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Abstract

In order to elucidate factors influencing the prognosis of small-cell lung cancer (SCLC), we reviewed the records of 253 patients with SCLC and evaluated 20 pretreatment prognostic factors by univariate analysis and Cox's multiple regression analysis. Recursive partitioning and amalgamation (RPA) was employed to identify subgroups with similar survival rates. Cox's multiple regression analysis identified five significant factors: extent of disease, number of metastatic sites, serum albumin, serum lactate dehydrogenase, and presence of weight loss. Among these, extent of disease was the most influential factor. RPA analysis revealed three subgroups predicting significantly different prognoses. The median survival time and 3-year survival rate were 18.4 months and 20.6%, respectively for the good-risk group (limited disease without weight loss), 13.5 months and 9.1%, respectively for the intermediate-risk group (limited disease with weight loss or extensive disease with less than two metastatic sites), and 9.2 months and 0%, respectively for the poor-risk group (extensive disease with two or more metastatic sites). These results will be useful for development of new staging system or subsequent stratification for randomized trials.

KEYWORDS: prognostic factors, Cox's multiple regression analysis, recursive partitioning and amalgamayion method, small-sell lung canser

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Prognostic Factors of Small-Cell Lung Cancer in Okayama Lung Cancer Study Group Trials

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In order to elucidate factors influencing the prognosis of small-cell lung cancer (SCLC), we reviewed the records of 253 patients with SCLC and evaluated 20 pretreatment prognostic factors by univariate analysis and Cox's multiple regression analysis. Recursive partitioning and amalgamation (RPA) was employed to identify subgroups with similar survival rates. Cox's multiple regression analysis identified five significant factors: extent of disease, number of metastatic sites, serum albumin, serum lactate dehydrogenase, and presence of weight loss. Among these, extent of disease was the most influential factor. RPA analysis revealed three subgroups predicting significantly different prognoses. The median survival time and 3-year survival rate were 18.4 months and 20.6%, respectively for the good-risk group (limited disease without weight loss), 13.5 months and 9.1%, respectively for the intermediate-risk group (limited disease with weight loss or extensive disease with less than two metastatic sites), and 9.2 months and 0%, respectively for the poor-risk group (extensive disease with two or more metastatic sites). These results will be useful for development of new staging system or subsequent stratification for randomized trials.

Key words: prognostic factors, Cox's multiple regression analysis, recursive partitioning and amalgamation method, small-cell lung cancer

Intensive chemotherapy currently used for small-cell lung cancer (SCLC) has yielded an improved response rate reaching approximately 90%, with complete response (CR) rates ranging from 30 to 50% (1, 2). Despite the high initial response rate, long-term disease-free survival is achieved in only 15 to 25% of patients with limited disease (LD) and less than 5% of those with extensive disease (ED) (1, 2). Accordingly, studies using alternating chemotherapy (3, 4) or high-dose chemotherapy with autologous bone marrow transplantation (5, 6) have been conducted. However, because of the limited number of patients enrolled and the diversity of patient characteristics, conclusive results have not been obtained (3-6).

In order to elucidate the reasons for the poor prognosis of SCLC, to compare studies at different institutions, and to predict treatment outcome, investigators have tried to identify prognostic factors in SCLC (7-11). The data reported up to this point show that good performance status (PS) and extent of disease have consistently been associated with prolonged survival (7-11).

In this report, we analyzed 253 SCLC patients enrolled in the chemotherapy protocol studies performed by the Okayama Lung Cancer Study Group. The objectives of the present study were identification of significant prognostic factors in SCLC and definition of patient subgroups with different survival potentials.

Patients and Methods

Study design and eligibility criteria. Data from 253 eligible patients enrolled in three chemotherapy trials conducted by the Okayama Lung Cancer Study Group between 1981 and 1992 were analyzed (Table 1). Eligibility criteria for these trials were as follows: a) histologically-or cytologically-proven SCLC,

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Table I Chemotherapy trials for patients with small-cell lung cancer

Period	Regimen	Number of patients	TRT	PCI
1981-1986	COMP-VAN alternating	101	Randomized trial for LD	Randomized trial for CRs
1986-1987	CAV-PVP hybrid pilot study	27		
1987-1992	CAV-PVP hybird *vs* comparative study	64	Mandatory for LD	Mandatory for CRs
	CAV-PVP sequential	61		

TRT: Thoracic radiotherapy; PCI: Prophylactic cranial irradiation; LD: Limited disease; CRs: Complete responders; COMP-VAN: Cyclophosphamide + vincristine + methotrexate + procarbazine + etoposide + adriamycin + nimustine; CAV-PVP: Cyclophosphamide + adriamycin + vincristine + cisplatin + etoposide.

b) no prior chemotherapy or radiotherapy, c) age of 75 years or less, d) ECOG PS of 0-3, e) presence of measurable or evaluable lesions, f) adequate function of bone marrow, liver, and kidneys, g) no concomitant malignancies, and h) informed consent.

In COMP-VAN alternating chemotherapy, a four-drug combination, COMP (cyclophosphamide: CPA 270 mg/m^2 iv days 1-5, vincristine: VCR 1.4 mg/m^2 iv day 1, methotrexate 6.5 mg/m^2 im days 1-5, and procarbazine 65 mg/m^2 po days 1-5), was alternated with a three-drug combination, VAN (etoposide: ETP 140 mg/m^2 po days 1-4, adriamycin: ADM 40 mg/m^2 iv day 1, nimustine 40 mg/m^2 iv day 1), every 4 weeks. The cycle was repeated until disease progression was confirmed (12). Randomized studies of thoracic irradiation (TI) at a dose of 40 Gy for patients with LD (12) and prophylactic cranial irradiation (PCI) at a dose of 40 Gy in patients who achieved CR were simultaneously conducted (13). The CAV-PVP hybrid regimen consisted of CAV (CPA 700 mg/m^2 iv, ADM 30 mg/m^2 iv, VCR 1.4 mg/m^2 iv) on day 1 and PVP (cisplatin 60 mg/m^2 iv, ETP 100 mg/m^2 iv for 2 days) on day 8. The cycle was repeated every 4 weeks for up to 6 cycles (14). In the CAV-PVP sequential regimen, CAV was given on days 1 and 8 and repeated every 4 weeks for the initial 3 cycles. PVP was then given on days 1 and 8 and repeated every 4 weeks for the subsequent 3 cycles (15). TI at a dose of 50 Gy for LD patients and PCI at a dose of 30 Gy for CR patients were given in the CAV-PVP regimens.

Staging criteria. The staging procedures for the trials included a complete blood cell count, a standard blood chemistry profile, chest roentgenogram, chest tomogram, bone scintigraphy with rentgenogram of suspected areas, computed tomographic scans of brain, chest, and abdomen, and bone marrow aspiration and biopsy. LD was defined as disease limited to one hemithorax, including the mediastinal, ipsilateral hilar and supraclavicular lymph nodes. Disease extending beyond one hemithorax or associated with cytology-proven malignant pleural or pericardial effusion was defined as ED. Data for patients' tumor-node-metastasis stages (TNM) were also available (16).

Pretreatment prognostic factors. Among the pretreatment prognostic factors previously reported, serum lactate dehydrogenase (LDH), albumin and alkaline phosphatase (ALP) were accepted as significant prognostic factors in the Third International Association for the Study of Lung Cancer Workshop on Small Cell Lung Cancer, in addition to extent of disease and PS (17). In this analysis, the following pretreatment factors were available for all patients in addition to the above factors: age (< 65 *vs* ≥ 65), sex, PS on ECOG scale (0-1 *vs* 2-3), presence or absence of pretreatment unexplained weight loss ($> 10\%$ of the body weight during the 6 months before diagnosis), extent of disease (LD *vs* ED), T factor (T1-2 *vs* T3-4), N factor (N0-2 *vs* N3), M factor (M0 *vs* M1), number of metastatic sites (0-1 *vs* ≥ 2), presence or absence of bone, liver, bone marrow, brain, or lung metastases, serum levels of Hb (normal *vs* low), albumin (≥ 4 g/dl *vs* < 4 g/dl), ALP (normal *vs* high), LDH (normal *vs* high), or CEA (< 2 times the upper limit of normal *vs* ≥ 2 times the upper limit), and CRP (negative *vs* positive).

Statistical methods. Differences in age (< 65, ≥ 65), sex, PS (0-1, 2-3), and extent of disease (LD, ED) between patients treated with COMP-VAN, CAV-PVP hybrid and CAV-PVP sequential regimens were assessed by chi-square test. All data concerning survival were updated to December 31, 1996. Survival curves were generated with the Kaplan-Meier method and compared by employing the log-rank test and generalized Wilcoxon test. Cox's multiple regression analysis was conducted in a backward stepwise fashion (with $P = 0.05$ to enter the model and $P = 0.1$ to be retained) to choose a multivariate model predicting overall survival for important prognostic factors.

Recursive partitioning and amalgamation (RPA) was used to define prognostic subgroups with similar survival

(18). This classification system, consisting of the two processes, is represented as a regression tree. Initially, the entire patient population is partitioned into two subgroups according to the variables that produce the most significant survival difference. This factor is determined by Cox's multivariate analysis. Each subgroup is again partitioned into two subgroups in the same manner. The partitioning process stops when no variable produces a further significant difference in survival between given subgroups; these subgroups are designated as the terminal subgroups. An amalgamation process, the second component of RPA analysis, joins the terminal subgroups of patients whose survival does not differ significantly from each other by log-rank test. This latter step produces the final prognostic subgroups (19).

Results

Patient characteristics, response, and survival. Table 2 summarizes the results of the chemotherapy trials, which were comparable with respect to age, gender, PS, and extent of disease. CR rates (32–47 %) and objective response (CR + PR) rates (87–96 %) were not significantly different. The median survival time (MST) and 3-year survival rate were also similar among the three trials, ranging from 12.7 months to 13.5 months and from 9.2 to 14.1 %, respectively. Fig. 1 shows the survival curves according to each regimen; a significant difference was not observed among the groups.

Univariate analysis of prognostic factors. Statistical analyses of the 20 pretreatment factors on survival are summarized in Table 3. Among pretreatment prognostic factors, extent of disease, PS, and presence

Table 2 Patient characterisitics

	COMP-VAN	CAV-PVP hybrid	CAV-PVP sequential
Total	101	91	61
Age: < 65	44	55	42
≧ 65	57	36	19
Sex: Male	79	76	52
Female	22	15	9
Performance status:			
0–1	60	72	51
2–3	41	19	10
Extent of disease:			
Limited disease	53	44	32
Extensive disease	48	47	29
Response rate (%):			
CR	47 (37–56)	43 (33–53)	32 (21–45)
CR + PR	93 (88–98)	96 (86–97)	87 (78–95)
MST (months):	12.7	13.0	13.5
	(10.9–14.5)	(10.7–15.3)	(11.1–15.9)
3-year survival rate:	11.9	14.1	9.2

CR: Complete response; PR: Partial response; MST: Median survival time. COMP-VAN; CAV-PVP: See legend to Table 1.
Numbers in parentheses show a 95% confidence interval.

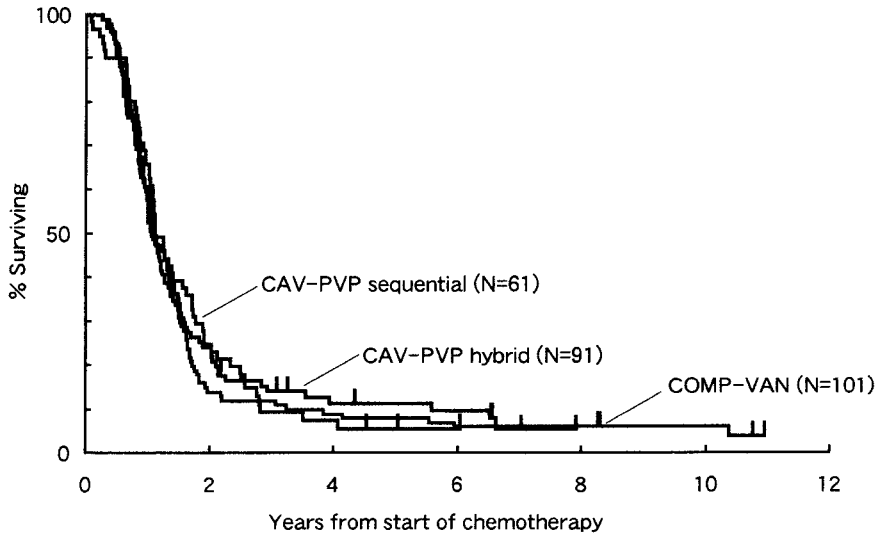

Fig. 1 Survival curves of patients with small-cell lung cancer according to chemotherapy regimens. There were no signficant differences in survival among the three groups. CAV-PVP; COMP-VAN: See legend to Table 1.

Table 3 Univariate analysis of various prognostic factors

Independent factors		Number of patients	MST (months)	Generalized Wilcoxon	Log-rank
Age	< 65	141	13.8	0.308	0.363
	≧ 65	112	12.7		
Sex	Male	207	13.0	0.282	0.282
	Female	46	14.0		
PS (ECOG)	0-1	193	14.7	0.002	0.002
	2-3	60	11.7		
BW loss	No	196	14.7	0.000	0.002
	Yes	57	11.6		
Disease extent	LD	129	17.9	0.000	0.000
	ED	124	11.7		
T factor	T1-2	168	15.3	0.004	0.007
	T3-4	85	14.0		
N factor	N0-2	193	14.0	0.016	0.077
	N3	60	11.6		
M factor	M0	145	16.0	0.000	0.000
	M1	108	11.3		
Number of meta	0-1	211	15.0	0.000	0.000
	≧ 2	42	8.9		
Bone meta	No	201	14.7	0.000	0.001
	Yes	52	11.2		
Liver meta	No	211	14.7	0.000	0.000
	Yes	42	9.7		
BM meta	No	232	13.8	0.002	0.000
	Yes	21	10.3		
Brain meta	No	235	13.6	0.056	0.159
	Yes	18	10.2		
Lung meta	No	243	13.5	0.293	0.459
	Yes	10	10.2		
Hb	Normal	158	14.7	0.061	0.015
	Low	95	11.2		
Albumin	≧ 4 g/dl	109	15.8	0.003	0.001
	< 4 g/dl	144	12.4		
ALP	Normal	217	13.5	0.234	0.090
	High	36	12.6		
LDH	Normal	152	15.9	0.000	0.000
	High	101	11.2		
CRP	Negative	211	16.1	0.001	0.006
	Positive	42	12.1		
CEA	< 2 × normal	192	14.5	0.053	0.033
	≧ 2 × normal	55	12.3		

MST: Median survival time; PS (ECOG): Performance status; BW: Body weight; LD: Limited disease; ED: Extensive disease; meta: Metastasis; BM: Bone marrow; ALP: Alkaline phosphatase; LDH: Lactate dehydrogenase; CRP: C-reactive protein; CEA: Carcino-embryonic antigen.

of weight loss (> 10 %) were significant prognostic factors. Neither age nor sex was significant. Regarding the clinical stage, the T factor (T1-2 *vs* T3-4), the M factor (M0 *vs* M1), the number of distant metastatic sites (0-1 *vs* > 2), and the presence or absence of bone, liver, and/or bone marrow metastases were all highly significant. The N factor (N0-2 *vs* N3) was only marginally significant. Serum LDH, albumin, and CRP were also significant prognostic factors, while the hemoglobin concentration and serum CEA showed only marginally significant relationship to survival.

Multivariate analysis of prognostic variables. Table 4 shows the results of multivariate analysis. Extent of disease was the most significant prognostic factor ($P = 0.0051$). The number of distant metastatic sites ($P = 0.0132$), serum albumin ($P = 0.0206$) and LDH ($P = 0.0242$), and presence or absence of weight loss ($P = 0.0494$) also were independent prognostic variables.

RPA analysis. The regression tree is shown in Fig. 2. The first and most significant prognostic variable that split the entire population was extent of disease (LD *vs* ED). In the subset with LD, the second most important variable was weight loss. There were no subsequent significant variables for the LD group without weight loss, which was then designated as terminal subgroup I. The LD group with more than 10 % weight loss was designated as terminal subgroup II. In the subset with ED, the second most important variable was the number of distant metastatic sites. In the ED group with two or more distant metastatic sites, no additional significant variables occurred. This was designated as terminal subgroup V. As an additional significant variable, the ED subset with < 2 distant metastatic sites was divided by the serum albumin level (normal *vs* low). The ED group with normal serum albumin was designated as terminal subgroup III, and the group with low albumin was terminal subgroup IV. The terminal subgroups I to V represented 107, 22, 32, 36 and 56 patients, respectively. The inset in Fig. 2 shows the results of statistical comparison

Table 4 Cox's regression analysis of 253 patients with small-cell lung cancer

Variables			Hazard ratio	*P*-value
Disease extent	LD	*vs* ED	1.54 (1.14-2.08)	0.0051
Number of meta	0-1	*vs* 2-3	1.68 (1.11-2.54)	0.0132
Albumin	≧ 4 g/dl	*vs* < 4 g/dl	1.39 (1.05-1.83)	0.0206
LDH	Normal	*vs* High	1.40 (1.04-1.87)	0.0242
Weight loss	No	*vs* Yes	1.37 (1.00-1.87)	0.0494

LD; ED; LDH: See legend to Table 3.
Numbers in parentheses show a 95% confidence interval.

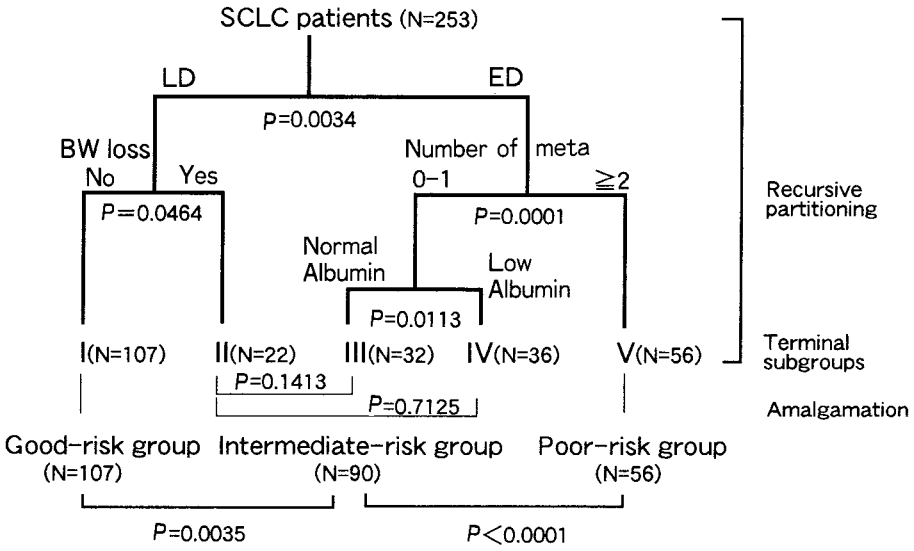

Fig. 2 Recursive partitioning and amalgamation (RPA) analysis of patients with small-cell lung cancer (SCLC). LD; ED; BW; meta: See legend to Table 3.

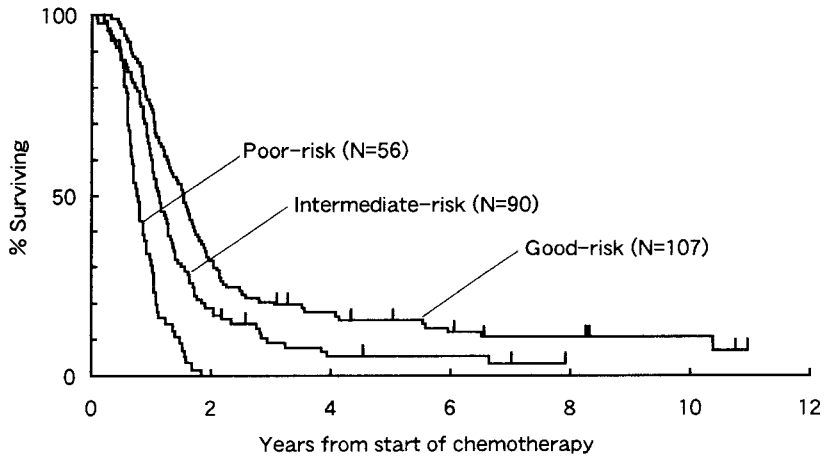

Fig. 3 Survival curves of patients with small-cell lung cancer divided into prognostic subgroups determined by RPA analysis. The three subgroups showed significant differences in survival. RPA: See legend to Fig. 2.

among the five terminal subgroups or combinations of terminal subgroups, as a part of the amalgamation algorithm for forming final subgroups with similar survival. Groups II, III and IV were combined into one subgroup because they showed similar survivals. Finally, we determined three subgroups based on significant differences in survival: good-risk (terminal subgroup I), intermediate-risk (terminal subgroups II, III and IV), and poor-risk (terminal subgroup V). For the good-risk group, CR rate was 58.9 % (95 % confidence interval: 95 % CI, 49.6–68.2 %), MST was 18.4 months (95 % CI, 15.7–21.1 months), and 3-year survival was 20.6 %. These data were significantly better than those for the intermediate-risk ($P = 0.0035$) and poor-risk groups ($P < 0.0001$); CR rate, MST, and 3-year survival were 37.8 % (95 % CI, 27.8–47.8 %), 13.5 months (95 % CI, 11.5–15.5 months), and 9.1 % for the intermediate-risk group and 16.1 % (95 % CI, 6.5–25.7 %), 9.2 months (95 % CI, 8.0–10.4 months), and 0 % for the poor-risk group, respectively. Fig. 3 shows the survival curves for these 3

subgroups. Among the poor-risk patients, none survived more than 3 years. By contrast, 3 patients in the intermediate-risk group and 11 patients in the good-risk group survived more than 3 years.

Discussion

Previous studies have identified extent of disease and PS as the most significant prognostic factors in SCLC (7-11). Other factors such as gender, age, serum LDH, albumin, and ALP have also been shown to have a significant relationship to survival (9, 11, 18). However, a consensus for the usefulness of these prognostic factors has not been arrived at.

In this study, we analyzed 20 pretreatment prognostic factors by univariate analysis with the generalized Wilcoxon test and log rank test. Then multivariate analysis with Cox's multiple regression evaluated the significant factors revealed by univariate analysis, followed by recursive partitioning and amalgamation for the factors significant by multivariate analysis. The primary objective of Cox's multiple regression analysis was to identify pretreatment prognostic factors which will have an impact on survival, while the RPA method classifies patients with similar survival.

By univariate analysis, 12 of 20 factors significantly related to survival. However, only extent of disease, number of distant metastatic sites, serum albumin, serum LDH, and weight loss were independently prognostic by multivariate analysis. In agreement with other reports (7-11), extent of disease was demonstrated to have the closest relationship to survival. However, PS was not predictive for outcome by multivariate analysis in this study, although PS has been a universally accepted prognostic variable for SCLC (7-11). We presume that the majority of patients with LD in the present study had good PS, which subsequently resulted in no significant relationship of PS to survival. In the Southwest Oncology Group (SWOG) study, age and absence of pleural effusion were significant factors relating to survival in addition to serum LDH and extent of disease (19). However, in our study, age had no significant relationship to survival because the number of patients older than 70 was small. Pleural effusion similarly had no relationship to survival because only 11 patients had pleural effusion at diagnosis, and all were evaluated as ED. Wolf *et al.* have reported a significant relationship of gender to survival (20). In their report, female patients had a higher CR rate (35 % *vs* 25 %), a superior MST (12.1 months *vs* 9.8 months), and a more favorable 2-year survival rate (19 % *vs* 8 %) than male patients. By contrast, MST was 14.0 months for females and 13.0 months for males in our analysis, not significantly different.

Using the RPA method, the SWOG distinguished four subgroups with significantly different survival and thus proposed a new staging system (19). Sagman *et al.* have reported on subgroups with different survival using extent of disease, mediastinal involvement, PS, gender, and serum LDH (21). We divided 253 SCLC patients into three subgroups with different survival potentials by evaluating extent of disease, pretreatment weight loss, and number of distant metastatic sites. This classification is simpler than previous reports (19, 21). Accordingly, this classification should be useful both for stratification of patients in subsequent randomized trials and prediction of survival for each patient.

In conclusion, analysis of prognostic factors will be useful for development of new staging or stratification system for randomized trials of chemotherapy. However, a prospective analysis or a meta-analysis will be required to obtain a consensus for prognostic factors.

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