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Original Research

Developing a clinical and PET/CT volumetric prognostic index for risk assessment and management of NSCLC patients after initial therapy

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Abstract

Background: Currently, individual clinical prognostic variables are used sequentially with risk-stratification after TNM staging in clinical practice for the prognostic assessment of patients with NSCLC, which is not effective for estimating the collective impact of multiple individual variables on patient outcomes. Here, we developed a clinical and PET/CT volumetric prognostic (CPVP) index that integrates the prognostic power of multiple clinical variables and metabolic tumor volume from baseline FDG-PET, for use immediately after definitive therapy. **Patients and methods**: This retrospective cohort study included 998 NSCLC patients diagnosed between 2004 and 2017, randomly assigned to two cohorts for modeling the CPVP index using Cox regression models examining overall survival (OS) and subsequent validation. **Results**: The CPVP index generated from the model cohort included pretreatment variables (whole-body metabolic tumor volume [MTVwb], clinical TNM stage, tumor histology, performance status, age, race, gender, smoking history) and treatment type. A clinical variable (CV) index without MTVwb and PET/CT volumetric prognostic (PVP) index without clinical variables were also generated for comparison. In the validation cohort, univariate Cox modeling showed a significant association of the index with overall survival (OS; Hazard Ratio [HR] 3.14; 95% confidence interval [95% CI] = 2.71 to 3.65, $p < 0.001$). Multivariate Cox regression analysis demonstrated a significant association of the index with OS (HR = 3.13, 95% CI = 2.66 to 3.67, $p < 0.001$). The index showed greater prognostic power (C-statistic = 0.72) than any of its independent variables including clinical TNM stage (C-statistic ranged from 0.50 to 0.69, all $p < 0.003$), CV index (C-statistic = 0.68, $p < 0.001$) and PVP index (C-statistic = 0.70, $p = 0.006$). **Conclusions**: The CPVP index for NSCLC patients has moderately strong prognostic power and is more prognostic than its individual prognostic variables and other indices. It provides a practical tool for quantitative prognostic assessment after initial treatment and therefore may be helpful for the development of individualized treatment and monitoring strategy for NSCLC patients.

Keywords: Prognostic index; Metabolic tumor burden; Non-small cell lung cancer; Survival analysis; 2-deoxy-2-[18F]fluoro-D-glucose; FDG; TNM stage

1. Introduction

Accurate prediction of survival in patients with non-small cell lung cancer (NSCLC) is essential for recommending initial therapy. Common pretreatment prognostic variables include tumor-node-metastasis (TNM) staging [1–3], whole-body metabolic tumor volume (MTVwb) [4–13], pre-treatment Eastern Cooperative Oncology Group (ECOG) performance status (PS) [14–17], histologic subtype [17,18], age [17–20], race [18], gender [17,18] and smoking history [20]. A second opportunity for prognostic assessment of patients arises after completion of initial therapy for future patient management. At that time, the initial treatment type the patients received was found to be important prognostic variable [21]. Effective treatment targets on the actionable oncogenes such as EGFR and ALK has provided new improving survival significantly among patients harboring the corresponding driver mutation [22–24]. However, currently, individual clinical prognostic variables are used sequentially after TNM staging with risk-stratification in clinical practice, which is not effective for estimating the collective impact of multiple individual prognostic variables on survival after initial therapy.

We previously developed the PVP index by combining the prognostic value of three variables, whole-body metabolic tumor volume (MTVwb), initial clinical TNM stage and patient age, for NSCLC patient risk assessment at baseline prior to treatment [25,26]. The PVP index provides a way to integrate the prognostic power of multiple prognostic variables. However, a prognostic index that in-

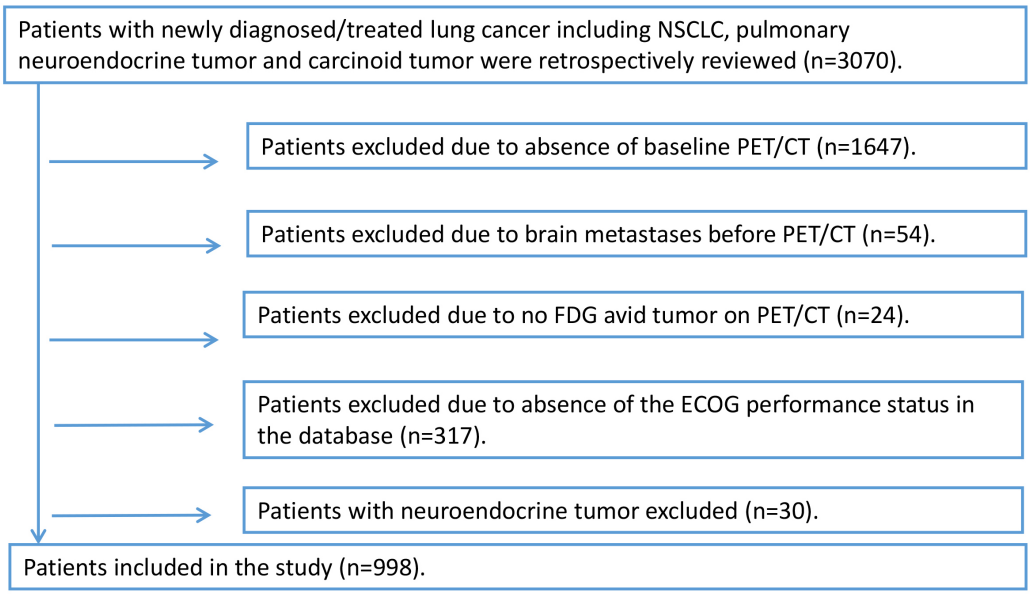

Fig. 1. Flow diagram illustrating study patient inclusion and exclusion. Of the 3070 patients with lung cancer including NSCLC, pulmonary neuroendocrine tumor and carcinoid tumor diagnosed and treated at our institution from 2004 to 2017, 1423 patients had baseline FDG PET/CT for the diagnosis and staging of the tumor. 54 patients were excluded due to presence of brain metastasis at time of PET/CT, 24 patients were excluded because the patients' tumor was not FDG avid, 317 patients were excluded because no ECOG performance status available in the patients' medical record, 30 patients with pulmonary neuroendocrine tumor and carcinoid tumor were excluded.

tegrates the prognostic power of multiple recognized baseline prognostic variables and an initial treatment type variable for prognostic assessment of NSCLC patients after initial therapy is not available in clinical practice. Such a prognostic index is clinically needed as it may influence patient follow-up planning and considerations for adjuvant therapy in some individuals. It may facilitate personalized discussions with patients and their families regarding expectations for the survival.

In this study, we developed a broadly integrated index, clinical and PET/CT volumetric prognostic (CPVP) index, for improved prognostic assessment after initial NSCLC treatment.

2. Materials and methods

2.1 Patient cohort

This study was approved by our university's Institutional Review Board (IRB protocol 16770A initially approved 2/10/2009, and IRB protocol 17-0877 initially approved 9/13/2017) and was compliant with the Health Insurance Portability and Accountability Act. The need for individual patient consent was waived. The study patients were selected from a total of 3070 patients with lung cancer including NSCLC, pulmonary neuroendocrine tumor and carcinoid tumor treated at our university medical center from January 2004 to May 2017. The inclusion criteria were: (1) having a pretreatment (baseline) whole-body PET/CT scan, (2) absence of known brain metastases, and (3) presence of FDG-avid tumor detected visually by radiologists. Patients with non-FDG-avid NSCLC were excluded from the study. Patients with pulmonary neuroendocrine tumor and carcinoid tumor were excluded based on the 2015 World Health Organization Classification of Lung Tumors [27]. Patient selection for the study is depicted in Fig. 1. A total of 998 NSCLC patients were included in the analysis. The patients' health information including treatment type, tumor histology, age, race, gender, smoking history, and comorbidities were compiled by our institution's Cancer Registry and verified by the authors. The Charlson comorbidity index without tumor weights (CCI) [28] was calculated. As all patients had NSCLC, tumor weights were not assigned to the cancer diagnosis [29]. Clinical TNM stage was assigned by the authors according to the AJCC (American Joint Committee on Cancer) 8th edition of TNM staging system [30] using data from the clinical history, physical examination, contrast enhanced CT studies, and whole-body PET/CT scans. Tumor pathology type was coded by our University Cancer Registry using the ICD-0-3 and the 2022 Solid Tumor Rules (cancer.gov), 3rd edition [31]. Pre-treatment PS score was evaluated by our oncology colleagues before initial treatment [32].

2.2 Imaging techniques

The PET/CT imaging protocol and measurement of whole-body metabolic tumor volume have been described previously [33–35]. The FDG PET/CT scans of 517 pa-

Table 1. Patient and tumor characteristics and group comparison.

Variables	Total patients	%	Modeling group	Validation group	*p*-value
All patients	998	100	495	503	
Treatment [a]					
Surgery					0.713
Surgery only	242	24.2	122	120	
with chemo	105	10.5	48	57	
with XRT	19	1.9	10	9	
with Chemo/XRT	107	10.7	59	48	
No surgery					
Chemo only	168	16.8	78	90	
XRT only	103	10.3	54	49	
Chemo/XRT	186	18.6	95	91	
No cancer-specific therapy	68	6.8	29	39	
TNM stage					0.323
Stage IA/B	238/82	23.8/8.2	118/45	120/37	
Stage IIA/B	43/100	4.3/10.0	20/54	23/46	
Stage IIIA/B/C	140/92/40	14.0/9.2/4.0	73/44/22	67/48/18	
Stage IVA/B	136/127	13.6/12.7	53/66	83/61	
Histology					0.085
Adenocarcinoma	543	54.4	265	278	
SCC	283	28.4	154	129	
Large cell carcinoma	37	3.7	20	17	
*NOS	135	13.5	56	79	
ECOG performance status					0.203
0	300	30.1	141	159	
1	540	54.1	266	274	
2–4	158	15.8	88	70	
Race					0.831
White	515	51.6	251	264	
Black	444	44.5	225	219	
Others**	39	3.9	19	20	
Gender					0.386
Female	542	54.3	262	280	
Male	456	45.7	233	223	
Smoking					0.653
Never#	94	9.4	48	46	
Current	329	33.0	169	160	
Prior	575	57.6	278	297	
ln(MTVwb) (mL, X ± SD)	3.15 ± 1.81		3.16 ± 1.8	3.15 ± 1.8	0.979
Age (years, X ± SD)	67.4 ± 10.1		67.0 ± 10.2	67.9 ± 10.1	0.148
SUVmaxwb (X ± SD)	11.3 ± 7.6		11.6 ± 7.6	11.0 ± 7.6	0.239
CCI [median (range)]	1 (0–8)		1 (0–8)	1 (0–8)	0.261

Notes: CCI, Charlson comorbidity index; Chemo/XRT, chemoradiation; MTVwb, whole-body metabolic tumor volume; N, number of patients; NOS, not otherwise specified; SCC, Squamous cell carcinoma

* Two patients with adenosquamous and three patients with sarcomatoid were included in the group. **Others race includes Asian, Hawaiian and Pacific islander, and unknown (in 6 patients in Total cohort); #two patients the smoking history was unknown included in the Never category; SD, standard deviation.

[a] Surgery was always performed with curative intent, but the intent of nonsurgical treatment was unknown, X, mean, SD, standard deviation.

tients (51.8%) were performed with a scanner (Reveal HD, CTI, Knoxville, TN, USA) [33]. FDG PET/CT scans of another 243 patients (24.4%) were acquired on a Siemens mCT scanner (Siemens Healthcare, Knoxville, Tennessee, USA) [35]. Two-hundred and thirty-eight patients obtained FDG PET/CT scans with adequate diagnostic quality judged by radiologists from outside hospitals (23.8%, scanned from June 2006 to March 2017) were also included in this study. In our medical center, whole-body FDG PET/CT scans were performed in accordance with the National Cancer Institute guidelines [36].

Two board-certified radiologists with experience in PET/CT imaging used the PET-edge tool of MIM software [37] (MIM Software Inc., Cleveland, OH) to measure the MTVwb and the SUVmaxwb, defined as the total MTV and the maximum SUV respectively of all visible tumors in the whole-body scan as previously described [33].

2.3 Statistical methods

Overall survival (OS) was the primary endpoint, which was calculated as the time from the baseline PET/CT scan to the date of death from any cause. Surviving patients were considered censored on the date of last contact. Patient survival status was determined using the Social Security Death Index and through clinical follow-up.

2.3.1 Randomization of patients for modeling and validation cohorts

Patients were randomly assigned to either a modeling or validation cohort. Patient and tumor characteristics were compared between the two cohorts using Pearson Chi-squared tests for all categorical variables, and student t-tests for normally distributed continuous variables including natural log transformed MTVwb, age and natural log transformed SUVmaxwb. Two-sample Wilcoxon rank-sum (Mann-Whitney) test was performed for non-normally distributed CCI. Log rank tests were performed for stage by stage survival comparison between the two cohorts.

2.3.2 CPVP index formulation

The method for the formulation of the CPVP index is same as we previously described by our group for developing PVP index with exception for different variable numbers [25,26]. There were a total 11 prognostic variables available in our database for the development of the CPVP index model including nine variables used in the CPVP index model and two other variables (CCI and SUVmaxwb). These variables have been shown to be associated with NSCLC prognosis [12,13,17–21,26,38]. We initially developed five candidate models with different numbers of the prognostic variables (5, 7, 9, 10 and 11 variables). The CPVP index model was then selected among the five candidate models based on their prognostic power as measured by C-statistic and parsimony of the models. CPVP index model selected from the candidate models contained nine variables (pre-treatment MTVwb, treatment type, clinical TNM stage, tumor histology, age, PS, race, gender, and smoking history). The CCI and SUVmaxwb were not included in the CPVP index as they had no significant prognostic contribution to the CPVP index model.

For constructing the CPVP index model, we used a multivariate Cox proportional hazards regression model to obtain hazard ratios (HRs) and regression coefficients for the ln(MTVwb) (natural log transformed MTVwb), NSCLC treatment type (with 3 groups: surgical, non-surgical, and no cancer-specific therapy), clinical TNM stage (with 3 groups: stage I or II, III, and IV), tumor histology (with four groups: adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and not otherwise specified), age, PS (with 3 groups: 0, 1, and $\geq$2), race (with 3 groups: White, Black and others), gender, and smoking history (with 3 groups: never, current and prior). This is because in a Cox model of OS, the HR of a prognostic variable represents a relative estimated contribution of that variable to the risk of death from any cause. Only the patients assigned to the model cohort were used for formulation of the CPVP index in this study. In the modeling of CPVP index, ln(MTVwb) was used as a continuous variable because it was more normally distributed than the MTVwb. Age was considered a continuous variable. The CPVP index was defined as the weighted sum of its individual independent variables using their respective Cox regression coefficients. To determine if the addition of the MTVwb from PET data made the CPVP index model perform significantly better than if the MTVwb were not included, a clinical variable (CV) index was constructed as the CPVP index excluding the MTVwb term. The previously published PVP index with three variables (MTVwb, clinical TNM stage and age) [26] was also constructed to determine if addition of six clinical variables (treatment type, tumor histology, PS, race, gender, and smoking history) made the CPVP index model perform significantly better than if they were not included.

2.3.3 Testing the prognostic value of the CPVP index

The CPVP index was validated for its prognostic value and compared with the CV index, PVP index and their individual independent variables in the validation cohort. For the validation purpose, the detailed NSCLC treatment types of eight groups (surgery only, surgery and chemotherapy, surgery and radiotherapy, surgery and chemo- and radiotherapy, chemotherapy only, radiotherapy only, chemo- and radio-therapy, and no cancer-specific therapy), and detailed clinical TNM stage (IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IVA, and IVB) were used in the analyses because the detailed forms of the variables were more prognostic than those included in the CPVP index equation and they are used in clinical practice. Schoenfeld residuals were used to test the proportional hazards assumption. The discriminatory power of the CPVP index was compared against the CV

Table 2. Estimated hazard ratio and Cox regression coefficients for formulation of the clinical and PET/CT volumetric prognostic index.

	HR	β (95% CI), p
ln(MTVwb)	1.21	0.191 (0.109–0.272), <0.001
Treatment		
Surgery	1.0 (Reference)	0
No Surgery	1.71	0.539 (0.241–0.837), <0.001
No cancer-specific therapy	3.34	1.204 (0.748–1.661), <0.001
TNM stage		
Stage I + II	1.0 (Reference)	0
Stage III	1.25	0.228 (–0.089–0.546), 0.15
Stage IV	2.05	0.715 (0.379–1.05), <0.001
Histology		
Adenocarcinoma	1.0 (Reference)	0
SCC	1.26	0.235 (–0.015–0.486), 0.066
LCC	0.87	–0.144 (–0.752–0.463), 0.642
NOS	1.00	0.001 (–0.346–0.348), 0.01
Age	1.02	0.017 (0.005–0.029), 0.004
ECOG performance status		
0	1.0 (Reference)	0
1	1.08	0.082 (–0.183–0.349), 0.542
≥2	1.36	0.304 (–0.027–0.635), 0.072
Race		
White	1.0 (Reference)	0
Black	1.02	0.018 (–0.215–0.252), 0.879
Others	0.76	–0.280 (–0.964–0.403), 0.421
Gender		
Female	1.0 (Reference)	0
Male	1.03	0.033 (–0.188–0.255), 0.768
Smoking		
Never	1.0 (Reference)	0
Current	1.68	0.521 (0.063–0.979), 0.026
Prior	1.73	0.548 (0.102–0.995), 0.016

β, Regression coefficient, 95% CI, 95% confidence interval, HR, hazard ratio. ln(MTVwb), natural log-transformed whole-body metabolic tumor volume; LCC, Large cell carcinoma; NOS, not otherwise specified; SCC, Squamous cell carcinoma.

index, PVP index and separately against each of its independent variables as determined by the C-statistic, specifically Gönen and Heller's K concordance statistic, which is a quantitative measure of accuracy of statistical models [39]. A higher C-statistic value for a model indicates greater discriminative power, with a value of 1.0 indicating perfect discrimination. C-statistic values between 0.7 and 0.8 indicate moderate predictive power for a model, while values between 0.6 and 0.7 indicate weak predictive ability [40]. The C-statistics were compared between models using a z-test of 500 bootstrapped iterations. We used Stata Version 14 (Stata Corp., College Station, TX) for all statistical analyses, with statistical significance defined at $p < 0.05$.

3. Results

3.1 Comparison of modeling and validation cohorts

The patient and tumor characteristics of both modeling and validation cohorts are described in Table 1. There was no significant difference between the modeling and validation cohorts in any of the variables used for generating the index or in clinical outcomes including overall and stage-by-stage comparison of OS between two cohorts. In total, 703 (70.4%) patients died before the end of the study period, and 295 patients were censored, with a median follow-up of 72.4 months (interquartile range = 45.5–101.8) for censored patients.

3.2 CPVP index formulation

For the modeling cohort the HRs and regression coefficients, of the variables for the development of the CPVP

index are listed in Table 2. We included all the nine variables listed in the Table 2 in the model, including race and gender variables which were not statistically significant in the multivariate cox regression model. This is because the literature suggested that these are important predictors for lung cancer survival, and all the variables were statistically significantly associated with overall survival in the univariate Cox regression model.

Using the regression coefficients, the CPVP index was formulated as follows:

CPVP index = 0.191 * ln(MTV) + 0.539 * I (No surgery) + 1.204 * I (No cancer-specific therapy) + 0.228 * I (TNM = III) + 0.715 * I (TNM = IV) + 0.235 * I (Squamous cell carcinoma) – 0.144 * I (Large cell carcinoma) + 0.001 * I (Histologic subtype not otherwise specified) + 0.017 * Age + 0.082 * I (PS = 1) + 0.304 * I (PS $\geq$2) + 0.018 * I (Black race) – 0.280 * I (Other race) + 0.033 * I (Male) + 0.521 * I (Current smoker) + 0.548 * I (Prior smoker). Eq. (1).

The indicator function for categorical variables I(·) is 1 when its argument is true and 0 when false. For clarification, in the second term in the equation for surgery, if a patient had no surgical treatment that is No Surgery, the index function 1. * indicates multiplication. The regression coefficient of reference category of each categorical variable is zero (Table 2). Therefore, the reference categories of the variables are not in the CPVP index equation. For example, surgical treatment category of the treatment variable is not in the equation because its regression coefficient is zero. No surgery indicates that a patient was treated with chemoradiation, and no cancer-specific therapy indicates a patient did not receive any cancer specific treatment. TNM = III indicates clinical TNM stage III and TNM = IV indicates clinical TNM stage IV; Age indicates a patient's age in years at time of baseline PET/CT study. There is no statistically significant difference in the index between the modeling cohort (mean $\pm$ SD = 2.99 $\pm$ 0.90) and validation cohort (mean $\pm$ SD = 3.03 $\pm$ 0.86) (p = 0.41). The range of the CPVP index of the 1st, 2nd, 3rd and 4th quartiles in the modeling cohort is 0.59 to 2.23, 2.24 to 2.97, 2.97 to 3.73 and 3.74 to 5.26, respectively. The range of the CPVP index of the 1st, 2nd, 3rd and 4th quartiles in the validation cohort is 0.48 to 2.37, 2.37 to 3.01, 3.01 to 3.67 and 3.67 to 5.69, respectively.

3.3 Validation of the prognostic value of the CPVP index

As shown in Table 3, univariate Cox regression analysis in the validation cohort revealed a significant association of OS with the CPVP index (HR = 3.14, 95% CI = 2.71–3.65, $p < 0.001$). The CPVP index had a higher prognostic value (C-statistic [C] = 0.72) than the CV index (C = 0.68), and independent variables of the CPVP index (C-statistics ranged from 0.50 to 0.69; all $p < 0.003$). The C-statistic CPVP index was also significantly greater than that of PVP index (C = 0.70, p = 0.006). These results indicate that the CPVP index and PVP index are moderately strong prognostic model (C $\geq$0.70) while the CV index and the individual independent variables of the CPVP index are weakly predictive (C <0.70) [38] and CPVP index is more prognostic than other index. Multivariate Cox regression analyses demonstrated significant association of the CPVP index (HR = 3.13, 95% CI = 2.66–3.67, $p < 0.001$) with OS after adjusting for patients' CCI and ln(SUVmaxwb).

The Kaplan-Meier OS based on quartiles of the CPVP index (Fig. 2A), clinical TNM stage (Fig. 2B) and the quartiles of CV index (Fig. 2C) in the validation cohort showed an association of these metrics with OS (all $p <$ 0.001). Separation of the survival curves was better in the CPVP index than for clinical TNM stage and CV index. The Kaplan-Meier curves of patients with clinical TNM stage IIIA NSCLC divided by the median CPVP index of the TNM sub-stage (3.05) show significant association of CPVP index with patients' overall survival within the stage (Fig. 2D).

4. Discussion

In this study, we developed a new instrument, the CPVP index, for individualized prognosis assessment of patients who have completed initial therapy for NSCLC. We have shown that the CPVP index has a significantly greater prognostic power than its individual independent variables, CV index and PVP index. The greater prognostic power of the CPVP index compared to the CV index indicates that the addition of the MTVwb from baseline whole-body PET/CT studies makes the model perform significantly better than if this PET measurement was not included. The greater prognostic power of the CPVP index than that PVP index is likely related to the inclusion of six clinical variables (treatment type, tumor histology, PS, race, gender, and smoking history).

The CPVP index has a higher C-statistic value than previously reported nomograms for prognosis of NSCLC (C-statistic values range from 0.60 to 0.70) [41–45]. The new CPVP index also demonstrated a higher C-statistic value than our previously reported PVP index for NSCLC (C-statistic value = 0.71). The improvement is likely due to the integration of multiple prognostic variables as the index is the summation of the hazard of death from any cause associated with the prognostic variables included in the index [25]. Kaplan-Meier curves for the validation cohort divided by the quartiles of the CPVP index also demonstrated better separation of the patient groups with different survival probability than those divided by clinical TNM stage.

We believe that our new CPVP index can help clinicians to estimate NSCLC patient prognosis at an early stage after treatment by further differentiating risk in a quantitatively more accurate and practically more efficient way. This helps inform decision making about adjuvant therapy and helps patients and their families have a clearer idea about prognosis. The index also may be used in situations

Table 3. Prognostic value comparison of clinical and PET/CT volumetric prognostic index and other variables, Univariate cox regression analysis of validation cohort.

Variables		N	HR (95% CI)	*p*-Value	C
CPVP index		503	3.14 (2.71, 3.65)	<0.001	0.72[†]
PVP index		503	4.00 (3.25, 4.91)	<0.001	0.70
CV index		503	3.17 (2.67, 3.76)	<0.001	0.68
ln(MTV_{WB})		503	1.51 (1.41, 1.62)	<0.001	0.69
Treatment				<0.001	0.67
Surgery					
	Surgery only	120	(reference)		
	with chemo	57	1.09 (0.72, 1.68)		
	with XRT	9	1.51 (0.65, 3.50)		
	with Chemo/XRT	48	1.25 (0.80, 1.98)		
No surgery					
	Chemo only	90	5.37 (3.83, 7.50)		
	XRT only	49	2.17 (1.43, 3.30)		
	Chemo/XRT	91	4.17 (2.97, 5.83)		
No cancer-specific therapy		39	5.23 (3.44, 7.96)		
TNM stage				<0.001	0.66
	IA	120	(reference)		
	IB	37	1.21 (0.75, 1.96)		
	IIA	23	1.40 (0.80, 2.43)		
	IIB	46	1.72 (1.12, 2.64)		
	IIIA	67	2.14 (1.47, 3.12)		
	IIIB	48	3.21 (2.14, 4.83)		
	IIIC	18	3.76 (2.09, 6.75)		
	IVA	83	3.09 (2.18, 4.39)		
	IVB	61	7.84 (5.38, 11.41)		
Tumor histology				<0.001	0.55
	Adenoc	278	(reference)		
	SCC	129	1.14 (0.89, 1.46)		
	LCC	17	1.38 (0.78, 2.43)		
	NOS	79	1.90 (1.44, 2.52)		
Age		503	1.01 (1.00, 1.02)	0.015	0.54
ECOG PS				<0.001	0.58
	0	159	(reference)		
	1	274	1.52 (1.20, 1.93)		
	≥2	70	2.72 (1.96, 3.80)		
Race				0.023	0.54
	White	264	(reference)		
	Black	219	1.34 (1.09–1.65)		
	Others	20	1.06 (0.59–1.91)		
Gender				0.71	0.50
	Female	280	(reference)		
	Male	223	1.04 (0.85–1.28)		
Smoking				0.47	0.51
	Never	46	(reference)		
	Current	160	1.23 (0.82–1.87)		
	Prior	297	1.28 (0.86–1.90)		

Notes: Adenoc, adenocarcinoma; C, Gönen and Heller's K concordance statistic; CCI, Charlson comorbidity index; CI, confidence interval; CPVP index, clinical and PET/CT volumetric prognostic index; CV index, clinical variable index; HR, hazard ratio; ln(MTVwb) is natural log-transformed whole-body metabolic tumor volume; LCC, Large cell carcinoma; N, number of patients; NOS, not otherwise specified; PVP index, PET/CT volumetric prognostic index; SCC, Squamous cell carcinoma

$p = 0.006$ for CPVP index vs. PVP index. $p = 0.002$ for CPVP index vs. ln(MTVwb).

[†] all $p < 0.001$ for CPVP index vs. CV index, eight categories of treatment, nine-level TNM stage, histology, age, ECOG PS, race, gender, and smoking status.

where quantitative risk assessment is needed, such as in clinical trials, where the CPVP index can be used to match the patients with similar prognosis for post-treatment intervention. The FDG PET/CT scans for this study cohort were performed with different scanners, and in some patients, the scans were obtained at outside institutions. Therefore, the

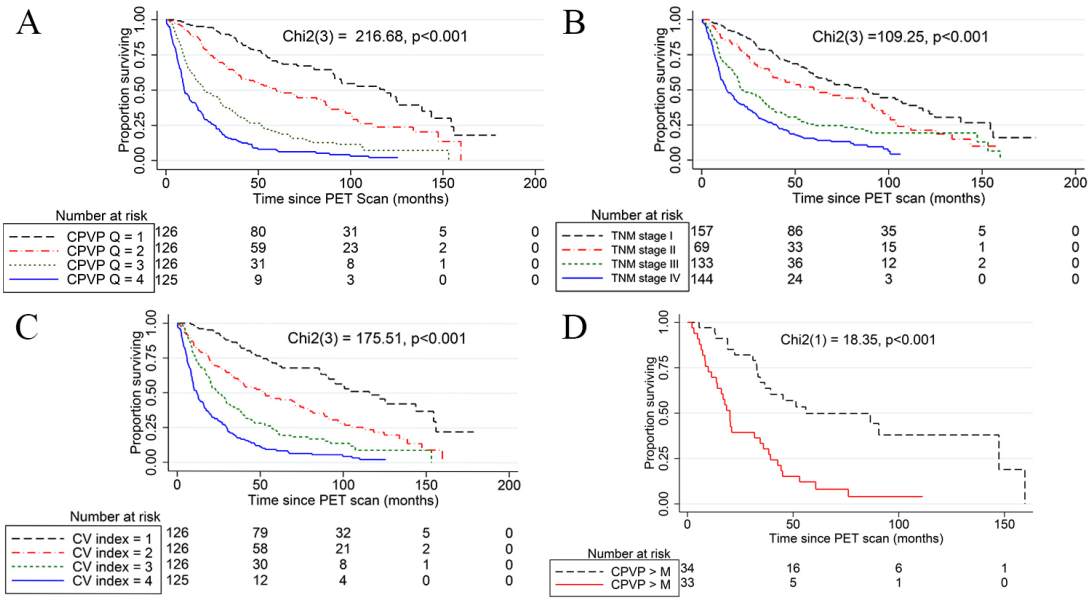

Fig. 2. Kaplan-Meier survival analysis and Log Rank test. (A) Kaplan-Meier curves show the significant association of the quartiles of the CPVP index (CPVP Q) with OS. The black dash, red dash-dot, green short-dash, and blue solid curves indicate the 1st, 2nd, 3rd and 4th quartiles of the CPVP index, respectively. The median OS of the 1st, 2nd, 3rd and 4th quartiles of the CPVP index was 115.8 months, 56.0 months, 20.8 months, and 9.8 months respectively. (B) Kaplan-Meier curves show the significant association of clinical TNM stage with OS. The black dash, red dash-dot, green short-dash, and blue solid curves indicate the clinical TNM stage I, II, III and IV, respectively. (C) Kaplan-Meier curves show the significant association of the quartiles of the clinical variable index (CV index Q) with OS. The black dash, red dash-dot, green short-dash, and blue solid curves indicate the 1st, 2nd, 3rd and 4th quartiles of the CV index, respectively. (D) The Kaplan-Meier curves of patients with clinical TNM stage IIIA NSCLC divided by the median CPVP index of the TNM sub-stage (3.05) show significant association of CPVP index with patients' overall survival. Black dash and red solid lines indicate CPVP index less than the median and greater than the median of the stage IIIA patients, respectively. M represents the median of CPVP index in stage IIIA patients.

FDG PET/CT scanners used in this study were heterogeneous and mimic real world situations, suggesting that the model developed based on this cohort may be generalized to other centers.

In addition, Kaplan-Meier curves for the validation cohort divided by the quartiles of the CPVP index also demonstrated better separation of the patient groups with different survival probability than those divided by clinical TNM stage. The median OS of the 1st, 2nd, 3rd and 4th quartiles of the CPVP index was 121.7 months, 59.6 months, 20.9 months, and 9.8 months, respectively. The Kaplan-Meier curves of patient groups with clinical TNM stage IIIA NSCLC divided by the median CPVP index of the TNM stage show significant survival difference in the patient groups within the same TNM stage IIIA. Therefore, we believe our new CPVP index can help clinicians to develop more effective post-treatment follow-up strategies at an early stage after initial treatment by further differentiating risk. One way to use CPVP index for patient follow-up is that we may use the quartiles of CPVP index and their estimated OS in the validation cohort to follow the NSCLC patients. If the CPVP index of a patient is $\leq$2.23, which belongs to 1st quartile of the CPVP index, the patient may be followed for a longer interval after initial therapy, like 5 years as her/his estimated median OS is 115.8 months; whereas if a patient's CPVP index $\geq$3.74 (4th quartile of the CPVP index), she/he needs to be followed within 5 months as her/his median OS is 9.8 months.

This study has some limitations. First, this is a retrospective study within a single academic institution. Validation with data from other institutions is needed to further establish the prognostic value of the CPVP index. Second, the study is limited by a relatively small sample size. This prevented us from formulating the CPVP index with more than three clinical TNM-stage groups. Similarly, some of the individual treatment type, tumor histology subtype and PS sub-groups also had relatively few patients. In addition, there were 135 cases (13.5%) whose tumor histological subtype is unknown. Third, the study is also limited by not being able to include genetic testing, new therapeutic methods such as targeted therapy and immune therapy. In addition, in the future the TNM staging system may be updated. With the advancement of genetic testing, more effective therapeutic methods and updating TNM staging system in NSCLC, the CPVP index needs to be updated by including these variables.

5. Conclusions

The CPVP index for NSCLC patients has moderately strong prognostic power and is more prognostic than its individual prognostic variables and other indices. It provides a practical tool for quantitative prognostic assessment after initial treatment and therefore may be helpful for the development of individualized treatment and monitoring strategy for NSCLC patients.

Abbreviations

CCI, Charlson comorbidity index; CPVP index, clinical and PET/CT volumetric prognostic index; CV index, clinical variable index; FDG, fluorodeoxyglucose; HR, hazard ratio; ln(MTVwb), natural log-transformed whole-body metabolic tumor volume; NSCLC, non-small cell lung cancer; PET/CT, Positron Emission Tomography - Computed Tomography; PS, Eastern Cooperative Oncology Group (ECOG) performance status; PVP index, PET/CT volumetric prognostic index.

Author contributions

LL—Validation, Investigation, Writing-Original Draft. JZ—Investigation. MKF—Conceptualization, Investigation and Writing - Review & Editing. DA—Writing - Review & Editing. JXZ—Conceptualization, Methodology, Writing - Review & Editing. YP—Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - Original Draft and Funding acquisition.

Ethics approval and consent to participate

The informed consent was waved for all participants. The institutional review board of the University of Chicago approved the study on 2/10/2009 and 9/13/2017, IRB protocol 16770A an d 17-0877.

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Conflict of interest

The authors declare no conflict of interest.

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