura[2], Aya Ohtsubo[1], Satoshi Shoji[1], Koichiro Nozaki[1], Tomohiro Tanaka[1], Yu Saida[1], Rie Kondo[1], Satoshi Hokari[1], Nobumasa Aoki[1], Yasuyoshi Ohshima[1], Toshiyuki Koya[1], Toshiaki Kikuchi[1]

[1]Department of Respiratory Medicine and Infectious Diseases, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [2]Niigata Cancer Center Hospital, Niigata, Japan

Contributions: (I) Conception and design: K Ichikawa, S Watanabe; (II) Administrative support: S Watanabe; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: K Ichikawa; (V) Data analysis and interpretation: K Ichikawa; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Satoshi Watanabe. Department of Respiratory Medicine and Infectious Diseases, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachidori, Chuouku, Niigata, 951-8510, Japan. Email: satoshi7@med.niigata-u.ac.jp.

Background: Procalcitonin (PCT) is a serological marker whose utility has been established in infectious disease areas. Although serum calcitonin is a prognostic predictor in patients with medullary thyroid carcinoma, the clinical usefulness of PCT remains unclear in lung cancer patients.

Methods: As a discovery cohort, we retrospectively analyzed consecutive patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) who received first-line chemotherapy at our institution, and PCT blood levels were measured. As the validation cohort, PCT blood levels were prospectively evaluated in SCLC patients before first-line chemotherapy. The correlation between a PCT increase and prognosis was examined in the discovery and validation cohorts.

Results: Twenty-three SCLC patients and 26 NSCLC patients were enrolled as the discovery cohort, and 30 SCLC patients were enrolled as the validation cohort. The PCT level in SCLC patients was significantly higher than that in NSCLC patients. The PCT level was not associated with WBC count and weakly associated with the CRP level. In both the discovery and validation cohorts, the median survival time was significantly shorter in SCLC patients with PCT-high than in SCLC patients with PCT-normal (discovery; 11.7 *vs.* 89.7 months, P<0.005, validation; 9.6 *vs.* 22.6 months, P<0.005).

Conclusions: It may be difficult to differentiate bacterial infections in SCLC patients by PCT, as PCT is elevated even in SCLC patients without infectious diseases. This is the first study to prospectively verify that pretreatment PCT levels have a significant negative correlation with prognosis in SCLC patients.

Keywords: Procalcitonin (PCT); non-small cell lung cancer (NSCLC); small cell lung cancer (SCLC); prognostic factors

Submitted Oct 14, 2021. Accepted for publication Dec 16, 2021.
doi: 10.21037/tlcr-21-838
View this article at: https://dx.doi.org/10.21037/tlcr-21-838

Introduction

Small cell lung cancer (SCLC) is one of the primary lung cancers of neuroendocrine origin and is strongly associated with smoking and characterized by rapid progression. SCLC is classified into limited disease (LD) and extensive disease (ED) depending on the degree of progression. Because of the sensitivity of SCLC to chemotherapy and radiation therapy, one of the standard initial treatments of SCLC is platinum-based chemotherapy with or without radiotherapy, which is known to cause febrile neutropenia in 10–20% of patients (1).

Procalcitonin (PCT) is a 13-kDa peptide consisting of 116 amino acids (2) that is usually synthesized in thyroid C cells as a precursor of calcitonin (3). PCT has a stable half-life of 24 to 30 hours and very low serum levels. In recent

years, PCT has attracted attention as an indicator of the severity of bacterial and fungal infections (4). In addition, compared to conventional inflammatory markers such as C-reactive protein (CRP) and leukocyte count, PCT has superior sensitivity and specificity in bacterial and fungal infections and is used to distinguish it from viral infections and noninfectious diseases (5). As its clinical usefulness has become known, a precise and simple test method for PCT has been established. The secretion of calcitonin from medullary thyroid carcinoma, SCLC, and neuroendocrine tumors has been reported (6,7). Specifically, in medullary thyroid carcinoma, an increase in serum calcitonin is known as a prognostic predictor (5). Neuroendocrine cells in the lung were suggested as the origin of SCLC (8). *Calcitonin related polypeptide alpha* encodes calcitonin and calcitonin gene-related peptide (CGPR). Because neuroendocrine cells widely express calcitonin gene related protein, tumorigenesis of these cells may result in elevation of production of PCT and calcitonin. The usefulness of calcitonin as a tumor marker or prognostic factor has been investigated in SCLC, but no conclusion has been reached (9). Similarly, PCT is also expected to be secreted from SCLC and might be a prognostic predictor in SCLC patients. Indeed, Patout *et al.* reported that the increase of serum PCT and the negative correlation between serum PCT level and prognosis in patients with lung cancer with neuroendocrine component (10). However, few reports so far have evaluated the increase in serum levels in patients with SCLC (11,12). As mentioned earlier, SCLC is usually treated with intense radiotherapy and chemotherapy, and fever often occurs during the course of treatment, but it is not known whether PCT is useful to distinguish between infectious and noninfectious fever when SCLC patients develop fever.

The purpose of this study was to evaluate serum PCT levels in patients with SCLC and to investigate the value of PCT as a prognostic factor. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-838/rc).

Methods

Patient population

Patients who were pathologically diagnosed with SCLC at our institution between February 2005 and January 2007 and had their PCT measured before receiving their first cycle of chemotherapy were retrospectively included. Patients who were diagnosed with non-small cell lung cancer (NSCLC) during the same period and had their PCT measured before receiving their first cycle of chemotherapy were also included. These patients were defined as the discovery cohort. We used our official institutional website as an opt-out method for the discovery cohort. This study was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN 000035975). It was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and the protocol was approved by the Institutional Review Board of Niigata University (No. 2020-0312). Patients in the validation cohort provided written informed consent. The eligibility criteria for the validation cohort included SCLC pathologically diagnosed at our institution between February 2013 and June 2017, absence of previous chemotherapy and target lesions according to the Response Evaluation Criteria for Solid Tumors (version 1.0). Consecutive patients who met the eligibility criteria were prospectively enrolled and served as the validation cohort. To confirm that there were no active infectious in the validation cohort, contrast-enhanced CT scans were performed prior to initial treatment.

Measurement of PCT concentration

Before the first cycle of systemic chemotherapy, blood samples were collected into a blood collection tube containing a serum-separating agent or EDTA and centrifuged at 3,000 rpm for 20 minutes. Serum was separated, frozen and stored at –80 ℃. The concentration of PCT was measured using chemiluminescent enzyme immunoassay by SRL (Tokyo, Japan). The cutoff value was defined as the upper limit of PCT and was defined as 0.05 ng/mL, and its correlation with prognosis was examined as mentioned below.

Statistical analysis

The differences in categorical variables between patients with a normal or high PCT concentration were determined using the chi-square test, as appropriate. Kaplan-Meier survival curves were constructed for overall survival (OS), and differences between groups were identified using the log-rank test. This analysis was two sided, with a 5% significance level and a 95% confidence interval. The correlation between PCT measurements and survival was determined by the Spearman rank correlation coefficient.

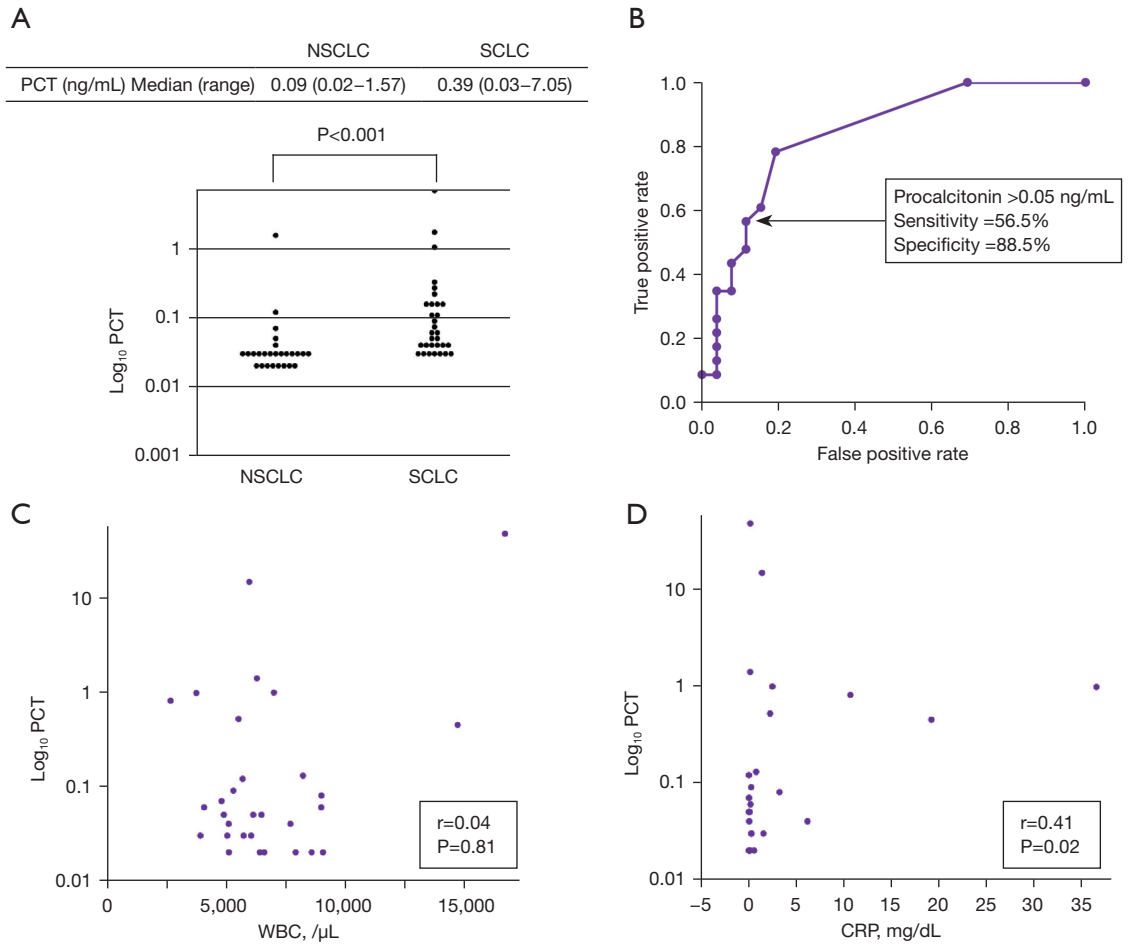

Figure 1 PCT is significantly elevated in patients with SCLC regardless of CRP and WBC. The distribution of pretreatment PCT values for NSCLC and SCLC patients in the discovery cohort is shown in a graph using the common logarithm (A). ROC curve created by calculating the sensitivity and specificity of PCT in SCLC as a control for NSCLC for each cutoff value of PCT, with the horizontal axis as 1-specificity and the vertical axis as sensitivity (B). The 0.05 used for the cutoff value is indicated by the arrow in the plot. Correlation between PCT and WBC count (C) and CRP level (D) in the validation cohort. PCT, procalcitonin; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ROC, receiver operating characteristic; WBC, white blood cell; CRP, C-reactive protein.

To identify the variables significantly associated with survival, multivariate logistic regression analysis was performed. All statistical analyses were performed using JMP 14.0.0 statistical software (SAS Institute, Cary, NC, USA).

Results

Patient population

As a discovery cohort, we enrolled 23 patients with SCLC and 26 patients with NSCLC. The respective PCT values are shown in *Figure 1A*. PCT was significantly higher in SCLC patients (P<0.001). The receiver operating characteristic (ROC) curve generated by calculating the sensitivity and specificity of PCT in NSCLC patients as controls for each PCT cutoff value is shown in *Figure 1B*. The horizontal axis is the specificity, and the vertical axis is the sensitivity; 0.05, which was used as the cutoff value in this study, is shown in the plot as an arrow. The sensitivity and specificity were 56.5% and 88.5%, respectively.

As the validation cohort, 30 of 48 patients who met the eligibility criteria and developed SCLC within the study period were enrolled in the study and analyzed. The characteristics of patients in the discovery and validation

Table 1 Baseline characteristics of the patients

Main characteristics	Discovery cohort, N=23	Validation cohort, N=30	P
Median age [range], y	62 [47–72]	67 [50–85]	0.005
Sex			0.118
Male	23 (100%)	27 (90%)	
Female	0 (0%)	3 (10%)	
Stage			0.206
LD	10 (43%)	13 (43%)	
ED	13 (57%)	17 (57%)	
ECOG performance status			0.177
0	7 (30%)	6 (20%)	
1	9 (39%)	14 (47%)	
2	2 (9%)	5 (17%)	
3	2 (9%)	3 (10%)	
4	0 (0%)	2 (7%)	
NA	3 (13%)	0 (0%)	
1st line chemotherapy			0.068
CDDP + ETP	10 (43%)	11 (37%)	
CDDP + CPT–11	1 (4%)	5 (17%)	
CBDCA + ETP	8 (35%)	12 (40%)	
Ifosphamide + CBDCA + ETP	4 (18%)	0 (0%)	
CDDP + PTX + AMR + NGT	0 (0%)	2 (7%)	
Radiotherapy			0.754
+	6 (26%)	9 (30%)	
–	17 (74%)	21 (70%)	
Surgery			0.440
+	1 (4%)	3 (10%)	
–	22 (96%)	27 (90%)	

cohorts are shown in *Table 1*. In the discovery cohort, all patients were male, the median age was 62 years (range, 47–72 years), 10 (43%) had LD, 16 (69%) had a performance status (PS) of 0–1, 6 (26%) received chemoradiotherapy, and one (4%) had prior surgery. The regimen of choice for first-line chemotherapy was cisplatin (CDDP)/etoposide (ETP) in 10 patients (43%), CDDP/irinotecan in one patient (4%), carboplatin (CBDCA)/ETP in 8 patients (35%), and ifosfamide/CBDCA/ETP in 4 patients (18%). In the validation cohort, 3 (10%) patients were female, and the median age of all patients was 67 years (range, 50–85 years). Thirteen (43%) patients had LD, 20 (67%) had a PS of 0–1, 9 (30%) received chemoradiotherapy, and 3 (10%) had prior surgery. The regimens selected for first-line chemotherapy were CDDP/ETP in 11 patients (37%), CDDP/irinotecan in 5 patients (17%), CBDCA/ETP in 12 patients (40%), and CDDP/paclitaxel/amrubicin/topotecan in 2 patients (7%). The correlation between PCT measured before the start of treatment in the validation cohort and white blood cell (WBC) count and CRP level is shown in *Figure 1C,1D*. There was no correlation between PCT and the WBC count and a weak correlation between PCT and CRP level. The validation cohort underwent contrast-enhanced CT scans prior to the start of initial therapy to ensure that there were no active infectious lesions.

Patient characteristics according to the PCT level

Table 2 shows the characteristics of the patients according to the level of PCT. *Figure 2* shows the distribution of PCT values in each group, with the vertical axis being the positive logarithm of the graph. In the discovery cohort, there were 13 patients (57%) in the PCT-high group. There were significantly more ED cases in the PCT-high group. All patients in the PCT-normal group had normal neuron-specific enolase (NSE) values that were significantly lower than those in patients in the PCT-high group. By contrast, all patients in the PCT-high group had high pro-gastrin-releasing peptide (ProGRP) levels, which tended to be higher than those in patients in the PCT-normal group.

In the validation cohort, there were 15 patients (50%) in the PCT-high group. Patients in the PCT-high group were significantly older than those in the PCT-normal group. While 4 patients in the PCT-normal group achieved complete response (CR), no patient the PCT-high group achieved CR, but there was no significant difference in the treatment effect between the two groups. Consistent with the discovery group, all patients in the PCT-high group had high ProGRP levels, which were significantly higher than those in patients in the PCT-normal group.

Overall survival

The Kaplan-Meier curves for OS in the PCT-normal and PCT-high groups are shown in *Figure 3A,3B*. In both the discovery and validation cohorts, OS was significantly

Table 2 Patient characteristics according to procalcitonin level

Characteristics	Discovery cohort			Validation cohort		
	PCT normal, N=10	PCT high, N=13	P	PCT normal, N=15	PCT high, N=15	P
Median age [range], y	65 [47–72]	62 [55–71]	0.975	65 [50–81]	73 [62–85]	0.002
Stage						
LD/ED	9/1	5/8	0.008	8/7	5/10	0.267
Number of metastatic organ						
0/1	10	10	0.052	12	12	0.623
≥2	0	3		3	3	
ECOG performance status						
0/1	5/3	2/6	0.358	3/9	3/5	0.117
2/3/4	1/0/1	1/2/2		3/0/0	2/3/2	
Response						
CR/PR	7/2	2/6	0.304	4/10	0/10	0.690
SD/PD/NA	0/1/0	3/0/2		1/0/0	1/2/2	
Tumor markers						
NSE normal/high/NA	10/0	5/8	<0.005	6/9/0	7/7/1	0.588
ProGRP normal/high	3/7	0/13	0.059	6/9	0/15	<0.005

	Discovery cohort		Validation cohort	
Procalcitonin	Normal	High	Normal	High
PCT (ng/mL) Median (range)	0.03 (0.03–0.05)	0.15 (0.06–7.05)	0.03 (<0.02–0.05)	0.13 (0.06–47.97)

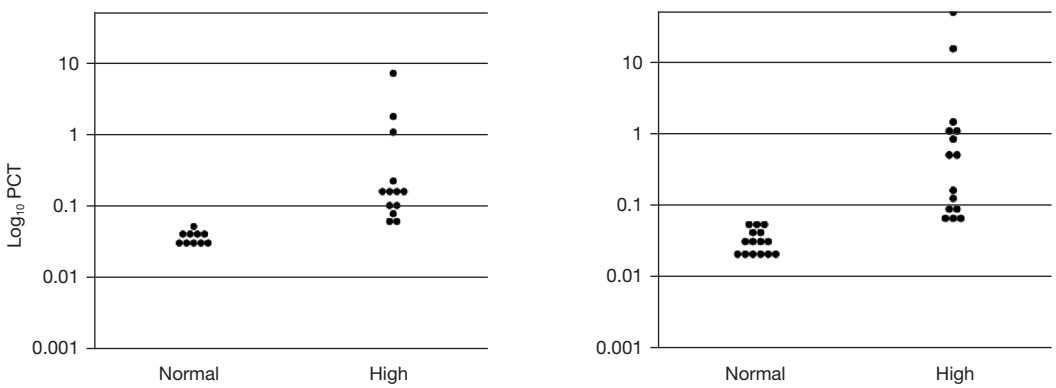

Figure 2 The distribution of PCT in SCLC patients. Pretreatment PCT values in the PCT-normal and PCT-high groups of SCLC patients in the discovery and validation cohorts are shown in graphs using a common logarithm. PCT, procalcitonin; SCLC, small cell lung cancer.

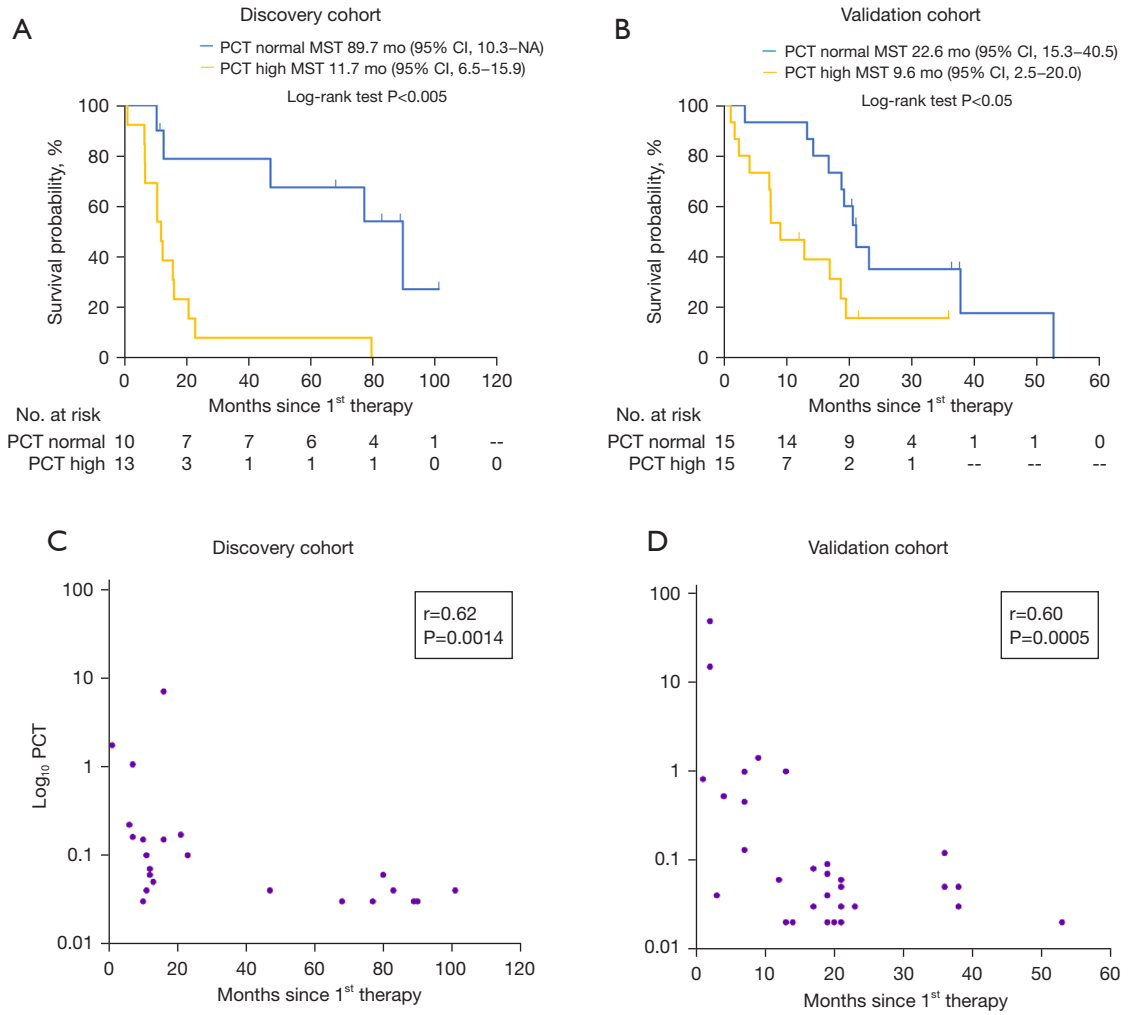

Figure 3 Prognostic significance of PCT in SCLC patients. Kaplan-Meier survival curves of patients in the PCT-normal and PCT-high groups in the discovery cohort (A) and validation cohort (B). Correlation between the PCT value and survival time in the discovery cohort (C) and validation cohort (D). PCT, procalcitonin; MST, median survival time; SCLC, small cell lung cancer.

shorter in the PCT-high group than in the PCT-normal group. In the discovery cohort, the median OS was 11.7 *vs.* 89.7 months (P<0.005). In the validation cohort, the median OS was 9.6 *vs.* 22.6 months (P=0.0175). *Figure 3C,3D* shows the correlation between PCT concentration and survival for all patients. Patients with higher PCT value had shorter survival time. There was a significant negative correlation between PCT levels and survival in both the discovery and validation cohorts. *Table 3* shows the results of univariate and multivariate Cox proportional hazards models for OS. In the discovery and validation cohorts, stage and PCT values were associated with a significantly short OS time, but in the discovery cohort, age was also associated with a significantly short OS time in the multivariate analysis. Furthermore, in the validation cohort, PCT was found to have the greatest impact on OS.

Discussion

In the discovery cohort, we found that PCT was not elevated in NSCLC patients, whereas in SCLC patients, PCT was often elevated in the uninfected state (*Figure 1A*). Therefore, it may be difficult to differentiate bacterial infections during fever in SCLC patients by PCT. In this study, 23 patients with SCLC were analyzed retrospectively as a discovery cohort, and 30 patients with SCLC were

Table 3 Univariate and multivariate Cox proportional hazard model results for OS

Characteristic	OS					
	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Discovery cohort						
Stage (ED *vs.* LD)	6.9	2.143–24.093	0.001	40.6	2.259–964.427	0.012
PCT (high *vs.* normal)	5.9	1.992–22.051	0.001	19.9	2.594–407.133	0.010
Sex (male *vs.* female)	–	–	–	–	–	–
Age (≥70 *vs.* <70)	3.9	0.840–14.415	0.078	2074.8	14.332–1431729	0.005
PS (2/3/4 *vs.* 0/1)	2.9	0.745–9.718	0.117	3.0	0.402–24.525	0.272
ProGRP (high *vs.* normal)	3.1	0.858–19.473	0.090	7.8	0.748–266.76	0.133
NSE (high *vs.* normal)	3.8	1.304–11.716	0.015	0.2	0.039–1.498	0.125
LDH (high *vs.* normal)	3.3	1.213–9.453	0.020	1.0	0.151–6.219	0.993
Na (low *vs.* normal)	2.6	0.949–7.245	0.062	6.2	0.867–50.982	0.063
Validation cohort						
Stage (ED *vs.* LD)	6.6	2.527–20.711	<0.001	18.0	2.709–156.014	0.003
PCT (high *vs.* normal)	2.8	1.165–7.048	0.022	51.3	7.0776–651.06	<0.001
Sex (male *vs.* female)	0.5	0.165–2.146	0.308	0.1	0.002–2.595	0.147
Age (≥70 *vs.* <70)	1.4	0.557–3.178	0.488	0.5	0.12–1.928	0.286
PS (2/3/4 *vs.* 0/1)	2.0	0.795–4.817	0.133	1.9	0.467–7.717	0.372
ProGRP (high *vs.* normal)	2.1	0.707–9.039	0.197	0.0	0.002–0.45	0.009
NSE (high *vs.* normal)	3.6	1.438–10.176	0.006	3.7	0.64–21.4	0.140
LDH (high *vs.* normal)	1.4	0.599–3.322	0.414	0.9	0.204–3.539	0.876
Na (low *vs.* normal)	2.3	0.974–5.405	0.057	1.4	0.262–7.046	0.699

OS, overall survival; LD, limited disease; ED, extensive disease; PCT, procalcitonin; PS, performance status, NSE, neuron-specific enolase; ProGRP, pro-gastrin-releasing peptide; LDH, lactate dehydrogenase; HR, hazard ratio; CI, confidence interval.

analyzed prospectively as a validation cohort. The results showed that PCT values measured before the first treatment were strongly associated with prognosis in all cohorts. We retrospectively found in the discovery cohort that there may be a correlation between PCT and SCLC prognosis. In the validation cohort, for the first time, we were able to prospectively validate the correlation between PCT levels and the prognosis of SCLC. Multivariate analysis revealed that PCT was an independent prognostic factor for SCLC. The results of the Kaplan-Meier survival analysis for LD and ED are shown in Figure S1. There was no significant difference between the two groups except for the number of ED cases in the validation cohort, but there was a trend toward a poor prognosis in patients with high PCT levels. In the discovery cohort and the validation cohort, the results of Kaplan-Meier survival analysis for the factors that showed significant differences in the multivariate analysis are shown in Figure S2. A previous retrospective study reported that liver metastasis, pleura metastasis, and 2 or more metastatic sites were correlated with serum PCT elevation (12). In the present study, patients with 2 or more metastatic organs tended to have high PCT level (*Table 2*). In the discovery cohort, significantly more patients had liver metastases in the PCT-high group (P=0.0093), whereas in the validation cohort, there were not significantly more patients with liver metastases in the PCT-high group (P=0.1896). There were no patients with a pleura metastasis in this study. Further study is warranted to evaluate whether

tumor burden and metastatic site is associated with serum PCT elevation.

Several previous reports have noted that PS and stage are prognostic predictors of SCLC (13-16). Regarding serological markers, some literature states that the serum ProGRP level (13), serum NSE level (13), serum Na level (16), and serum lactate dehydrogenase (LDH) level (16,17) at the time of diagnosis are prognostic factors. We also investigated these factors with univariate and multivariate analyses (*Table 3*) and found that PCT was the most powerful prognostic factor among them. This validation suggests that PCT may be a new prognostic factor for SCLC. On the other hand, nothing is known about the mechanism by which PCT affects the prognosis of SCLC. In sepsis, PCT is secreted by endotoxin-stimulated macrophages from adipocytes throughout the body via TNFα, IL-1β, IL-6, etc. (17-21). In contrast, in patients with small cell carcinoma, PCT is thought to be secreted by SCLC cells themselves (22). In sepsis, PCT itself has been suggested to be harmful (23), and part of the mechanism is thought to be that PCT inhibits CGPR, a hormone that is beneficial in sepsis (24). PCT is nontoxic in healthy individuals, and the details of the mechanism by which PCT affects the prognosis of patients with SCLC are not clear. However, in septic patients, PCT has been reported to suppress activated specific T-cell immunity and may affect host antitumor immunity (25). The current standard of care for ED-SCLC is shifting to combination therapy with cytotoxic anticancer agents and immune checkpoint inhibitors (26,27). The clinical significance of PCT in such treatment also needs to be examined. It is hoped that future basic research will elucidate the mechanism by which PCT affects the prognosis of SCLC and lead to the development of new treatment methods.

The current study has several limitations. Primary limitation of our study is relatively small sample size. Because this study was conducted in a single institution, it took a long time to recruit SCLC patients. Although previous studies have shown that PS is a significant prognostic factor in SCLC patients, our study did not demonstrate the impact of PS on the prognosis of SCLC patients (*Table 3*). Because relatively higher HRs for OS were observed in both discovery and validation cohorts, small sample size of this study may affect these results. Furthermore, we assessed the PCT values only before the initial therapy. The evaluation of PCT values at different time points during and after chemotherapy may provide useful information about the relationship between decrease of PCT values and treatment outcomes in SCLC patients. Although the current standard of care for ED-SCLC is the combination of cytotoxic anticancer agents and immune checkpoint inhibitors, this study did not include SCLC patients treated with immunotherapy. We are currently investigating the relationship between PCT values, prognosis and immune status in SCLC patients treated with chemo-immunotherapy. Additionally, the secretion of PCT from SCLC needs to be determined. A previous study reported that PCT expression was not observed in tumor tissues from SCLC patients (11). We have a plan to stain tumor tissues from SCLC patients with PCT and evaluate the concentration of PCT in supernatant of small cell cancer cell lines.

In summary, in patients with SCLC, it may be difficult to differentiate bacterial infections by PCT. In our study, we prospectively validated and reported for the first time that PCT is a prognostic factor in SCLC patients.

Acknowledgments

Part of this study has been presented at the 12th Annual Meeting of the Japanese Society of Clinical Oncology. The authors thank the patients and their families for their cooperation, and the doctors who shared the research with us.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-838/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-838/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-838/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-838/coif). KI received lecture fees from AstraZeneca, Chugai Pharma, Bristol-Myers, Boehringer Ingelheim, Ono Pharmaceutical, Taiho Pharmaceutical Novartis International AG and Daiichi Sankyo Company; SW received lecture fees from AstraZeneca, Chugai Pharma, Ono Pharmaceutical, Bristol-

Myers, Boehringer Ingelheim, Eli Lilly, MSD, Taiho Pharmaceutical, Pfizer, Novartis and Daiichi Sankyo; SM received lecture fees from Chugai Pharmaceutical, Taiho Pharmaceutical, Pfizer, Eli Lilly, Boehringer-Ingelheim Japan, Ono Pharmaceutical, AstraZeneca, Novartis, MSD, Bristol-Myers Squibb, Kyowa Hakko Kirin and Abbive; SS received lecture fees from AstraZeneca, Chugai Pharma, Taiho Pharmaceutical and MSD; KN received lecture fees from AstraZeneca, Boehringer Ingelheim, Taiho Pharmaceutical and MSD; SH received lecture fees from GlaxoSmithKline inc; NA received lecture fees from MSD and Meiji Seika Pharma; YO received lecture fees from Boehringer-Ingelheim Japan and Meiji seika pharma; T Koya received lecture fees from AstraZeneca, Boehringer-Ingelheim, Sanofi Genzyme, Novartis, Daiichi Sankyo, Kyorin Pharmaceutical and GlaxoSmithKline; T Kikuchi received lecture fees from Chugai Pharma, Boehringer Ingelheim, Eli Lilly, MSD K.K., Astellas Pharma Inc., Taiho Pharmaceutical Co., Ltd., Bristol-Myers Squibb Company, Pfizer Japan Inc., Daiichi Sankyo Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Japan BCG Laboratory, Ono Pharmaceutical Co., Ltd., Novartis Pharma K.K., Mylan N.V., AstraZeneca, Roche Diagnostics K.K., Shionogi & Co., Ltd., TEIJIN PHARMA Ltd. and KYORIN Pharmaceutical Co., Ltd. The other 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. This study was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN 000035975). It was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and the protocol was approved by the Institutional Review Board of Niigata University (No. 2020-0312). Patients in the validation cohort provided written informed consent.

References

1. Timmer-Bonte JN, de Boo TM, Smit HJ, et al. Prevention of chemotherapy-induced febrile neutropenia by prophylactic antibiotics plus or minus granulocyte colony-stimulating factor in small-cell lung cancer: a Dutch Randomized Phase III Study. J Clin Oncol 2005;23:7974-84.
2. Le Moullec JM, Jullienne A, Chenais J, et al. The complete sequence of human preprocalcitonin. FEBS Lett 1984;167:93-7.
3. Roos BA, Okano K, Deftos LJ. Evidence for a pro-calcitonin. Biochem Biophys Res Commun 1974;60:1134-40.
4. Becker KL, Snider R, Nylen ES. Procalcitonin assay in systemic inflammation, infection, and sepsis: clinical utility and limitations. Crit Care Med 2008;36:941-52.
5. Massaro KS, Costa SF, Leone C, et al. Procalcitonin (PCT) and C-reactive protein (CRP) as severe systemic infection markers in febrile neutropenic adults. BMC Infect Dis 2007;7:137.
6. Goltzman D, Potts JT Jr, Ridgway RC, et al. Calcitonin as a tumor marker. Use of the radioimmunoassay for calcitonin in the postoperative evaluation of patients with medullary thyroid carcinoma. N Engl J Med 1974;290:1035-9.
7. Silva OL, Becker KL, Primack A, et al. Ectopic secretion of calcitonin by oat-cell carcinoma. N Engl J Med 1974;290:1122-4.
8. Sutherland KD, Proost N, Brouns I, et al. Cell of origin of small cell lung cancer: inactivation of Trp53 and Rb1 in distinct cell types of adult mouse lung. Cancer Cell 2011;19:754-64.
9. Sappino AP, Carter S, Ellison M, et al. Plasma calcitonin in small cell lung cancer: prognostic significance. Br J Cancer 1983;48:881-2.
10. Patout M, Salaün M, Brunel V, et al. Diagnostic and prognostic value of serum procalcitonin concentrations in primary lung cancers. Clin Biochem 2014;47:263-7.
11. Itoga M, Tanaka H, Taima K, et al. Procalcitonin expression in patients with large cell neuroendocrine carcinoma of the lung. BMC Res Notes 2021;14:25.
12. Avrillon V, Locatelli-Sanchez M, Folliet L, et al. Lung cancer may increase serum procalcitonin level. Infect Disord Drug Targets 2015;15:57-63.
13. Petrović M, Bukumirić Z, Zdravković V, et al. The prognostic significance of the circulating neuroendocrine markers chromogranin A, pro-gastrin-releasing peptide,

and neuron-specific enolase in patients with small-cell lung cancer. Med Oncol 2014;31:823.
14. Li J, Dai CH, Chen P, et al. Survival and prognostic factors in small cell lung cancer. Med Oncol 2010;27:73-81.
15. Arinc S, Gonlugur U, Devran O, et al. Prognostic factors in patients with small cell lung carcinoma. Med Oncol 2010;27:237-41.
16. Hansen O, Sørensen P, Hansen KH. The occurrence of hyponatremia in SCLC and the influence on prognosis: a retrospective study of 453 patients treated in a single institution in a 10-year period. Lung Cancer 2010;68:111-4.
17. Kang MH, Go SI, Song HN, et al. The prognostic impact of the neutrophil-to-lymphocyte ratio in patients with small-cell lung cancer. Br J Cancer 2014;111:452-60.
18. Linscheid P, Seboek D, Nylen ES, et al. In vitro and in vivo calcitonin I gene expression in parenchymal cells: a novel product of human adipose tissue. Endocrinology 2003;144:5578-84.
19. Redl H, Schlag G, Tögel E, et al. Procalcitonin release patterns in a baboon model of trauma and sepsis: relationship to cytokines and neopterin. Crit Care Med 2000;28:3659-63.
20. Redl H, Schiesser A, Tögel E, et al. Possible role of TNF on procalcitonin release in a baboon model of sepsis. Shock 2001;16:25-7.
21. Whang KT, Vath SD, Becker KL, et al. Procalcitonin and proinflammatory cytokine interactions in sepsis. Shock 2000;14:73-8.
22. Cate CC, Pettengill OS, Sorenson GD. Biosynthesis of procalcitonin in small cell carcinoma of the lung. Cancer Res 1986;46:812-8.
23. Nylen ES, Whang KT, Snider RH Jr, et al. Mortality is increased by procalcitonin and decreased by an antiserum reactive to procalcitonin in experimental sepsis. Crit Care Med 1998;26:1001-6.
24. Sexton PM, Christopoulos G, Christopoulos A, et al. Procalcitonin has bioactivity at calcitonin receptor family complexes: potential mediator implications in sepsis. Crit Care Med 2008;36:1637-40.
25. Bucova M, Záhorec R, Buc M. Clinical immunology Immunomodulatory effect of recombinant human procalcitonin on mitogenic activity of lymphocytes. Cent Eur J Immunol 2006;31:87-93.
26. Horn L, Mansfield AS, Szczęsna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018;379:2220-9.
27. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019;394:1929-39.

Cite this article as: Ichikawa K, Watanabe S, Miura S, Ohtsubo A, Shoji S, Nozaki K, Tanaka T, Saida Y, Kondo R, Hokari S, Aoki N, Ohshima Y, Koya T, Kikuchi T. Prognostic significance of procalcitonin in small cell lung cancer. Transl Lung Cancer Res 2022;11(1):43-52. doi: 10.21037/tlcr-21-838

