Development and Validation of a New Clinical Prognosis Prediction Model for Metabolism in Cancer Patients

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Abstract

Background: Metabolic reprogramming has emerged as an important feature of cancer, and the metabolism-related indexes are closely related to prognosis. Therefore, we develop and verify a large sample clinical prediction model to predict the prognosis in patients with solid tumors.

Methods: This retrospective analysis was conducted on a primary cohort of 5006 patients with solid tumor from INSCOC database. A total of 1720 cancer patients treated at the Fujian Cancer Hospital was used to form the validation cohort. A multivariate Cox regression analysis was performed to test the independent significance of different factors and then establish the model. The prediction model was simplified into a nomogram to predict the 1-, 3-and 5-year OS rates. To determine the discriminatory and predictive accuracy capacity of the model, the C-index and calibration curve were evaluated.

Results: Multivariate analysis indicated that age, smoking history, tumor stage, tumor metastasis, PGSGA score, FBG, NLR, ALB, TG, and HDL-C were independent factors. Moreover, the nomogram combining the score and clinical parameters can predict patient survival accurately.

Conclusions: Clinical indicators based on metabolism reprogramming coould well fit and predict the prognosis of cancer patients, and could provide assistance for the individual treatment of tumor patients in the clinic.

Introduction

Cancer is the most threatening disease to human beings. Its incidence rate has been rising globally, and it is the most fatal disease in the world. Some experts believe that cancer is mainly caused by gene mutation, but the effect of gene targeted therapy is not significant in the fight against cancer[1–2]. The mutations in cancer are diverse, and the gene mutations found in cancer are complex and heterogeneous, it is difficult to identify the key rate limiting genes for targeted treatment of tumors [3]. This suggests that genetic mutations may be not the origin of cancer. A few decades ago, Warburg[4] first theorized that mitochondrial damage causes energy metabolism defects and leads to cancer. When the respiration of tumor cells is damaged, the retrograde response (RTG) is activated, which transmit signals from mitochondria to nucleus, affecting the stability of the genome and leading metabolic reprogramming [5–6]. This propound a theory that cancer is essentially a metabolic disease.

Metabolic reprogramming in cancer cells alters glucose metabolism, lipid metabolism, amino acid metabolism, and tumor microenvironment (TME), leading to cancer progression[7]. The rapidly proliferation of cancer cells needs to balance the decomposition and anabolic at the same time. Therefore, metabolism related indicators can reflect tumor growth. Recent reports have suggested that patient prognosis is associated with certain molecular biomarkers involved in tumor metabolism. However, expensive and time-consuming laboratory metabolomics technology is required. In contrast, blood tests from clinical patients are convenient and can be widely used in clinical application. The

changes of metabolic markers in blood test can reflect tumor metabolic reprogramming and the prognosis of patients. Therefore, we developed and validated a metabolic based prognostic prediction model to predict the survival of patients with solid tumors and support the decision making on early therapy.

Materials And Methods

Materials

This retrospective analysis was conducted on a primary cohort of solid tumor patients from INSCOC(Investigation on Nutritional Status and its Clinical Outcomes of Common Cancers)database. The INSCOC is a nation-wide cross-sectional survey on nutritional status and clinical outcome in patients with malignant tumors. Patients were derived from the Investigation on Nutrition Status and its Clinical Outcome of Common Cancers (INSCOC) project of China (registered at chictr.org.cn, ChiCTR1800020329). Patients were evaluated from January 2013 to August 2018 at 30 tertiary public hospitals in China. Inclusion criteria: 1) a histologic diagnosis of malignant solid tumors; 2) a complete medical history record and follow-up data available. An independent cohort of cancer patients with the same inclusion criteria were enrolled from the Fujian Cancer Hospital, and this cohort was used to form the external validation cohort. The follow-up time was 1-60 months in both primary cohort and validation cohort, and the outcome was patient's death. The study was approved by the Ethics Committees of all participating institutions and all data was analyzed anonymously. The study is reported in accordance with the TRIPOD guidance for transparent reporting of prediction models[8].

Data collection

Demographic and clinicopathological data were collected, including sex, age, smoking history, drinking history, PGSGA score (Patient Generated Subjective Global Assessment score), NRS2002 score (Nutrition risk screening score), primary tumor site, tumor metastasis, TP (total protein), ALB (albumin), PAB (prealbumin), FBG (fasting blood-glucose), TC (total cholesterol), TG (triglyceride), HDL-C (high density lipoprotein cholesterol), LDL-C (low density lipoprotein cholesterol), WBC(white blood cell), NLR(neutrophil/lymphocyte ratio). All continuous variables were converted to categorical variables according to clinical standard. Regardless of tumor type or origin, metabolic abnormalities are common features of most cancer cells. Therefore, 15 kinds of malignant solid tumors were included in the study and classified by human systems. The NLR is an inflammatory marker which has been investigated as a prognostic indicator in post-therapeutic recurrence and survival of patients with cancer[9–10]. In our study, NLR was classified according to the optimum cutoff value(Figure.S1). PGSGA was adapted from the SGA (Subjective Global Assessment) and widely used for clinical assessment of malnutrition in cancer patients[11]. Patients with PGSGA score≥4 need nutritional interventions and symptomatic treatment. NRS 2002 is recommended by The European Society of Clinical Nutrition and Metabolism (ESPEN) as a nutritional risk screening method for patients[12]. Patients with NRS 2002 score ≥3 are at risk of

malnutrition and require nutritional support. Variables where >10% of values were missing, or patients with a missing value for a specific variable, were excluded from the analysis. The missing data in selected variables were multiply imputed to generate a complete data set.

Statistical analysis

We used a primary cohort of solid tumor patients from INSCOC database to develop a clinical prediction model. Categorical variables were reported as whole numbers and proportions. The overall survival (OS) was calculated using the Kaplane-Meier method and the log-rank test. Univariate analysis was performed for all variables, and the variables with P values < 0.05 were included in multivariate analysis. A multivariate Cox regression analysis was performed to test the independent significance of different factors. The variables were selected by stepwise regression and then fit a more parsimonious model. Nomograms are a pictorial representation of a complex mathematical formula that use two or more known variables to calculate an outcome. The resulting model was simplified into a nomogram to predict the 1-, 3-and 5-years OS rates. We also did a decision-curve analysis to assess the clinical usefulness of the model.

The area under ROC curve (AUC) was used to evaluate the predictive accuracy. Calibration curves were assessed graphically by plotting the observed rates against the predicted probabilities to evaluate the agreement. Brier score was used to evaluate probability calibration. Nomograms are a pictorial representation of a complex mathematical formula that uses two or more known variables to calculate an outcome. The resulting model was simplified into a nomogram to predict the survival of patients with solid tumors. To assess the performance of our model, the discriminative performance of the model was measured using Harrell's C-statistic. An internal validation step was performed to counteract the possible overfitting of our model to the data. The bootstrapping techniques (B = 100) was used to validate and correct the over-optimism of the models ,and obtained the optimism-corrected measures of C- statistic.

In all analyses, p values < 0.05 were considered to indicate statistical significance. All analyses were performed using the R software, version 3.6.1.

Results

Clinicopathological characteristics

In the primary cohort, there were 5006 patients who met the inclusion criteria were finally enrolled in the study, the median follow-up time was 30.3 months. For the validation cohort, we studied 1703 patients admitted to a single institution, the median follow-up time was 27.0 months. The demographic features and clinical characteristics of the primary and validation cohorts are presented in Table 1. Figure S2 shows the cumulative survival free between primary cohort and validation cohort. Log-Rank test showed that P=0.052. This means there was no significant difference between the two cohorts.

Table 1
Patient characteristics

Demographic or clinical characteristic	Primary cohort (n =5006)		Validation cohort (n = 1703)	
	No. of Patients	%	No. of Patients	%
Sex				
Male	2517	50.3	942	55.3
Female	2489	49.7	761	44.7
Primary tumor site				
Digestive system	1797	35.9	1343	78.9
Reproductive system	1067	21.3	88	5.2
Respiratory system	1339	26.8	184	10.8
Nervous system	302	6.0	4	0.2
Urogenital system	72	1.4	10	0.6
Others	429	8.6	74	4.3
Age				
≤65yr	3328	66.5	1281	75.2
>65yr	1678	33.5	422	24.8
Smoking history				
No	3025	60.4	996	58.4
Yes	1981	39.6	707	41.6
Drinking history				
No	4053	81.0	1377	80.9
Yes	953	19.0	326	19.1
Tumor stage				
I	694	13.9	139	8.1
II	1011	20.2	304	17.9
III	1348	26.9	553	32.5
IV	1953	39.0	707	41.5
Tumor metastasis				
No	3726	74.4	1193	70.1

Demographic or clinical characteristic	Primary cohort (n =5006)		Validation cohort (n = 1703)	
	No. of Patients	%	No. of Patients	%
Yes	1280	25.6	510	29.9
PGSGA score				
<4	2475	49.4	967	56.8
≥4	2531	50.6	736	43.2
NRS2002 score				
<3	3993	79.8	1140	66.9
≥3	1013	20.2	563	33.1
TP				
<60 g/L	618	12.3	134	7.9
60-80 g/L	4245	84.8	1464	86.0
>80 g/L	143	2.9	105	6.1
ALB				
<35g/L	814	16.3	473	27.8
≥35 g/L	4192	83.7	1230	72.2
PAB				
<280mg/L	4373	87.4	1340	78.7
≥280 mg/L	633	12.6	363	21.3
FBG				
<6.1 mmol/L	3392	67.8	1322	77.6
≥6.1 mmol/L	1614	32.2	381	22.4
TC				
<5.2 mmol/L	4275	85.4	1367	80.3
≥5.2 mmol/L	731	14.6	336	19.7
TG				
<1.7 mmol/L	3502	70.0	1265	74.3
≥1.7 mmol/L	1504	30.0	438	25.7
HDL-C				

Demographic or clinical characteristic	Primary cohort (n =5006)		Validation cohort (n = 1703)	
	No. of Patients	%	No. of Patients	%
<1.55 mmol/L	2390	47.7	689	40.5
≥1.55 mmol/L	2616	52.3	1014	59.5
LDL-C				
<3.4 mmol/L	3955	79.0	1039	61.0
≥3.4 mmol/L	1051	21.0	664	39.0
WBC				
<4×10^9/L	970	19.4	117	6.9
4-10×10^9/L	3641	72.7	1429	83.9
>10×10^9/L	395	7.9	157	9.2
NLR				
<3.08	3503	70.0	1217	71.5
≥3.08	1503	30.0	486	28.5

Model development

All variables listed in Table 2 were used for univariate and multivariate Cox regression analysis. On multivariate analysis, the presence of age > 65yr (HR 1.69, 95%CI 1.53-1.87), smoking history (HR 1.45, 95%CI 1.32-1.59), the tumor was in stage III (HR 1.40, 95%CI 1.17-1.66) and stage IV (HR 1.46, 95%CI 1.25-1.72), tumor metastasis (HR 2.36, 95%CI 2.14-2.61), PGSGA score≥4(HR 1.46, 95%CI 1.32-1.61), FBG≥6.1 mmol/L(HR 2.63, 95%CI 2.39-2.91), NLR≥3.08(HR 1.25, 95%CI 1.13-1.38) were the independent risk factors of overall survival. In addition, ALB≥35 g/L (HR 0.71, 95%CI 0.63-0.80), TG≥1.7 mmol/L(HR 0.77, 95%CI 0.69-0.86), HDL-C≥1.55 mmol/L (HR 0.65, 95%CI 0.59-0.72) were the protective factors of overall survival. The HR of the prediction model was shown by forest plot (Figure 1). We simplified the model into a nomogram (Figure 2). The nomogram based on these ten factors was developed to predict the 1, 3, 5 years of OS in cancer patients. The scales of the nomogram reflect coefficients from the Cox model rescaled to a user-friendly 100-pointrange.

Table 2
The results of the univariate and multivariate Cox regression analysis of the primary cohort

Variables	Univariable model		Multivariable analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex				
Male	Reference			
Female	0.65(0.59-0.71)	<0.001		
Primary tumor site				
Digestive system	Reference			
Nervous system	0.91(0.73-1.14)	0.40		
Reproductive system	0.41(0.35-0.49)	<0.001		
Respiratory system	1.82(1.63-2.03)	<0.001		
Urogenital system	0.69(0.41-1.14)	0.15		
Others	1.21(1.02-1.43)	0.03		
Age				
≤65yr	Reference		Reference	
>65yr	2.35(2.14-2.58)	<0.001	1.69(1.53-1.87)	<0.001
Smoking history				
No	Reference		Reference	
Yes	1.63(1.49-1.80)	<0.001	1.45(1.32-1.59)	<0.001
Drinking history				
No	Reference			
Yes	1.35(1.21-1.52)	<0.001		
Tumor stage				
I	Reference		Reference	
II	1.08(0.89-1.31)	0.43	1.09(0.90-1.31)	0.395
III	1.59(1.34-1.89)	<0.001	1.40(1.17-1.66)	<0.001
IV	1.82(1.54-2.13)	<0.001	1.46(1.24-1.72)	<0.001
Tumor metastasis				

Variables	Univariable model		Multivariable analysis	
No	Reference		Reference	
Yes	2.89(2.62-3.18)	<0.001	2.30(2.08-2.54)	<0.001
PGSGA score				
<4	Reference		Reference	
≥4	1.89(1.72-2.09)	<0.001	1.44(1.30-1.59)	<0.001
NRS2002 score				
<3	Reference			
≥3	1.35(1.21-1.51)	<0.001		
TP				
<60 g/L	Reference			
60-80 g/L	0.77(0.67-0.88)	<0.001		
>80 g/L	0.86(0.63-1.16)	0.31		
ALB				
<35g/L	Reference		Reference	
≥35 g/L	0.43(0.39-0.48)	<0.001	0.65(0.58-0.73)	<0.001
PAB				
<280mg/L	Reference			
≥280 mg/L	0.69(0.59-0.81)	<0.001		
FBG				
<6.1 mmol/L	Reference		Reference	
≥6.1 mmol/L	3.59(3.27-3.96)	<0.001	2.82(2.55-3.11)	<0.001
TC				
<5.2 mmol/L	Reference			
≥5.2 mmol/L	0.88(0.77-1.01)	0.068		
TG				
<1.7 mmol/L	Reference		Reference	
≥1.7 mmol/L	0.73(0.65-0.81)	<0.001	0.73(0.65-0.82)	<0.001
HDL-C				

Variables	Univariable model		Multivariable analysis	
<1.55 mmol/L	Reference		Reference	
≥1.55 mmol/L	0.59(0.54-0.65)	<0.001	0.64(0.58-0.71)	<0.001
LDL-C				
<3.4 mmol/L	Reference			
≥3.4 mmol/L	0.88(0.78-0.99)	0.043		
WBC				
<4×10^9/L	Reference			
4-10×10^9/L	0.99(0.88-1.12)	0.89		
>10×10^9/L	1.72(1.44-2.05)	<0.001		
NLR				
<3.08	Reference		Reference	
≥3.08	1.80(1.63-1.98)	<0.001	1.23(1.12-1.36)	<0.001

Model validation

In primary cohort, Harrell's C- statistic was 0.775 (95% CI, 0.765-0.786). Furthermore, the calibration plot for the probability of survival at 5 years was closely follow the ideal line of 45 degrees, indicating optimal agreement between the prediction by model and the actual observed survival (Figure. 3A). The Brier score was 0.169 (95% CI, 0.152-0.186). The model yielded AUC values of 0.812 (95% CI, 0.794-0.830) for predicting mortality at 5 years after admission (Figure. 3C).

Internal validation with bootstrapping revealed the optimism-corrected C-statistic of the predictive model was 0.776, and the optimism-corrected Brier score was 0.169. Both the average optimism of C-statistic and Brier score were less than 0.001, reflecting a small degree of over-optimism. In the external validation cohort, there was also a good calibration curve for the risk estimation, indicating that the model is well-calibrated (Figure. 3B). The Brier score was 0.185 (95% CI, 0.158-0.212), and Harrell's C- statistic was 0.771 (95% CI, 0.752-0.790). The AUC values for predicting mortality at 5 years was 0.786 (95% CI, 0.741-0.832) (Figure. 3D). The decision-curve analysis showed that the prediction model is the higher line on the decision curve, which indicates that the prediction model leads to a higher net benefit and greater clinical utility (Figure.S3).

Discussion

Cancer is a significant public health problem and is the second leading cause of death globally[13]. Metabolic alterations of tumors are recognized as one of the hallmarks of cancer[14]. Cancer cells support energy to maintain tumor progression and proliferation by adopting to metabolic changes. A huge number of cancer cells show metabolic reprogramming, including the reprogrammed glucose, lipid and amino acid metabolism to satisfy high proliferation requests. FBG, ALB, TG and HDL-C can well reflect metabolic changes as routine clinical detection items, so they were included in this study. In addition, tumor cells need to survive drastic changes in the microenvironment such as hypoxia, nutrient storage, acidic pH and chronic inflammation[15]. The tumor microenvironment enforces metabolic plasticity and promotes tumor proliferation and progression[16]. Therefore, this study included PGSGA score as a sensitive to evaluate nutritional status, and included NLR as an inflammatory marker. Besides, we included some other indicators related to the survival and prognosis of tumor patients, such as age, smoking history, tumor stage and tumor metastasis, so as to more comprehensively predict the prognosis of cancer patients. There were also many indicators that can reflect tumor metabolism and microenvironment, but they were not included in this model due to the incomplete data, missing values>10%, being removed by stepwise regression and the results of multivariate analysis were meaningless.

A clinical prediction model can provide tailored estimation on prognosis and help physician with associated decision making in daily practice. At present, many indicators of tumor metabolism are based on experimental metabolomics technologies, which cannot be widely popularized in clinical practice because of its high cost and long detection cycle. Therefore, we used routine clinical detection indicators in prediction model. In order to develop an accurate clinical prediction model, we conducted strict quality control. First, in order to build a reliable and accurate prediction model, the sample size should be large enough and the data should be complete. We screened from INSCOC database and included a large sample of 5006 in this study to ensure the quality of data development. Second, we ensured that the data covered common types of tumors, and all factors included in the prediction model are commonly assessed in routine clinical examinations. In this way, the universality of the prediction model can be guaranteed to the greatest extent and can be widely used in clinical practice, which is clearly a practical advantage. The model is available as a nomogram. Nomograms have emerged as a simpler, yet more advanced method to calculate the prognosis of different cancers. By integrating diverse prognostic and determinant variables to generate the probability of a clinical outcome, the nomogram fulfills a necessary role in oncological personalized medicine. In this study, the nomogram could predict an individual's 1-, 3- and 5-year survival rates with good accuracy which was verified in the validation cohort. This nomogram can evaluate the prognosis of patients conveniently and help clinicians adopt preventive and therapeutic strategies.

Normally, the main way for the body to obtain energy is the oxidative phosphorylation of glucose under aerobic conditions. In cancer cells, even in the presence of oxygen, the main pathway of glucose metabolism is aerobic glycolysis, termed Warburg effect[4], which reflects the reprogramming of tumor glucose metabolism. Hyperglycemia is a common phenomenon in patients with advanced cancer[17].

Hyperglycemia can provide cancer cells with a high glucose fuel source to support rapid proliferation, drive glycolysis metabolic pathway, and lead to worse prognosis. Hyperglycemia can indirectly influence cancer cells through an increase in the levels of insulin/IGF-1, thus activating the PI3K/AKT/mTOR signaling pathway and promoting the development of cancer[18]. Beyond that, hyperglycemia has a direct impact on cancer cell proliferation, metastasis, invasiveness, and antiapoptotic qualities [19–21]. In our study, FBG ≥ 6.1 mmol / L (HR 2.63, 95% CI 2.39-2.91) is considered as one of the risk factors affecting the survival of tumor patients, which confirms the harm of hyperglycemia. Hyperglycemia can promote glycolysis and raise the prevalence and mortality of certain malignancies. FBG is the most intuitive index to reflect blood glucose, which can be a prediction index for cancer progression and glucose metabolism [22–23].

Therefore, patients with FBG ≥ 6.1 mmol / L should be carried out appropriate diet or drug intervention to improve the prognosis.

In cancer cells, the protein synthesis and decomposition are enhanced, but the anabolism exceeds the catabolism, and can even capture the protein from normal tissues, in order to meet the needs of their own growth. The amino acid metabolism of the tumor was also changed, tumor cells can obtain energy through glutamine and other amino acids. These changes will lead to severe protein consumption, negative nitrogen balance and hypoproteinemia. Patients with hypoproteinemia have a greater risk of recurrence and mortality, which can be corrected by albumin supplementation. Albumin (Alb) is an acute phase protein that decreases with inflammation and due to other reasons, such as malnutrition, increased age and metabolic disorder. Albumin reflects nutritional state and response to amino acid metabolism, and is associated with the prognosis of cancer patients. In our study, ALB≥35 g/L (HR 0.71, 95%CI 0.63-0.80) was the protective factors of overall survival. Kao HK et al.[24] showed that patients with increased serum albumin level can have better prognosis. Therefore, albumin can not only reflect amino acid metabolism, but also predict survival and prognosis as a biomarker [25–26].

Nowadays, there are increasing evidences of the role of lipid metabolism alterations as biomarkers of cancer prognosis and survival. Together with the Warburg effect and the increased glutaminolysis, lipid metabolism plays a key role in cancer metabolic reprogramming. Extremely proliferative cancer cells exhibit an intense lipid and cholesterol avidity, which they satisfy by increasing the uptake of dietary or exogenous lipids and lipoproteins[27]. In addition, the increase of de novo fatty acid synthesis and lipid synthesis in cancer cells requires efficient and complementary lipolytic mechanisms to accommodate the intracellular lipid content and provide materials for tumor cell proliferation[28]. This long-term metabolic change will lead to the depletion of stored fat, and promote cancer cell metastasis[29]. TG and HDL, as lipid indexes reflecting lipid metabolism, are closely related to prognosis. Studies showed that a high level of HDL-C can reduce the risk and progression of cancer[30–31]. In our study, HDL-C≥1.55 mmol/L (HR 0.65, 95%CI 0.59-0.72) were protective factor of survival. However, the association between TG and the survival of tumor patients is contradictory. Some studies observed that high level TG can improve the survival of cancer patients[32–33]. On the contrary, other studies[30–34] has shown that high TG can lead to poor

prognosis in cancer patients. In our study, TG≥1.7 mmol/L(HR 0.77, 95%CI 0.69-0.86) were protective factor of survival. Rhonda Arthur et al.[35] showed that TG were not associated with cancer death, but associated with risk of cardiovascular death. This reduced the proportion of cancer cases of death in subjects with elevated TG levels. However, the detailed mechanisms and the biological significance of them require further investigation. In conclusion, Lipid-metabolic can associate with cancer survival and have been proposed as prognosis biomarkers of cancer[36].

In our study, PGSGA score≥4(HR 1.46, 95%CI 1.32-1.61) and NLR≥3.08(HR 1.25, 95%CI 1.13-1.38) were the independent risk factors of overall survival. PGSGA score≥4 indicates the malnutrition in cancer patients, and these patients often have poor prognosis and low survival[37]. In this study, increased NLR was associated with decreased OS. NLR is the ratio of lymphocytes to neutrophils, the two types of cells are part of the human immune system and play a key role in TME. The immune cells in the TME can detect and eliminate the abnormal cells or tumor cells and protect the body from damage caused by tumor cells. Kao HK et al[24]. considered that an elevated NLR indicates an imbalance between the innate and acquired immune response, which might be linked to a poorer prognosis. This elevation may reflect an inflammatory microenvironment that lymphocytes can have tumor suppressing effects and have been linked with better prognosis[38], whereas neutrophils can create a favorable tumor microenvironment by remodeling the extracellular matrix and angiogenesis, thus enabling the tumor to growth and spread[39–40]. Therefore, NLR can be used as a biological indicator of inflammation to predict the prognosis of cancer patients.

Some limitations of this study should be discussed when considering the results. First, cancer patients still have a lot of laboratory indicators reflecting the metabolic situation in clinic, so it is necessary to add more factors to improve the model in the future. In addition, although internal validation was performed to prevent over-interpreting the data, and external validation verify our findings are applicable in single center, we need a prospective multicenter study to confirm the results in the future.

Conclusion

Although the interactions between cancer metabolism and clinical prognosis are intricate. We emphasize their importance and develop a model based on cancer metabolism to predict the prognosis of tumor patients. This proves the correlation between cancer metabolism and clinical prognosis. This prognosis prediction model can accurately predict the prognosis through rapid and economical blood tests, and can be widely used in clinical practice.

Declarations

DATA AVAILABILITY STATEMENT

The INSCOC data that support the findings of this study are available from Chinese Cancer Society Nutrition and Support Committee but restrictions apply to the availability of these data, which were used

under license for the current study, and this INSCOC data relates to the confidentiality of multiple clinical center and patient privacy, so it is not convenient to disclose. Data are however available from the authors upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Capital Medical University Affiliated Beijing Shijitan Hospital. The patients/participants provided their written informed consent to participate in this study. All methods were carried out in accordance with relevant guidelines and regulations. We don't consent for the publication of identifying images or other personal or clinical details of participants that compromise anonymity.

COMPETING INTERESTS

The authors declare no conflicts of financial and non-financial competing interests.

AUTHOR CONTRIBUTIONS

(I) Conception and design: HT, ZY, HS, BR. (II) Administrative support: HS, BR. (III) Provision of study materials or patients: XS, SL, BW, WZ. (IV) Collection and assembly of data: BZ, XW, ZZ, PJ, LW, LD, NG. (V) Data analysis and interpretation: HT, ZY. (VI) Manuscript writing: HT; (VII) Final approval of manuscript: HS, BR. All authors contributed to the article and approved the submitted version.

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Disclosure of conflicts of interest

The authors have nothing to disclose.

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Figures

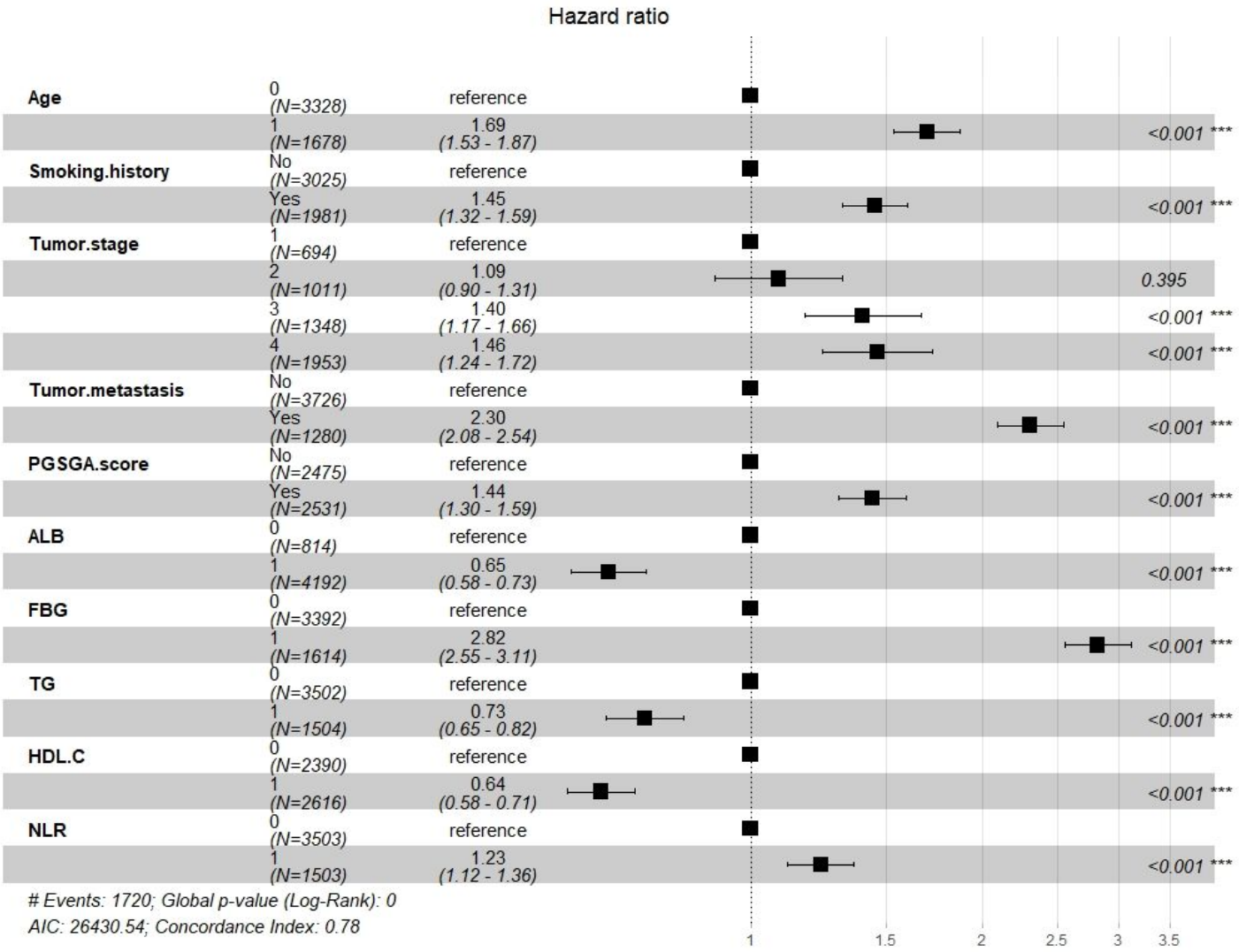

Figure 1

The forest plot showed the results of the prediction model. The HR of the multivariate Cox regression analysis model was shown by forest plot.

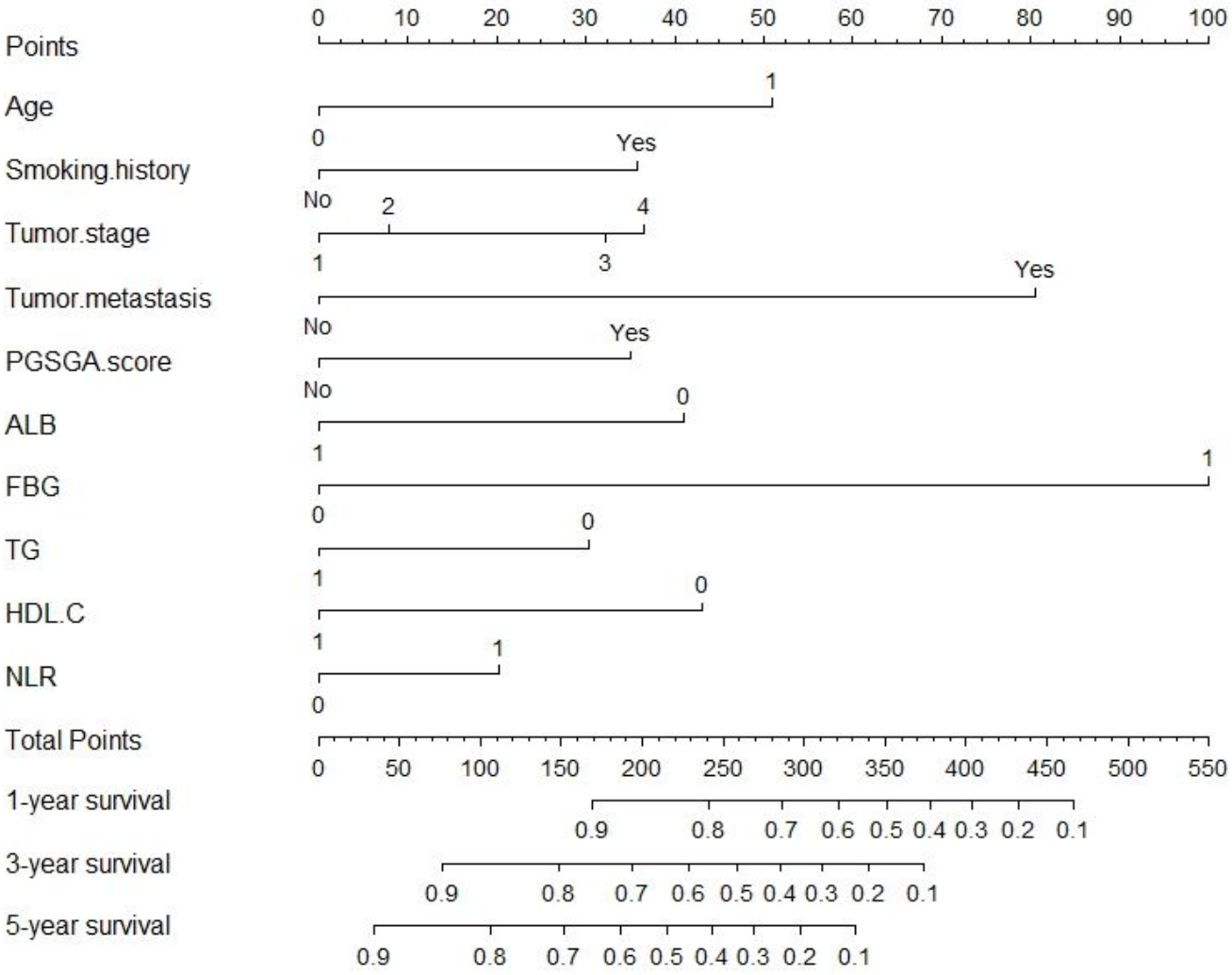

Figure 2

The nomogram developed to predict the overall survival of cancer patients with metabolic reprogramming. To use the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable's value. The sum of these numbers is located on the Total Points axis, and a line is drawn downward to the survival axes to determine the likelihood of survival at 1, 3 or 5 years.

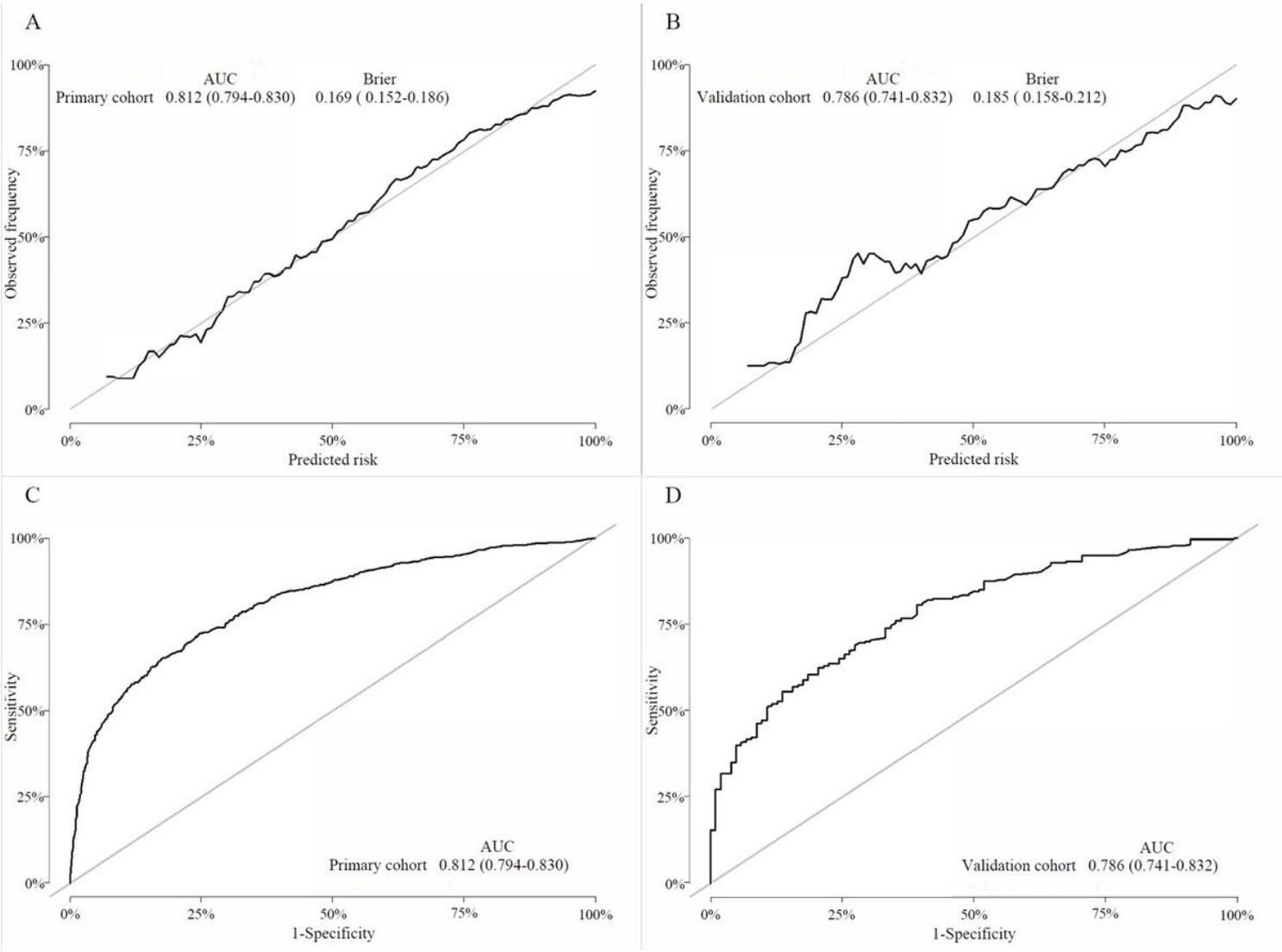

Figure 3

The calibration curve and area under the ROC curves (AUC) for predicting 5 years survival in primary cohort and validation cohort. Calibration plot showing the optimal agreement between the prediction and actual observation in primary cohort(A) and validation cohort(B).The ideal line with 45° slope represents a perfect prediction (the predicted probability equals the observed probability). Area under the ROC curves (AUC) for predicting the survival at 5 years in the primary cohort (C) and the validation cohort (D).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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