Neuroendocrinology Letters Volume 43 No. 6 2022
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL ARTICLE

Construction and evaluation of a prognosis prediction model for thyroid carcinoma based on lipid metabolism-related genes

Zhixing WANG[1], Fan WANG[1]

1 Medical College, Jiangsu Vocational College of Medicine, Yancheng, Jiangsu 224005, China.

Correspondence to: Fan Wang
Medical College, Jiangsu Vocational College of Medicine, Yancheng, Jiangsu 224005, China, No. 283 of Jiefang South Road, Yandu District, Yancheng 224005, China
TEL: 86-18816239362, E-MAIL: 12154@jsmc.edu.cn

Submitted: 2022-06-10 Accepted: 2022-11-14 Published online: 2022-11-14

Key words: **thyroid carcinoma; lipid metabolism; prognosis; gene set enrichment analysis; survival model**

Neuroendocrinol Lett 2022; **43**(6):323–332 **PMID:** 36586126 NEL430622C03

Abstract

BACKGROUND: Thyroid cancer is one of the most common tumors worldwide, and the molecular studies on lipid metabolism disorders in thyroid cancer remain unclear.
AIM: This study intends to explore the model constructed by lipid metabolism genes to evaluate the prognosis of thyroid cancer.
METHODS: The data of thyroid cancer patients were obtained by The Cancer Genome Atlas database. The cancerous tissue from the thyroid gland was used to evaluate specific genes. Besides, Gene Set Enrichment Analysis (GSEA) and Cox proportional hazard regression models were adopted to identify the lipid metabolism genes of thyroid cancer. The survival status of patients with a risk score was analyzed by the Kaplan-Meier method, and the accuracy of the risk score was evaluated by the receiver operating characteristic (ROC) curve.
FINDINGS: Age, tumor node metastasis stage, and risk score were independent prognostic factors for thyroid cancer. FADS1, WNT3A, PCDHA2 and ITGA5 were high-risk genes. The prognostic risk score model was established according to the four lipid metabolism genes. The overall survival of patients with high-risk thyroid cancer was significantly lower than that of low-risk patients in this study.
DISCUSSION: According to the above findings, FADS1, WNT3A, PCDHA2, and ITGA5 are unfavorable factors for the prognosis of thyroid cancer in the pathway of lipid metabolism. A prognostic model composed of the above four genes was constructed, and it was confirmed that the model was not affected by age and sex.
CONCLUSION: The prognosis prediction model for thyroid cancer based on lipid metabolism related genes was successfully constructed, and the model had good predictive ability for the prognosis of thyroid cancer patients.

Abbreviations:

AUC	- area under the curve	HR	- hazard ratio
ES	- enrichment scores	KEGG	- Kyoto Encyclopedia of Genes and Genomes
FC	- Fold-change	mRNA	- micro-RNA
GO	- Gene ontology	OS	- overall survival
GSEA	- Gene Set Enrichment Analysis	ROC	- receiver operating characteristic
GSVA	- Gene set variation analysis	TCGA	- The Cancer Genome Atlas

THCA - thyroid cancer
TME - Tumour microenvironment
TNM - Tumour-node-metastasis
WGCNA - Weighted correlation network analysis.

BACKGROUND

Thyroid cancer (THCA) is the most common type of endocrine cancer globally, and its incidence has been increasing rapidly worldwide in recent years (Ancker *et al.* 2019). At present, surgery is still the main treatment for THCA. Most patients have a very good prognosis, with a 90% 10-year survival rate. However, there are still some patients at risk of postoperative recurrence (Grant, 2015). Therefore, prediction of the risk of poor prognosis of THCA is crucial for the treatment of THCA. The pathogenesis of THCA is influenced by genetic, environmental and other factors, among which lipid metabolism genes are most closely related (Albi *et al.* 2017; Coperchini *et al.* 2017).

Studies have shown that lipid metabolism disorders not only affect the growth of primary tumours but also mediate their progression and metastasis (Cao, 2019; Merino *et al.* 2017), which is one of their most obvious metabolic changes. In a limited study of fatty acid metabolism in THCA, it was found that the content of lipid metabolites in THCA was different from that in normal thyroid tissue (Jelic, 2021). Past studies have found that *FADS1* expression is dysfunctional in many cancers, and knocking down *FADS1* can not only inhibit tumour growth and migration, but it can also enhance the cytotoxicity of chemotherapeutic drugs (Zhao *et al.* 2020).

The classical wingless and *Int-1 (Wnt)* signalling pathway is a highly conserved intercellular signal transduction pathway in postnatal animals. Its signal transduction plays an important role in tissue development, homeostasis and regeneration (Zhang & Wang, 2020). A total of 19 *Wnt* ligands and 10 frizzled receptors have been described in mammals. The *Wnt* pathway includes the classical *Wnt/β-catenin* pathway, the non-classical planar cell polarity and the *Wnt*/calcium pathway. Some studies have found that the activation of the *Wnt* signal pathway caused by the imbalance of *Wnt3a* expression is closely related to the occurrence of tumours (Bugter *et al.* 2021; Krishnamurthy & Kurzrock, 2018).

The abnormal expression of *ITGA5* is closely related to the occurrence and development of cancer (Seguin *et al.* 2015). The *ITGA5* gene is an important member of the integrin family, which is in chromosome *12q11–q13* and encodes fibronectin protein *ITGA5*. It has tissue and functional specificity. It mainly binds to extracellular matrix proteins and regulates biological functions such as cell adhesion, proliferation, apoptosis and movement. It also performs different biological functions in various cancers (Wu *et al.* 2017; Das *et al.* 2018).

So far, the prognostic mechanism of THCA has not been fully understood. Further research on fat metabolism genes will help to provide new ideas and approaches for the development of cell energy metabolism-targeting drugs and clinical treatment for THCA.

In this study, The Cancer Genome Atlas (TCGA) database was used to obtain the clinical information and expression data of patients with THCA, and to identify lipid metabolism genes closely related to the overall survival (OS) rate of patients with THCA. The prognostic risk scoring system based on four lipid metabolism gene signatures can promote the understanding of the pathogenesis of THCA and improve its level of diagnosis and treatment.

MATERIALS AND METHODS

Research data

The data were collected from TCGA database (https://portal.gdc.cancer.gov/). The cancerous tissue from the

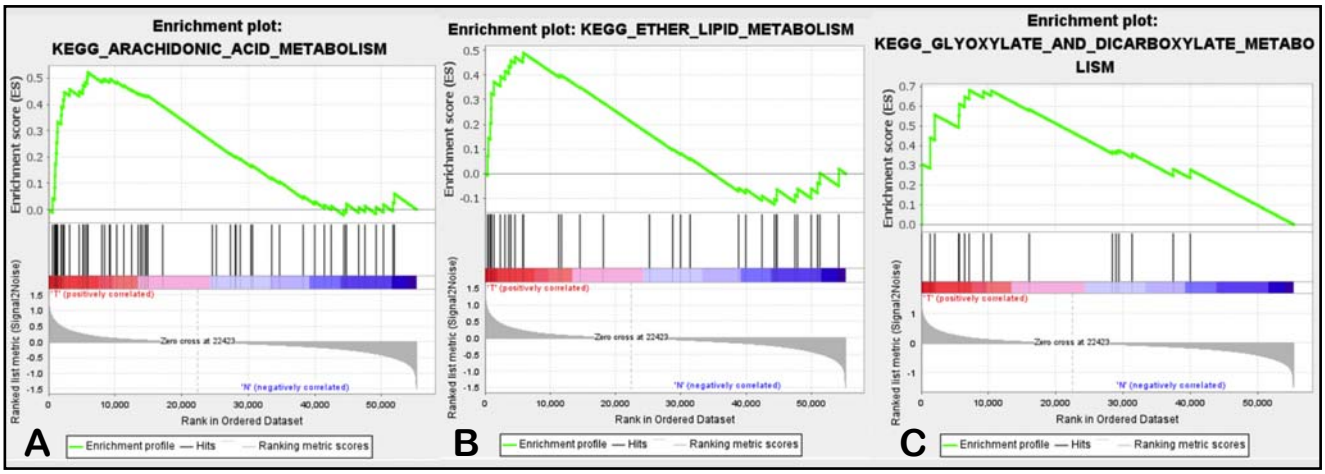

Fig. 1. Enrichment analysis of lipid metabolism genes
(A. p=0.010 KEGG_ARACHIDONIC_ACID_METABOLISM; B. p=0.028 KEGG_ETHER_LIPID_METABOLISM; C. p=0.019 KEGG_GLYOXYLATE_AND_DICARBOXYLATE_METABOLISM); KEGG: Kyoto Encyclopedia of Genes and Genomes.

Tab. 1. Five univariate Cox regression related lipid metabolism genes in THCA

gene	HR	HR.95L	HR.95H	coxPvalue
PCDHA5	7536.730002	11.28942476	5031460.886	0.00713608
FADS1	2.254320872	1.524251326	3.334071297	0.000046818
WNT3A	1.507435865	1.112846726	2.041936983	0.008037894
PCDHA2	85.37575602	3.10736884	2345.720798	0.008522279
ITGA5	1.16685192	1.067241988	1.275758842	0.000700486

Annotation: HR:hazard ratio; THCA:thyroid cancer.

thyroid gland was used to evaluate specific genes. The selection conditions were that the primary cancer focus was 'thyroid', the project name was 'TCGA–THCA', the expression data type was 'HTSeq-FPKM', the data type was 'transcript', and the experimental method was the 'RNA-Seq' technique. The data matrix included 510 patients with THCA and 58 healthy controls. The datasets of 24 genes related to lipid metabolism were searched from the official website for GSEA (http://www.gsea-msigdb.org/gsea/downloads.jsp).

Gene set enrichment analysis

The 24 downloaded datasets were enriched and analysed by the GSEA v4.1.0 software. In addition, the standardised effective lipid metabolism-related gene dataset was screened. The lipid metabolism genes and their expression were extracted from the 24 downloaded datasets. The difference analysis and filtering were carried out using the Limma package of the R software, where $p < 0.05$. A combination of differential gene expression and survival data was analysed.

Construction of the prognostic model of lipid metabolism

Univariate Cox regression analysis was adopted to determine the genes involved in lipid metabolism that affected the OS rate, and then multivariate Cox regression was adopted to search for the genes associated with lipid metabolism and obtain the hazard ratio (HR). The screened lipid metabolism genes were classified by type as dangerous (HR > 1) or protective (0 < HR < 1). The prognostic risk score model was established according to the linear combination of expression levels. The risk score was weighted by the regression coefficient obtained from the multiple Cox regression analysis. With the survival package in R v4.0.2, the lipid metabolism prognostic model with the lowest Akaike information criterion value in THCA was constructed by the multivariate Cox regression method, and the patient risk value was the output. According to the median value, the patients were divided into two groups, and the survival curves of these were drawn. In addition, the ROC curve was adopted to judge the validity of the model diagnosis, draw the risk curve, and analyse the independent prognosis.

The mutation and difference analysis of the model gene

The mutation of the model gene was analysed by the online network cBioPortal (http://www.cbioportal.org/). THCA samples from TCGA dataset were selected to analyse the mutation frequency and types of lipid metabolism genes in the prognostic model. The Limma package was used to analyse the difference.

Statistical method

The Limma package was adopted for differential gene filtering. Univariate Cox regression was adopted to assess screen lipid metabolism-related genes for prognosis. The survival package in R was adopted for the survival analysis. The Kaplan–Meier survival curve and logarithmic rank method were adopted to estimate the accuracy of the risk parameters. Then, multivariate Cox analysis was performed to determine whether the risk parameters were independent of other clinical features. All the above statistical analyses were carried out with R v4.0.2, and $p < 0.05$ indicated that there was a statistically significant difference.

RESULTS

Enrichment analysis of lipid metabolism in thyroid carcinoma

The clinical data and micro-RNA (mRNA) expression datasets of 510 patients with THCA were obtained. After screening 24 datasets, 3 datasets remained. Most of these genes were found to be active in tumour samples, with enrichment scores (ES) of 0.52, 0.49 and 0.68, and normalised ES of 1.60, 1.53 and 1.63, respectively. The normalised p values were 0.01, 0.028 and 0.019. The false detection rate values were 0.01, 0.028 and 0.019, respectively, and these were corrected by the

Tab. 2. Four OS-related lipid metabolism genes in THCA

ID	coef	HR
FADS1	0.81038907	2.24878275
WNT3A	0.367097812	1.443539108
PCDHA2	5.30453006	201.2464065
ITGA5	0.141790924	1.152335698

Annotation: HR:hazard ratio; THCA: thyroid cancer; OS:overall survival.

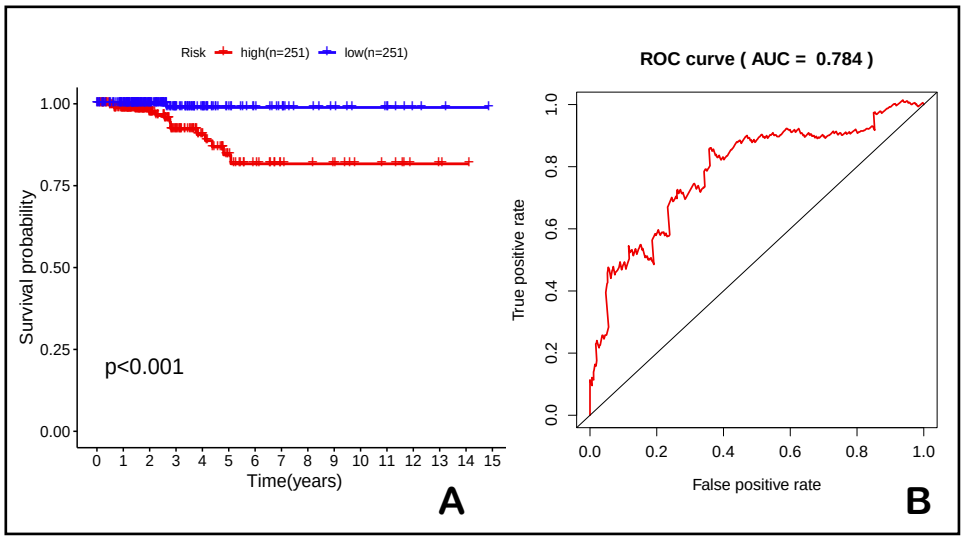

Fig. 2. Survival analysis and ROC curve of prognostic model of lipid metabolism
(A. $p < 0.001$;
B. ROC curve, AUC=0.784)
ROC: receiver operating characteristic; AUC: area under the curve

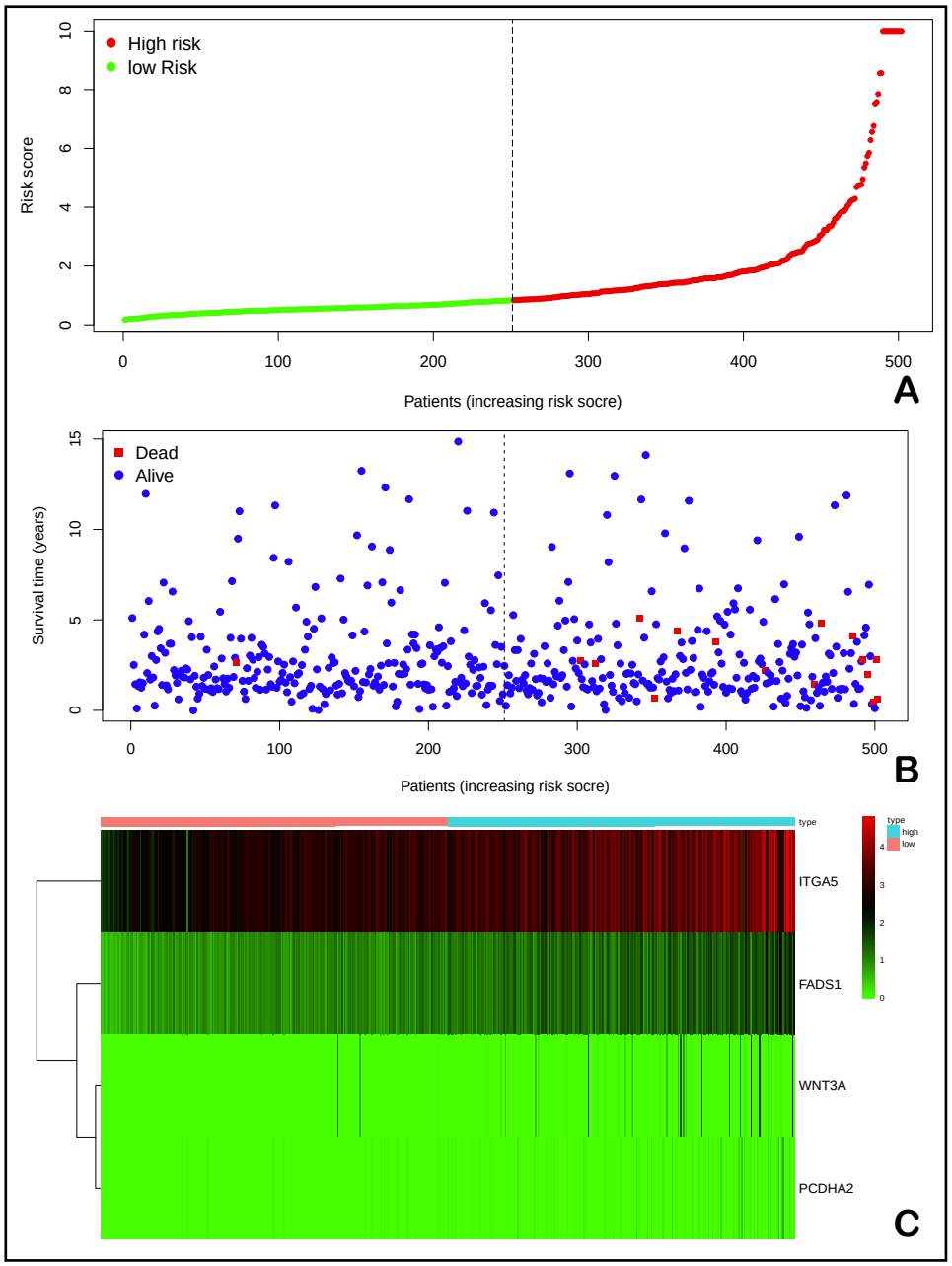

Fig. 3. Risk curve
(A. Risk score distribution;
B. Survival time;
C. The heat map)

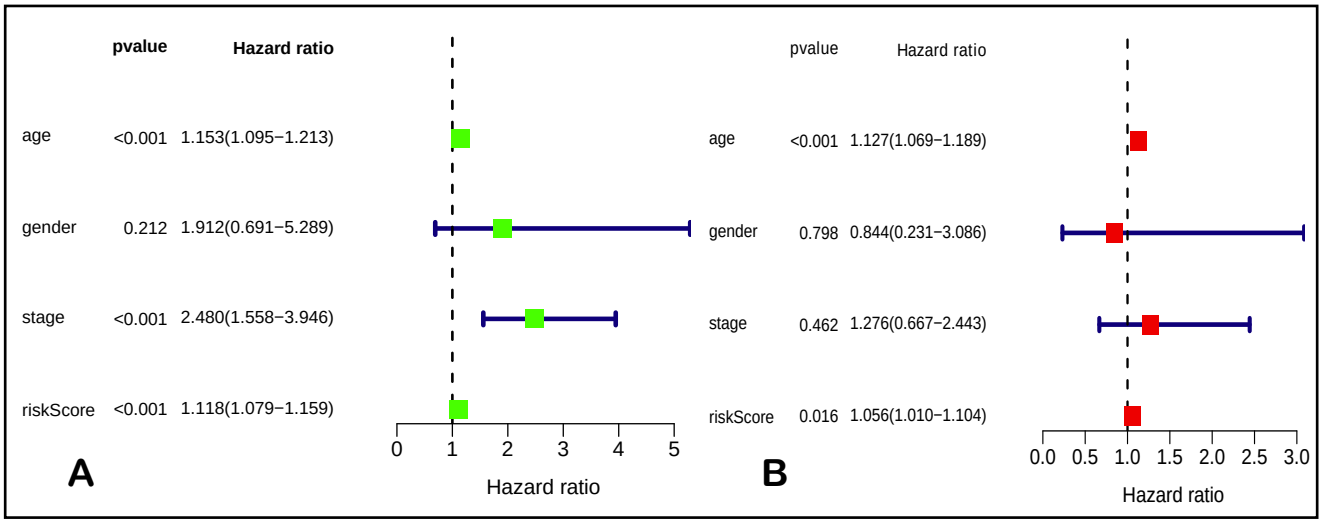

Fig. 4. Independent prognostic analysis
(A. Univariate analysis; B. Multivariate analysis)

lipid metabolic factor set size and the multiple hypothesis test (Fig. 1). The GSEA confirmed that three lipid metabolism-related genes, arachidonic acid, ether lipid and glyoxylate and dicarboxylate, were upregulated in THCA.

Lipid metabolism genes related to the prognosis of thyroid carcinoma

We used univariate Cox regression analysis to determine which genes were differentially expressed in THCA based on lipid metabolism-related gene expression in 24 gene sets. A significant correlation was found between OS and the expression of five genes related to lipid metabolism in patients with THCA (Table 1). Next, multivariate Cox regression analysis further confirmed that the four lipid metabolism-related genes of *FADS1*, *WNT3A*, *PCDHA2* and *ITGA5* were independent prognostic markers of THCA, the HR values were all greater than 1, all of them were of high risk type, and the survival rate of patients was low (Table 2).

The prognostic model of lipid metabolism in THCA

The prognostic model composed of *FADS1*, *WNT3A*, *PCDHA2* and *ITGA5* was constructed by multivariate Cox regression. The risk value was calculated according to the equation:

$$risk\ value = FADS1\ expression \times 0.8104 + WNT3A\ expression \times 0.3671 + PCDHA2\ expression \times 5.3045 + ITGA5\ expression \times 0.1418$$

Using the median value as the dividing line, the patients were put into two groups: high-risk (251 THCA samples) and low-risk (251 THCA samples). There was a significant difference in prognosis between high- and low-risk groups according to the survival curve ($p < 0.001$) (Fig. 2A). Based on the ROC curve, the area under the curve (AUC) value was 0.784%, indicating that the model has predictive value (Fig. 2B).

Risk curve

The patients' risk score distribution (Fig. 3A) and survival status (Fig. 3B) are displayed, and the heat map shows the expression profiles of the four kinds of mRNA (Fig. 3C). As the risk score of patients increased, this resulted in a gradual increase in mortality, as well as a significant reduction in survival time. Also, high levels of *FADS1*, *WNT3A*, *PCDHA2* and *ITGA5* expression were seen in the high-risk group.

Independent prognostic univariate and multivariate analysis

By comparing the prognostic value of risk parameters with clinicopathological parameters in univariate and multivariate analysis, it was found that gender and grade were not very good predictors of prognosis in patients with THCA. However, the risk score could effectively assess the patient's prognosis in the present study. Notably, the p value for age was less than 0.01, and the prognostic value was significant (Fig. 4).

Mutation and difference analysis of the model gene

The changes of four risk genes found by analysing the cBioPortal database (482 THCA samples in http://cbioportal.org)) were evaluated. The results showed that a total of 4 samples (0.8%) had mutations in the risk genes. The *FADS1* gene changed in 0.4% of the cases, showing missense mutations; amplification mutations occurred in 0.2% of the *WNT3A* and *PCDHA2* genes; and no mutation occurred in the *ITGA5* gene (Fig. 5). The expression of *FADS1*, *WNT3A*, *PCDHA2* and *ITGA5* was upregulated in both normal and tumour samples. The p value of *FADS1* and *WNT3A* was less than 0.05 and the p value of *PCDHA2* and *ITGA5* was

less than 0.001, meaning the difference is very significant (Fig. 6).

Survival curve of clinical characteristics and model verification of clinical grouping

Using Kaplan–Meier analysis and logarithmically ranked survival curves, it was shown that the prognosis was poor for patients in the high-risk group. The univariate Cox regression analysis of OS showed that some clinicopathological factors can predict THCA survival, including age and risk score. The Kaplan–Meier survival curve was adopted to verify the above conclusions, which showed consistent results. Age over 65 years old (Fig. 7A), Stage III–IV (Fig. 7B), gender (Fig. 7C), T3–4 stage (Fig. 7D), M1 stage (Fig. 7E), and N1–3 stage (Fig. 7F) were associated with a poor prognosis. These results further confirm the reliability of the analysis. After further data mining and stratified analysis, the survival curve was not affected by age (≤65 or >65 years old).

It can be considered that the four lipid metabolism genes are reliable prognostic indicators for patients with THCA, and the prognosis of patients in the high-risk group is poor (Fig. 8A). The risk parameters based on the lipid metabolism gene tags can be adopted to predict the prognosis of patients with THCA (Fig. 8B). However, when we divided patients with THCA into different subgroups according to the tumour–node–metastasis (TNM) stage, the risk parameter could no longer be used as a single prognostic indicator for the T1-2 THCA M1 (Fig. 8C) subgroup or Stage I–II (Fig. 8D). This indicates that this risk parameter is affected by TNM staging and grading of patients with THCA, which needs to be further explored.

DISCUSSION

Lipid metabolism plays an important role in the structural basis and energy supply of healthy cells and also in the development and progression of cancer. Much attention has been paid to the lipid metabolism of tumours, and the detection of related metabolites, metabolic genes and proteins has been widely applied in the study

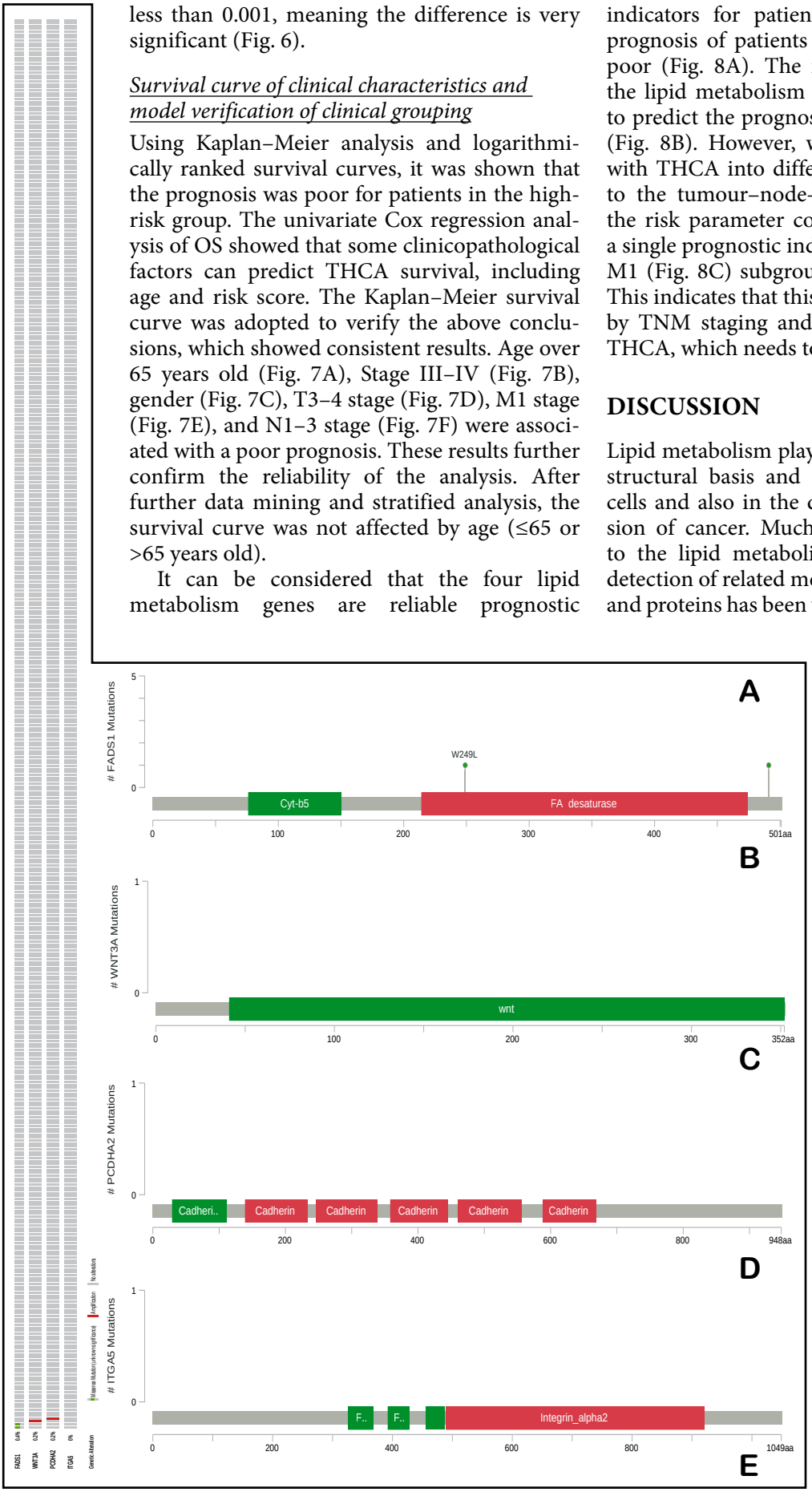

Fig. 5. Mutation of prognostic model gene

(A. The changes of four risk genes by analyzing the cBioPortal database; B. FADS1 mutations; C. WNT3A mutations; D. PCDHA2 mutations; E. ITGA5 mutations)

FADS1: fatty acid desaturase 1;
WNT3A: Wnt family member 3A;
PCDHA2: protocadherin alpha 2;
ITGA5: integrin subunit alpha 5.

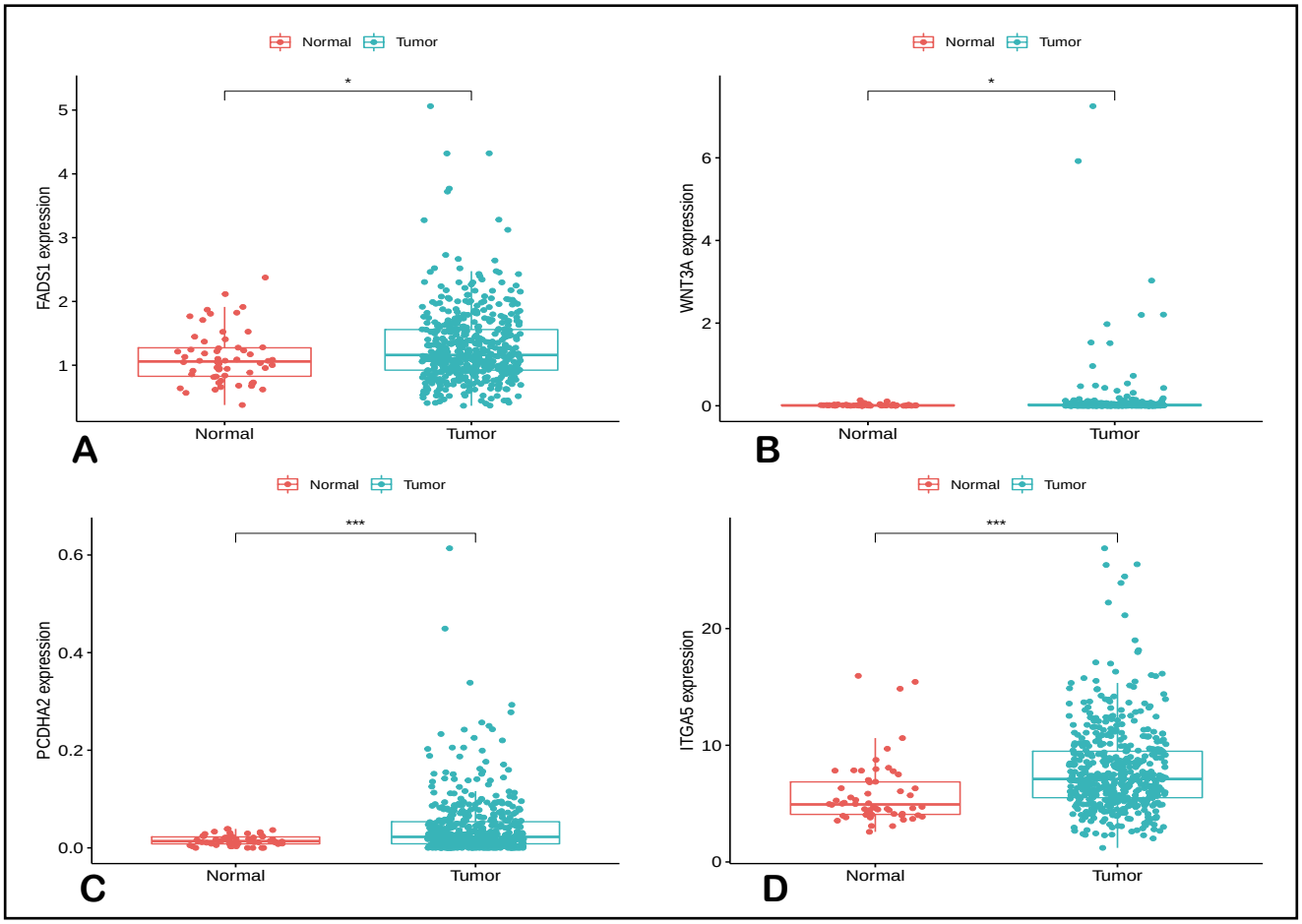

Fig. 6. Difference analysis of prognostic model genes
(A. FADS1 expression; B. WNT3A expression; C. PCDHA2 expression; D. ITGA5 expression); FADS1: fatty acid desaturase 1; WNT3A: Wnt family member 3A; PCDHA2: protocadherin alpha 2; ITGA5: integrin subunit alpha 5.

of tumours in recent years (Vander *et al.* 2017). Wen *et al.* established a four-gene-signature relapse risk model, and the results showed that the lipid metabolism-related gene profiles represent potential markers for prognosis and treatment decisions in patients with papillary THCA (Wen *et al.* 2021). In our previous study, we found that 10 lipid metabolism-related genes APOL4, NR1H3, SLC25A5, APOL3, OSBPL1A, DYNLT1, IMMT, MAP2K6, ZDHHC8, and RAB2A, which are closely associated with the prognosis of breast invasive carcinoma patients and constructed a prognostic risk scoring system based on 10 lipid metabolism genes tags (Wang *et al.* 2022).

This study mainly discusses the model constructed by lipid metabolism-related genes *FADS1*, *WNT3A*, *PCDHA2* and *ITGA5* to evaluate the prognosis of THCA. Previous studies have shown that high *WNT3A* content was observably connected with differentiated THCA (Biagini GLK *et al.* 2022). Besides, *WNT3A* promoted dedifferentiation, proliferation, and metastasis of THCA by activating β-catenin (Lv *et al.* 2021). In addition, the level of *ITGA5* was enhanced in papillary thyroid cancer tissue (Chernaya *et al.* 2018). In this study, we found that the expression of *FADS1*, *WNT3A*, *PCDHA2* and *ITGA5* was upregulated in THCA tumour samples, which was alike with the results of Chernaya *et al.* (Chernaya *et al.* 2018).

In addition, Zhong *et al.* exposed that 5-mRNA prognostic signature for papillary thyroid carcinoma (ADRA1B, RIPPLY3, PCOLCE, TEKT1 and SALL3) was identified to classify the patients into high-and low-risk subgroups (Zhong *et al.* 2020). Moreover, Zhang *et al.* also confirmed that age, extent of disease (EOD), T stage, N stage, and treatment may correlate with OS and disease-specific survival (DSS) in patients with primary squamous cell carcinoma of the thyroid (Zhang *et al.* 2021). In this paper, univariate and multivariate Cox analyses showed that age, TNM stage and risk score were independent prognostic factors for THCA. Multivariate Cox proportional hazard regression analysis confirmed that *FADS1*, *WNT3A*, *PCDHA2* and *ITGA5* were high-risk genes. The prognostic risk score model was established according to the four lipid metabolism gene tags. The OS of patients with THCA with high risk scores was significantly lower than patients with low risk scores in the model samples. The AUC of the 5-year OS of the risk score model is 0.784, confirming that the model has predictive value.

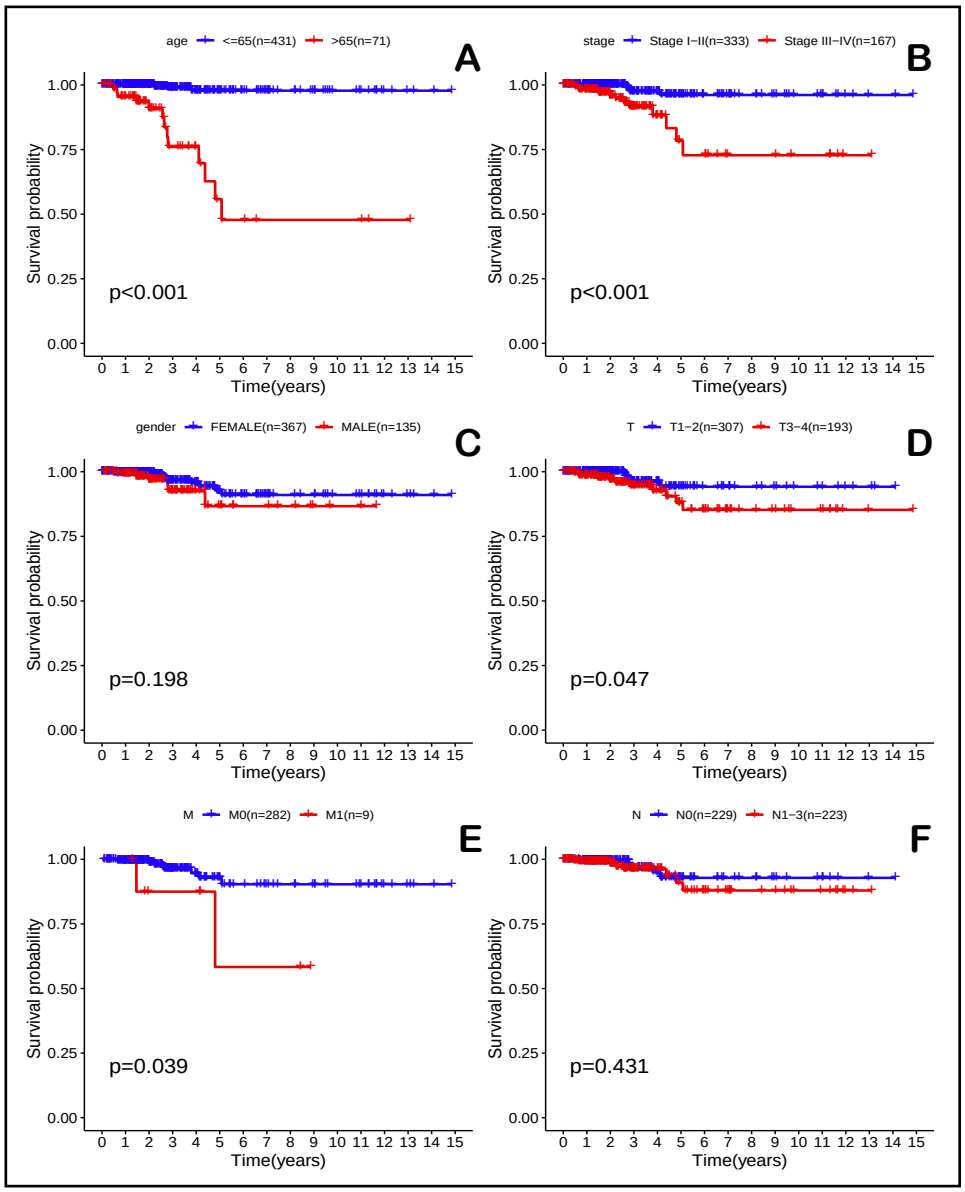

Fig. 7. Relationship between risk score distribution and clinical parameters
(A. $p<0.001$ Survival probability of Age;
B. $p<0.001$ Survival probability of Stage;
C. $p=0.198$ Survival probability of Gender;
D. $p=0.047$ Survival probability of T;
E. $p=0.039$ Survival probability of M;
F. $p=0.431$ Survival probability of N)

Consequently, it is concluded that *FADS1*, *WNT3A*, *PCDHA2* and *ITGA5* in the pathway of lipid metabolism are unfavourable factors for the prognosis of THCA. In addition, this study constructed a prognostic model composed of *FADS1*, *WNT3A*, *PCDHA2* and *ITGA5*, and confirmed that the model was not affected by age or gender, and the risk parameter could not be adopted as prognostic indicators of the T1-2 THCA M1 subgroup or Stage I–II alone.

Strength and limitations

To our knowledge of the strengths and limitations of this study, this is the first multi-gene risk prediction model for THCA based on lipid metabolism genes. There is a limitation to the study, which is that the data matrix is less included in the healthy control group. In the future, fewer included objects can be considered as a proportion in the experimental or control groups to further verify the credibility and feasibility of the prognostic risk scoring model based on the lipid metabolism gene label.

CONCLUSION

In this study, a prognostic risk scoring model was constructed based on lipid metabolism gene signatures and validated by survival analysis, ROC curve drawing, risk function assessment and independent prognostic analysis. It was found that *FADS1*, *WNT3A*, *PCDHA2* and *ITGA5* are tumour markers for evaluating the prognosis of patients with THCA, all of which are high-risk genes. The parameters showed that four genes worsened the prognosis of patients with THCA. Gene-related technologies have been maturely applied in medical and other fields and are widely used in personalised medicine, tumours, and genetic diseases. Taken together, these results provide new ideas and methods for the development of THCA-targeted drugs for

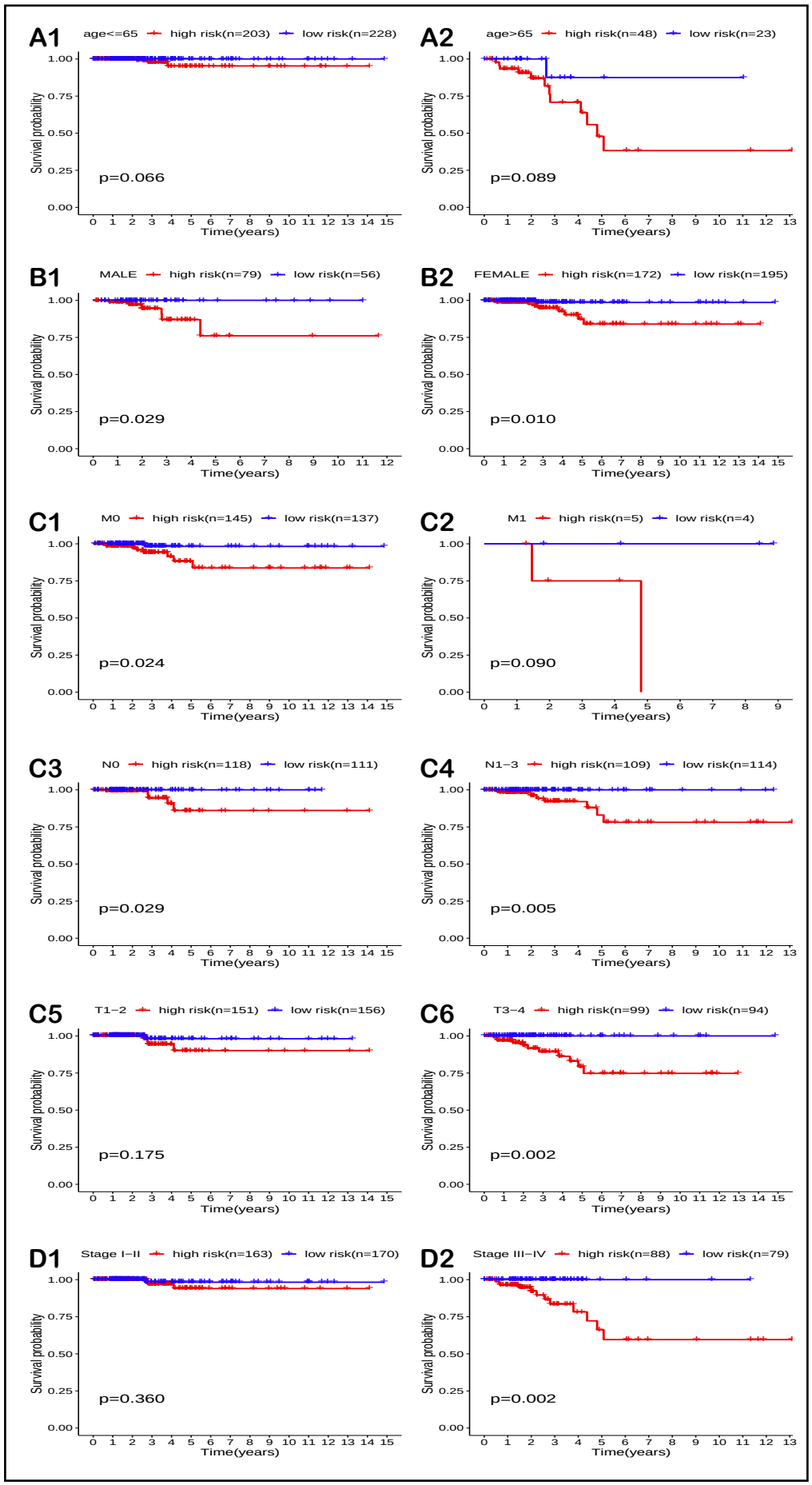

Fig. 8. Prognostic value of Kaplan-Meier curve in evaluating risk parameters of patients in clinical feature grouping (A1: p=0.066 Survival probability of Age ≤ 65; A2: p=0.089 Survival probability of Age > 65; B1: p=0.029 Survival probability of Male; B2: p=0.010 Survival probability of Female; C1: p=0.024 Survival probability of M0; C2: p=0.090 Survival probability of M1; C3: p=0.029 Survival probability of N0; C4: p=0.005 Survival probability of N1-3; C5: p=0.175 Survival probability of T1-2; C6: p=0.002 Survival probability of T3-4; D1: p=0.360 Survival probability of Stage I-II; D2: p=0.002 Survival probability of Stage III-IV)

cellular energy metabolism and the clinical treatment of THCA and can also help clinicians determine the prognosis of patients with THCA and develop personalised treatment plans.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Jiangsu Vocational College of Medicine.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated during the current study are available in the TCGA database (https:// portal.gdc.cancer.gov/repository).

COMPETING INTERESTS

All of the authors had no personal, financial, commercial, or academic conflicts of interest separately.

FUNDING

Significance of lipid metabolism related genes in prognostic evaluation of patients with thyroid cancer. Grant ID: 20214108

AUTHORS' CONTRIBUTIONS

Zhixing Wang conceived of the study, and Zhixing Wang and Fan Wang participated in its design and data analysis and statistics and Fan Wang helped to draft the manuscript. All authors read and approved the final manuscript

ACKNOWLEDGMENTS

Not applicable.

REFERENCES

1 Albi E, Cataldi S, Lazzarini A, Codini M, Beccari T, Ambesi-Impiombato FS, et al (2017). Radiation and Thyroid Cancer. Int J Mol Sci. **18**(5): 911.
2 Ancker OV, Krüger M, Wehland M, Infanger M, Grimm D (2019). Multikinase Inhibitor Treatment in Thyroid Cancer. Int J Mol Sci. **21**(1): 10.
3 Biagini GLK, Ribas C, Higashi HD, Hirata VY, Zella MAK, Bartolomei I, et al. (2022). Wnt3a but not CDX-2 expression is associated with differentiated thyroid cancer. Rev Assoc Med Bras. **68**(3): 400–404.
4 Bugter JM, Fenderico N, Maurice MM (2021). Mutations and mechanisms of WNT pathway tumor suppressors in cancer. Nat Rev Cancer. **21**(1): 5–21.
5 Cao Y (2019). Adipocyte and lipid metabolism in cancer drug resistance. J Clin Invest. **129**(8): 3006–3017.
6 Chernaya G, Mikhno N, Khabalova T, Svyatchenko S, Mostovich L, Shevchenko S, et al. (2018). The expression profile of integrin receptors and osteopontin in thyroid malignancies varies depending on the tumor progression rate and presence of BRAF V600E mutation. Surgical Oncology. **27**(4): 702–708.
7 Coperchini F, Awwad O, Rotondi M, Santini F, Imbriani M, Chiovato L (2017). Thyroid disruption by perfluoro octane sulfonate (PFOS) and perfluorooctanoate (PFOA). J Endocrinol Invest. **40**(2): 105–121.
8 Das V, Kalyan G, Hazra S, Pal M (2018). Understanding the role of structural integrity and differential expression of integrin profiling to identify potential therapeutic targets in breast cancer. J Cell Physiol. **233**(1): 168–185.
9 Grant CS (2015). Recurrence of papillary thyroid cancer after optimized surgery. Gland Surg. **4**(1): 52–62.
10 Jelic MD, Mandic AD, Maricic SM, Srdjenovic BU (2021). Oxidative stress and its role in cancer. J Cancer Res Ther. **17**(1): 22–28.
11 Krishnamurthy N, Kurzrock R (2018). Targeting the Wnt/beta-catenin pathway in cancer: Update on effectors and inhibitors. Cancer Treat Rev. 2018; **62**: 50–60.
12 Lv J, Feng ZP, Chen FK, Liu C, Jia L, Liu PJ, et al. (2022). M2-like tumor-associated macrophages-secreted Wnt1 and Wnt3a promotes dedifferentiation and metastasis via activating beta-catenin pathway in thyroid cancer. Molecular Carcinogenesis. **60**(1): 25–37.
13 Merino Salvador M, Gómez de Cedrón M, Moreno Rubio J, Falagán Martínez S, Sánchez Martínez R, Casado E, et al (2017). Lipid metabolism and lung cancer. Crit Rev Oncol Hematol. **112**: 31–40.
14 Seguin L, Desgrosellier JS, Weis SM, Cheresh DA (2015). Integrins and cancer: regulators of cancer stemness, metastasis, and drug resistance. Trends Cell Biol. **25**(4): 234–40.
15 Vander Heiden MG, DeBerardinis RJ (2017). Understanding the Intersections between Metabolism and Cancer Biology. Cell. **168**(4): 657–669. (Original location 312–347)
16 Wen S, Luo Y, Wu W, Zhang T, Yang Y, Ji Q, et al. (2021). Identification of lipid metabolism-related genes as prognostic indicators in papillary thyroid cancer. Acta Biochim Biophys Sin (Shanghai). **53**(12): 1579–1589.
17 Wu D, Xu Y, Ding T, Zu Y, Yang C, Yu L (2017). Pairing of integrins with ECM proteins determines migrasome formation. Cell Res. **27**(11): 1397–1400.
18 Zhang X, Zhu G, Tang B, Huang H, Chen C, Zheng S, et al. (2021). A characterization and prognosis prediction model for primary squamous cell carcinoma of the thyroid. Gland Surg. **10**(4): 1325-1338.
19 Zhang Y, Wang X (2020). Targeting the Wnt/β-catenin signaling pathway in cancer. J Hematol Oncol. **13**(1): 165.
20 Zhao R, Tian L, Zhao B, Sun Y, Cao J, Chen K, et al (2020). FADS1 promotes the progression of laryngeal squamous cell carcinoma through activating AKT/mTOR signaling. Cell Death Dis. **11**(4): 272.
21 Zhong LK, Gan XX, Deng XY, Shen F, Feng JH, Cai WS, et al. (2020). Potential five-mRNA signature model for the prediction of prognosis in patients with papillary thyroid carcinoma. Oncology Letters. **20**(3): 2302–2310.
22 Wang ZX, Wang F (2022). Identification of Ten-Gene Related to Lipid Metabolism for Predicting Overall Survival of Breast Invasive Carcinoma. Contrast Media Mol Imaging. **2022**(11): 8348780.