# Circulating PCSK9: A new frontier in cancer risk stratification for obese diabetics

LIEN-CHENG TSAO[1,2*], CHEN-LING KUO[3*], YU-SHAN CHENG[3], CHING-SHAN HUANG[3], CHIN-SAN LIU[4-6] and SHIH-LI SU[3,7]

[1]Department of Surgery, Changhua Christian Hospital, Changhua 50006, Taiwan, R.O.C.; [2]Department of General Surgery, Taichung Municipal Geriatric Rehabilitation General Hospital, Taichung 406004, Taiwan, R.O.C.; [3]Vascular Medicine and Diabetes Research Center, Institute of ATP, Changhua Christian Hospital, Changhua 50006, Taiwan, R.O.C.; [4]Center of Regenerative Medicine and Tissue Repair, Institute of ATP, Changhua Christian Hospital, Changhua 50006, Taiwan, R.O.C.; [5]Department of Neurology, Vascular and Genomic Center, Institute of ATP, Changhua Christian Hospital, Changhua 50006, Taiwan, R.O.C.; [6]Graduate Institute of Integrative Chinese and Western Medicine, China Medical University, Taichung 40402, Taiwan, R.O.C.; [7]Division of Endocrinology and Metabolism, Department of Internal Medicine, Diabetes Education Center, Changhua Christian Hospital, Changhua 50006, Taiwan, R.O.C.

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**Abstract.** This study investigated potential plasma biomarkers associated with cancer risk and mortality in patients with type 2 diabetes mellitus (T2DM), a population known to have an increased cancer incidence and poorer outcomes compared with non-diabetic individuals. Traditional metabolic indicators, including blood pressure, blood glucose and blood lipids, have limited predictive value for cancer risk, highlighting the need for novel clinical biomarkers. In total, 141 subjects with T2DM were enrolled in this study. Plasma inflammatory and lipid-related biomarkers included cluster of differentiation 147 (CD147), cyclophilin A (CyPA), cytokines, oxidized low-density lipoprotein (oxi-LDL), oxi-LDL antibody and proprotein convertase subtilisin/kexin type 9 (PCSK9). Among all participants, 37.6% were obese (body mass index ≥27 kg/m$^2$). During 10 years of follow-up, all-cause mortality reached 35% and cancer incidence was 16%. Obese diabetic patients exhibit elevated oxi-LDL, soluble intercellular adhesion molecule-1, PCSK9, CD147 and CyPA levels. Deceased patients had a higher incidence of cancer and significantly lower plasma CD147 levels than surviving patients. Receiver operating characteristic curve analysis identified PCSK9 as a potential predictor of cancer occurrence in obese individuals with T2DM [area under the curve (AUC)=0.726], whereas CD147 showed modest predictive value in non-obese patients with diabetes (AUC=0.665). These findings suggest that plasma PCSK9 and CD147 may be associated with cancer occurrence in specific subgroups of patients with T2DM. However, larger prospective studies are required to confirm these associations and to further evaluate their potential value in cancer risk assessment.

*Correspondence to:* Dr Shih-Li Su, Division of Endocrinology and Metabolism, Department of Internal Medicine, Diabetes Education Center, Changhua Christian Hospital, 135 Nanhsiao Street, Changhua 50006, Taiwan, R.O.C.
E-mail: 89933@cch.org.tw

Professor Chin-San Liu, Department of Neurology, Vascular and Genomic Center, Institute of ATP, Changhua Christian Hospital, 135 Nanhsiao Street, Changhua 50006, Taiwan, R.O.C.
E-mail: liu48111@gmail.com

*Contributed equally

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## Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease accompanied by a broad spectrum of comorbidities that collectively contribute to reduced life expectancy. Epidemiological data from the Danish National Diabetes Registry show that the incidence of cancer in diabetic patients aged 40-70 years increases by 7.2-10.6% annually (1). Furthermore, diabetic patients with cancer experience higher mortality rates than their non-diabetic counterparts (2), and T2DM is considered an independent risk factor associated with increased mortality of colorectal cancer (3). Nationwide registry studies have demonstrated that patients with diabetes have significantly increased cardiovascular disease (CVD)-related risks of mortality and death than controls, underscoring the broad systemic consequences of diabetes (2,4).

Traditional CVD risk factors, including high blood pressure, obesity, diabetes and high lipid profiles, are indispensable for cardiovascular risk prediction but may be insufficient to capture the full spectrum of disease risk (5). However, despite the availability of markers for tumor detection, no reliable surrogate biomarker currently exists to predict cancer risk or cancer-related mortality in patients with diabetes. Therefore, it is essential to find practical and clinically measurable

biomarkers that can predict cancer-related outcomes in addition to biochemical controls.

Accumulating evidence suggests that several novel circulating biomarkers that may be linked to the pathophysiology of diabetes, CVD and cancer. Proprotein convertase subtilisin/kexin type 9 (PCSK9) influences cholesterol homeostasis and cardiovascular risk through regulation of low-density lipoprotein (LDL) receptor degradation. Emerging evidence implicates PCSK9 in cancer progression and metastasis through the modulation of apoptosis and tumor cell survival. Cluster of differentiation 147 (CD147), an immunoglobulin superfamily glycoprotein also known as extracellular matrix metalloproteinase inducer, facilitates nutrient transport, inflammatory cell recruitment and matrix metalloproteinase activation, thereby promoting tumor invasion and metastasis. Oxidized LDL antibodies (oxi-LDL-Abs) serve as indicators of oxidative stress and immune activation, whereas cyclophilin A (CyPA), an intracellular chaperone, contributes to inflammation, endothelial dysfunction, malignant transformation and cellular senescence (6). Chronic low-grade inflammation is a hallmark of diabetes and has been implicated in both cardiovascular and cancer development. Previous studies have suggested potential associations between inflammatory or lipid-related biomarkers and metabolic or oncogenic processes (6,7); however, most available evidence is derived from short-term or cross-sectional studies. Consequently, the long-term relationships between these circulating biomarkers and cancer occurrence or mortality in patients with diabetes remain incompletely understood. Therefore, the present study aimed to investigate whether circulating biomarkers, including CD147, CyPA, oxi-LDL, oxi-LDL-Abs and PCSK9, are associated with cancer occurrence and mortality during long-term follow-up in patients with T2DM.

## Materials and methods

*Participants*. A total of 141 participants with T2DM were recruited at the Changhua Christian Hospital (CCH; Changhua, Taiwan) from March 2010 to February 2011. Baseline clinical data and plasma samples were collected at enrollment, and cancer occurrence and vital status were subsequently ascertained over a ~10-year follow-up period, through to February 2022. Patients with a confirmed diagnosis of diabetes who had received treatment for at least 12 months were included. Participants with a history of infectious diseases, liver disease, cancer or autoimmune diseases were excluded from the study. According to the standards of the Taiwan Health Promotion Administration, a body mass index (BMI) ≥27 kg/m$^2$ was used to define obesity (8). Cancer diagnoses and vital status were verified through a review of medical records, International Classification of Diseases codes and information available through Taiwan's National Health Insurance system. During the 10-year follow-up period, cancer occurred in 23 of the 141 patients with T2DM (16.3%). The identified cancer types included gastrointestinal cancer (n=9), breast cancer (n=3), cervical cancer (n=3), oral cancer (n=3), lung cancer (n=2), prostate cancer (n=2) and thyroid cancer (n=1). Baseline demographic characteristics, family history and medical histories were collected using standardized questionnaires. The cohort study was approved by the Institutional Review Board (IRB) of the CCH conducted under two ethics approvals: i) IRB ID: 071228 (March 2010 to March 2011), and ii) IRB ID: 161220 (February 2017 to February 2022). Blood samples were collected in the morning after an 8-h fast, and plasma was promptly separated by centrifugation, aliquoted and stored at -80˚C until analysis.

*Biochemical measurements*. Serum lipid profiles were determined using an automated enzymatic colorimetric method on a DxC 800 analyzer from Beckman Coulter, Inc., plasma oxi-LDL-Abs using an ELISA kit (cat. no. BI-20032; Biomedica Medizinprodukte GmbH), plasma oxi-LDL using an ELISA kit (cat. no. 10-1143-01; Mercodia AB) and plasma PCSK9 concentrations using an ELISA kit (cat. no. CY-8079, Medical & Biological Laboratories Co., Ltd.). Plasma inflammatory biomarkers, including high-sensitivity C-reactive protein (cat. no. DCRP00B, hs-CRP) and plasma cytokine and adhesion molecules, were measured using ELISA kits (DY202 for IL-2, DY204 for IL-4 and DY206 for IL-6) from R&D Systems, Inc., while plasma CyPA (cat. no. USEA979Hu) and CD147 (cat. no. USEB540Hu) were quantified using ELISA kits from Wuhan USCN Business Co., Ltd., in accordance with the manufacturer's instructions.

*Statistical analysis*. Statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp.). Continuous variables are presented as the mean ± standard deviation and categorical variables are expressed as frequencies and percentages. Comparisons of continuous baseline characteristics and inflammatory biomarkers between groups were performed using an unpaired independent-samples Student's t-test, whereas categorical variables, including mortality and cancer incidence, were compared using the $\chi^2$ test. A two-sided $P<0.05$ was considered to indicate statistical significance.

After 10 years of follow-up, Cox proportional hazards regression analyses were performed to estimate adjusted hazard ratios (aHRs) and corresponding 95% confidence intervals (CIs) for the association between plasma biomarkers and cancer incidence. Plasma CD147 concentrations were dichotomized according to the median plasma concentration of the study population (3,196 pg/ml) and categorized as low (<3,196 pg/ml) or high (≥3,196 pg/ml). Plasma PCSK9 concentrations were categorized into tertiles based on their distribution within the study population (<170.5, 170.5-238 and ≥239 ng/ml). BMI was categorized according to the obesity criteria of the Taiwan Health Promotion Administration (<27 and ≥27 kg/m$^2$) (9).

Two multivariate Cox regression models were constructed. Model 1 was adjusted for age, sex and BMI, whereas Model 2 was adjusted for BMI alone. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminatory ability of plasma biomarkers for predicting 10-year cancer incidence. Areas under the ROC curves (AUCs) and corresponding 95% CIs were calculated.

## Results

*Baseline characteristics and long-term clinical outcomes*. In this cohort, a total of 141 participants with T2DM were enrolled and followed up for up to 10 years. Participants had a mean

Table I. Basic demographic data of diabetes patients.

| Group of patients | Diabetes (n=141) |
|---|---|
| Basic characteristics | |
| Age, years | 70±9 |
| Male sex | 58 (41) |
| BMI, kg/m$^2$ | 26±4 |
| BMI ≥27 | 53 (37.6) |
| Mortality after 10 years | 49 (34.8) |
| Morbidity of cancer after 10 years | 23 (16.3) |
| Smoking index | 19±11 |
| Inflammatory factors (reference ranges) | |
| IL-2, pg/ml | 25.03±13.90 |
| IL-4, pg/ml | 0.17±0.85 |
| IL-6, pg/ml | 12.49±11.46 |
| Hs-CRP, mg/dl (<1.0) | 0.06±0.05 |
| Lipid profile | |
| LDL-cholesterol, mg/dl (<130) | 101±22 |
| Total cholesterol, mg/dl (<200) | 174±29 |
| HDL-cholesterol, mg/dl (>40) | 50±13 |
| Triglyceride, mg/dl (<150) | 136±122 |

Values are expressed as the mean ± standard deviation for continuous variables and n (%) for categorical variables. Reference ranges are provided where available for routine laboratory parameters. For non-routine biochemical analyses and exploratory inflammatory biomarkers, universally established clinical reference ranges are not available. BMI, body mass index; smoking index, pack per day x years; Hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IL, interleukin.

age of 70±9 years and 41% were male (n=58). Participants had a mean BMI of 26±4 kg/m$^2$ and 37.6% met the criteria for obesity (BMI ≥27 kg/m$^2$). Over the 10-year follow-up period, 34.8% of the patients (n=49) died and 16.3% (n=23) developed cancer (Table I).

*Clinical and biomarker characteristics according to obesity status*. Among the 141 participants with T2DM, 52 were classified as obese and 89 as non-obese. Patients in the obese group had a significantly higher use of antihypertensive medications compared with those in the non-obese group (70 vs. 30%, P<0.001), suggesting a higher prevalence of hypertension among obese participants. In addition, obese participants exhibited significantly elevated serum insulin levels relative to non-obese participants (52.46±48.53 vs. 30.46±38.77 $\mu$g/l, P=0.007). Drug use, lipid profiles and 10-year cancer-related morbidity rates did not differ significantly between obese and non-obese groups (Table II).

Compared with non-obese patients with diabetes, those with both obesity and diabetes exhibited significantly higher plasma levels of oxi-LDL (P=0.004), PCSK9 (P=0.013), soluble intercellular adhesion molecule-1 (sICAM-1) (P=0.028), CyPA (P=0.012) and CD147 (P=0.006) (Table II).

These findings indicate that obesity in diabetic patients is associated with elevated oxidative stress and endothelial activation markers, accompanied by a reduced antibody response to oxidized lipoproteins, suggesting a state of intensified vascular inflammation and metabolic dysregulation.

*Association between plasma biomarkers and cancer occurrence*. Over a 10-year follow-up, multivariate Cox proportional hazards analysis identified plasma CD147 as an independent predictor of cancer-related morbidity in patients with T2DM. In Model 1, elevated CD147 levels were associated with a 4.45-fold increased cancer risk (aHR=4.45, P=0.021). By contrast, PCSK9, BMI, sex and age were not statistically significant predictors in the model. For validation, Model 2, which adjusted for BMI alone, also demonstrated that plasma CD147 remained a robust and significant predictor of cancer risk (aHR=10.00, P=0.026) (Table III). These results consistently highlight plasma CD147 as a strong independent biomarker associated with long-term cancer occurrence in patients with diabetes, independent of adiposity and conventional metabolic risk factors.

*Clinical and biomarker characteristics according to survival status*. Of the patients with T2DM, the incidence of cancer was significantly higher among those who died than among survivors, irrespective of obesity status (obese: 44.7 vs. 14.3%, P=0.018; non-obese: 29.7 vs. 3.8%, P=0.001). However, in both the obese and non-obese diabetic groups, patients who died exhibited significantly higher plasma CD147 levels than survivors (obese: P=0.008; non-obese: P=0.006). Among obese patients with T2DM, deceased individuals had significantly lower high-density lipoprotein (HDL) cholesterol levels compared with survivors (P=0.008) and exhibited a trend toward lower plasma CyPA concentrations (P=0.060). In addition, patients who died had significantly higher plasma levels of soluble vascular adhesion molecule-1 (sVCAM-1) than surviving patients in the non-obese group (P=0.022). In the obese group, sVCAM-1 levels were numerically higher among patients who died than among survivors; however, this difference did not reach statistical significance (P=0.092; Table IV). Collectively, these findings indicate that elevated plasma CD147 and sVCAM-1 levels are associated with increased mortality risk in patients with diabetes, whereas reduced HDL cholesterol may further contribute to adverse outcomes among those with obesity.

*Obesity-stratified biomarker profiles and ROC analyses for cancer occurrence*. In the non-obese diabetic group, patients diagnosed with cancer exhibited significantly elevated plasma CD147 concentrations compared with those without cancer (P=0.034). A similar trend was observed in the obese diabetic group, although the difference was not statistically significant (Table V). ROC curve analysis demonstrated that plasma CD147 had a moderate predictive value for cancer in the non-obese diabetic group, with an AUC of 0.665 (95% CI, 0.534-0.795; P=0.036) (Fig. 1A). The optimal cutoff value determined by the maximum Youden index was 3,162.3 pg/ml, corresponding to a sensitivity of 68.8% and a specificity of 62.2%. Among patients with obesity, diabetes and cancer, plasma PCSK9 levels were significantly higher than those in obese diabetic patients

Table II. Characteristics of patients with diabetes (with and without obesity).

| Item | BMI<27 (n=89) | BMI≥27 (n=52) | P-value |
|---|---|---|---|
| Basic characteristics | | | |
| Age, years | 71±9 | 69±9 | 0.257 |
| Male sex | 40 (45) | 18 (35) | 0.108 |
| Disease duration, years | 13±9 | 15±7 | 0.190 |
| Mortality after 10 years | 36 (41) | 14 (27) | 0.630 |
| Morbidity of cancer after 10 years | 13 (14.6) | 10 (19.2) | 0.360 |
| Statin usage[a] | 38 (43) | 23 (45) | 0.143 |
| Anti-hypertensives[a] | 27 (30) | 36 (70) | 0.001 |
| Metabolic factors (reference ranges) | | | |
| Insulin, $\mu$U/ml (2.0-20.0) | 30.46±38.77 | 52.46±48.53 | 0.007 |
| HbA1c, % (<5.7) | 7.84±2.31 | 7.78±1.55 | 0.850 |
| Total cholesterol, mg/dl (<200) | 171±30 | 177±27 | 0.270 |
| Triglyceride, mg/dl (<150) | 121±91 | 160±160 | 0.067 |
| LDL-cholesterol, mg/dl (<130) | 99±23 | 104±22 | 0.236 |
| HDL-cholesterol, mg/dl (>40) | 52±14 | 48±11 | 0.070 |
| Inflammatory and biomolecular factors | | | |
| IL-2, pg/ml | 24.83±13.78 | 25.02±14.21 | 0.941 |
| IL-4, pg/ml | 0.16±0.88 | 0.18±0.82 | 0.880 |
| IL-6, pg/ml | 12.53±12.16 | 11.39±7.24 | 0.541 |
| Oxidized-LDL antibody, U/l | 540±349 | 306±165 | 0.002 |
| Oxi-LDL, mg/dl | 55.82±22.37 | 67.02±20.87 | 0.004 |
| sICAM-1, mg/dl | 298±93.4 | 339±11 | 0.028 |
| sVCAM-1, mg/dl | 1111±410 | 1145±320 | 0.602 |
| sE-selectin, mg/dl | 41.48±19.05 | 44.06±21.19 | 0.466 |
| PCSK9, $\mu$g/l | 212±76.93 | 250±94.69 | 0.013 |
| Plasma CyPA, ng/ml | 83.33±34.12 | 96.10±35.02 | 0.012 |
| Plasma CD147, pg/ml | 3283±1204 | 3778±986.6 | 0.006 |

Values are expressed as the mean ± standard deviation or n (%). Student's t-test was performed for statistical comparisons. [a]McNemar's test was used for this paired categorical comparison. sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; IL-2, interleukin 2; PCSK9, type 9 proprotein convertase subtilisin/kexin type 9; CyPA, cyclophilin A; CD147, differentiation 147; oxi-LDL, oxidised low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, glycated hemoglobin A1c.

without cancer (P=0.029; Table V). The AUC for PCSK9 in predicting cancer among obese diabetic patients was 0.726 (95% CI, 0.543-0.910; P=0.035) (Fig. 1B), which was superior to that of CD147 and CyPA. The optimal cutoff value for plasma PCSK9 was 193.1 ng/ml, yielding a sensitivity of 100.0% and a specificity of 36.6%. These results indicate that elevated plasma CD147 is associated with cancer risk in non-obese diabetic patients, whereas PCSK9 serves as a stronger predictor of cancer in obese patients, suggesting distinct biomarker profiles across different metabolic phenotypes of diabetes.

## Discussion

In the present study, the predictive value of circulating CD147 and PCSK9 levels for cancer risk among obese and non-obese patients with T2DM was investigated. The results indicated that higher PCSK9 concentrations were associated with increased cancer risk in obese patients with diabetes. Elevated CD147 levels are associated with cancer in non-obese diabetic patients (2). Further multivariate Cox analysis indicated that plasma CD147 was independently associated with an increased risk of cancer (P=0.021). This highlights the robustness of CD147 as a potential biomarker, beyond conventional demographic and metabolic risk factors. After 10 years of follow-up, in patients with T2DM, high CD147 levels were significantly associated with cancer (P=0.026). Importantly, although this association was statistically significant in Model 2 (aHR=9.998; 95% CI=1.324-75.498), the wide confidence interval indicates uncertainty in the effect size, and it therefore warrants cautious interpretation. Taken together, these results suggest that diabetes and obesity play important roles in cancer development and mortality. Furthermore, the present data indicate that distinct circulating biomarkers may be useful for risk stratification: Plasma PCSK9 with obesity and diabetes and plasma CD147 in obese and non-diabetic patients. Nevertheless, residual confounding factors cannot be fully excluded, emphasizing the need for larger, age-matched, multicenter studies to validate these observations.

Table III. Multivariate Cox regression analysis of plasma CD147 and PCSK9 in predicting cancer morbidity after 10 years.

A, Model 1 (adjusted for age, gender, BMI)

| Variable | [a]HR | 95% CI | P-value |
|---|---|---|---|
| Plasma CD147 (high vs. low)[a] | 4.45 | 1.26-15.76 | 0.021 |
| Plasma PCSK9 (tertile)[b] | 0.70 | 0.21-2.29 | 0.552 |
| BMI (≥27 vs. <27 kg/m$^2$) | 0.75 | 0.30-1.85 | 0.530 |
| Sex (male vs. female) | 1.21 | 0.51-2.87 | 0.664 |
| Age | 1.00 | 0.97-1.04 | 0.975 |

B, Model 2 (Adjusted for BMI only)

| Variable | [a]HR | 95% CI | P-value |
|---|---|---|---|
| Plasma CD147 (high vs. low)[a] | 10.00 | 1.32-75.50 | 0.026 |
| Plasma PCSK9 (tertile)[b] | 0.83 | 0.47-1.45 | 0.511 |

[a]Plasma CD147 was dichotomized according to the median plasma CD147 concentration (<3,196 vs. ≥3,196 pg/ml). [b]Plasma PCSK9 was categorized into tertiles (<170.5, 170.5-238 and ≥239 ng/ml). BMI was categorized as <27 and ≥27 kg/m$^2$ according to the obesity criteria of the Taiwan Health Promotion Administration. aHR, adjusted hazard ratio; BMI, body mass index; CD147, cluster of differentiation 147; PCSK9, proprotein convertase subtilisin/kexin type 9; CI, confidence interval.

Table IV. Subgroup analysis of patients with diabetes (with or without obesity) according to survival status.

| | BMI <27 kg/m$^2$ (n=89) | | | BMI ≥27 kg/m$^2$ (n=52) | | |
|---|---|---|---|---|---|---|
| Group of patients | Alive (n=52) | Deceased (n=37) | P-value | Alive (n=14) | Deceased (n=38) | P-value |
| Age, years | 69±8 | 74±7 | 0.006 | 69±7 | 67±14 | 0.332 |
| Male sex | 23 (44) | 18 (49) | 0.679 | 4 (29) | 16 (42) | 0.490 |
| Morbidity of cancer after 10 years | 2 (3.8) | 11 (29.7) | 0.001 | 2 (14.3) | 17 (44.7) | 0.018 |
| Total cholesterol, mg/dl | 173±31 | 169±31 | 0.535 | 180±29 | 169±21 | 0.229 |
| Triglyceride, mg/dl | 127±107 | 117±73 | 0.636 | 172±191 | 143±36 | 0.601 |
| LDL-cholesterol, mg/dl | 99±19 | 100±27 | 0.757 | 103±23 | 105±17 | 0.791 |
| HDL-cholesterol, mg/dl | 54±15 | 48±13 | 0.086 | 50±11 | 40±10 | 0.008 |
| sICAM-1, mg/dl | 289±85.77 | 312.0±105.4 | 0.292 | 332±85 | 371±192 | 0.528 |
| sVCAM-1, mg/dl | 1030±329 | 1193±432 | 0.022 | 1110±252 | 1301±493 | 0.092 |
| sE-selectin, mg/dl | 41.74±21.50 | 40.15±14.19 | 0.715 | 47.23±22.59 | 38.78±17.52 | 0.262 |
| PCSK9, $\mu$g/l | 215.1±76.48 | 212.6±80.67 | 0.887 | 253.7±102.0 | 251.6±74.88 | 0.943 |
| Plasma CyPA, ng/ml | 87.56±30.43 | 100.1±47.75 | 0.503 | 100.9±28.42 | 89.15±48.82 | 0.060 |
| Plasma CD147, pg/ml | 3372±946 | 3810±872 | 0.006 | 3569±811 | 4406±1159 | 0.008 |
| Oxi-LDL antibody, U/l | 782.9±828.8 | 611.1±572.3 | 0.495 | 401.4±285.4 | 249.3±90.66 | 0.227 |
| Oxi-LDL, mg/dl | 56.41±23.64 | 54.79±21.85 | 0.991 | 68.33±22.80 | 70.10±14.98 | 0.568 |

Student's t-test was performed for statistical comparisons. McNemar's test was used for this paired categorical comparison. sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; PCSK9, type 9 proprotein convertase subtilisin/kexin type 9; CyPA, cyclophilin A; CD147, cluster of differentiation 147; oxi-LDL, oxidised low-density lipoprotein; HDL, high-density lipoprotein.

Patients with diabetes have been reported to exhibit a 10-20% higher incidence of cancer compared with individuals without diabetes (1). Furthermore, diabetes is recognized as an independent risk factor for mortality from several malignancies, including colorectal, pancreatic, breast, liver and bladder cancers, regardless of BMI status (9,10). Cancer often suppresses antitumor immunity through metabolic and signaling reprogramming. CD147 can promote immune

Table V. Subgroup analysis of patients with diabetes (with or without obesity) according to cancer morbidity.

| | BMI <27 kg/m$^2$ (n=89) | | | BMI ≥27 kg/m$^2$ (n=52) | | |
|---|---|---|---|---|---|---|
| Group of patients | Non-cancer (n=76) | Cancer (n=13) | P-value | Non-cancer (n=42) | Cancer (n=10) | P-value |
| Oxi-LDL antibody, U/l | 782.9±828.8 | 611.1±572.3 | 0.495 | 401.4±285.4 | 249.3±90.66 | 0.227 |
| Oxi-LDL, mg/dl | 56.41±23.64 | 54.79±21.85 | 0.991 | 68.33±22.80 | 70.10±14.98 | 0.568 |
| sICAM-1, mg/dl | 273.5±84.09 | 319.4±107.2 | 0.069 | 329.0±118.6 | 300.1±74.46 | 0.527 |
| PCSK9, $\mu$g/l | 202.1±69.55 | 198.5±65.21 | 0.850 | 226.3±64.89 | 288.5±79.13 | 0.029 |
| Plasma CyPA, ng/ml | 82.63±33.41 | 88.04±44.29 | 0.993 | 93.67±29.27 | 102.4±53.32 | 0.993 |
| Plasma CD147, pg/ml | 3252±1257 | 3604±912.9 | 0.034 | 3653±962.9 | 4258±1002 | 0.096 |

sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; PCSK9, type 9 proprotein convertase subtilisin/kexin type 9; CyPA, cyclophilin A; CD147, cluster of differentiation 147; oxi-LDL, oxidised low-density lipoprotein.

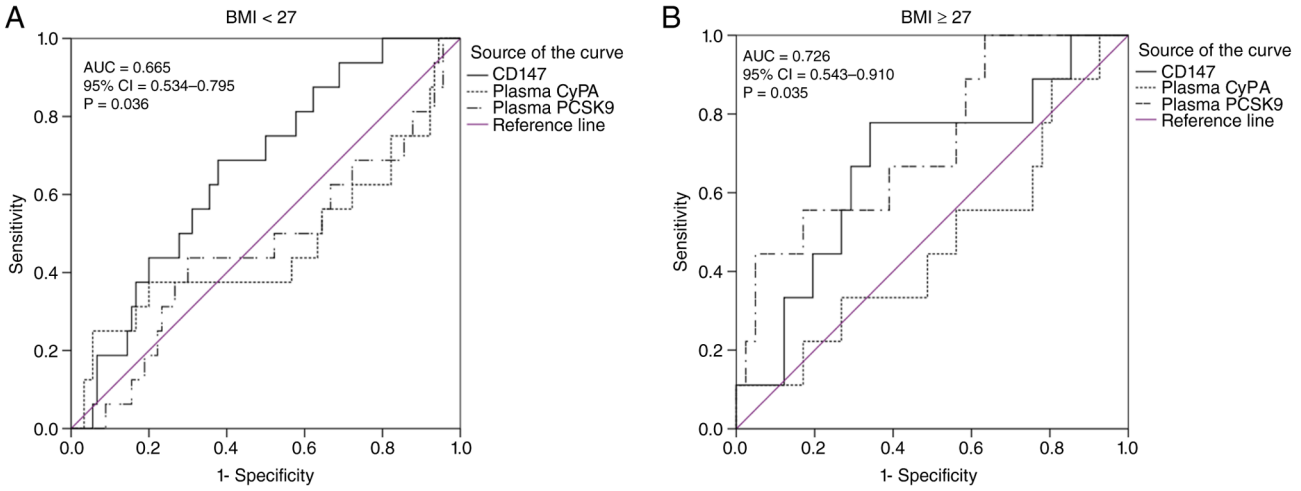


Figure 1. ROC curve analysis of plasma biomarkers for predicting 10-year cancer incidence in patients with type 2 diabetes stratified by BMI. (A) In patients with BMI <27 kg/m$^2$, plasma CD147 demonstrated significant discriminatory performance (AUC=0.665; 95% CI, 0.534-0.795; P=0.036), with an optimal cutoff value of 3,162.3 pg/ml (sensitivity, 68.8%; specificity, 62.2%). CyPA and PCSK9 showed no significant discriminatory ability. (B) In patients with BMI ≥27 kg/m$^2$, plasma PCSK9 demonstrated the highest discriminatory performance (AUC=0.726; 95% CI, 0.543-0.910; P=0.035), with an optimal cutoff value of 193.1 ng/ml (sensitivity, 100.0%; specificity, 36.6%). CD147 and CyPA showed no significant discriminatory ability. BMI, body mass index; ROC, receiver operating characteristic; AUC, area under the ROC curve; PCSK9, type 9 proprotein convertase subtilisin/kexin type 9; CyPA, cyclophilin A.

escape through multiple mechanisms. As a molecular chaperone of monocarboxylate transporter 1 (MCT1) and MCT4, the CD147-MCT complex is crucial for tumor lactate transport and glycolytic conversion, which consumes glucose, acidifies the tumor microenvironment and impairs T-cell function. Elevated lactate levels further promote tumor-infiltrating lymphocyte dysfunction and broad immunosuppression (7,10). In addition, metabolic stress in fatty liver disease and fibrosis is associated with increased glucose transporter expression; notably, solute carrier family 2 member 1 (SLC2A1/GLUT1) is upregulated in advanced NAFLD-related hepatocellular carcinoma with steatosis and fibrosis (11,12). CD147 also forms a complex with CD98hc (SLC3A2), activating the PI3K/Akt pathway, which drives tumor cell proliferation and is associated with adverse prognosis in multiple cancers (13). Collectively, these pathways may provide biological context for the observed association between circulating CD147 levels and cancer occurrence in patients with diabetes, particularly in metabolically dysregulated conditions, such as diabetes.

Barone *et al* (14), in an analysis of 23 studies, estimated that diabetes confers a 41% higher risk of mortality relative to non-diabetic populations (HR=1.41; 95% CI, 1.28-1.55), which is higher than that of individuals without diabetes. Obesity has also been associated with an increased risk of all-cause cancer mortality (HR=1.23, 95% CI, 1.01-1.50) (14,15). Consistent with prior reports, higher rates of cancer, all-cause mortality and obesity were observed in patients with diabetes in the present study. Both diabetes and obesity appear to contribute to increased risks of cancer and mortality. Notably, although obesity and cancer were more prevalent in the diabetic population than in non-diabetic individuals, cancer incidence among patients with diabetes did not differ significantly according to obesity status.

IL-2, IL-6 and hs-CRP are key players in the immune response and inflammation and have been linked to apoptosis and oxidative stress mechanisms. Although IL2, IL6 and hs-CRP are commonly used indicators of chronic inflammation in clinical practice, their differences cannot be observed

when diabetes itself is already in a state of chronic and persistent inflammation (6,16).

PCSK9 is a circulating protein that plays a central role in the regulation of LDL metabolism (15,17). Although statin therapy is known to increase PCSK9 levels, significantly higher PCSK9 concentrations were observed in obese patients with diabetes in the present study, despite comparable statin use rates and LDL cholesterol levels. However, the association between obesity and circulating PCSK9 levels remains inconclusive (17). Higher circulating PCSK9 levels have been observed in obese individuals compared with those of normal weight or overweight (18,19). However, other studies have reported an inverse association between waist circumference and PCSK9 levels in women (20). While Chan *et al* (21) identified a positive correlation between PCSK9 and adiposity indices, other investigators observed no association between PCSK9 and body composition parameters (14). In the present study, obese patients with diabetes exhibited elevated plasma PCSK9 concentrations compared with their non-obese counterparts, with a significant positive correlation between PCSK9 levels and obesity (rho=0.245, P=0.001; data not shown).

Previous studies have reported associations between PCSK9 levels and myocardial infarction as well as CVD (15,17,18). However, a meta-analysis found no significant association between plasma PCSK9 concentrations and CVD risk (17). Although PCSK9 inhibitors have been shown to improve cardiovascular outcomes and reduce all-cause mortality rates, circulating PCSK9 concentrations may not independently predict mortality (21). Although Schlegel *et al* (22) observed an inverse association between PCSK9 levels and mortality in end-stage liver disease, no significant difference in circulating PCSK9 concentrations between deceased and surviving diabetic patients was detected in the present study, regardless of BMI status.

In addition to its established role in cholesterol homeostasis, PCSK9 has recently been implicated in cancer biology. It promotes immune evasion by facilitating the degradation of major histocompatibility complex class I molecules on tumor cells, thereby limiting its recognition by cytotoxic T lymphocytes (23,24). Experimental studies have demonstrated that PCSK9 inhibition enhances antitumor immunity and improves response to immune checkpoint blockade (17,18,23). In addition, PCSK9-mediated dysregulation of cholesterol metabolism may contribute to tumor growth and metastasis. These previously reported mechanisms may partially explain the observed association between higher plasma PCSK9 levels and cancer occurrence in obese patients with diabetes. However, among patients with non-obese diabetes, where metabolic stressors such as CD147 predominate, PCSK9's contribution to the risk of cancer appears less pronounced.

Higher circulating CD147 levels have been observed in the context of obesity. Wilson *et al* (25) described a positive association between BMI and CD147 levels in an animal model, and the findings of the present study similarly indicate a positive correlation between BMI and plasma CD147 levels (rho=0.157, P=0.012; data not shown).

In the present study, among patients with diabetes, those who died exhibited a higher prevalence of cancer and elevated plasma CD147 levels, regardless of BMI status. Previous studies have reported associations between elevated CD147 expression and adverse oncologic characteristics in several cancers (13,26,27).

CD147 has been investigated as a potential prognostic biomarker in upper gastrointestinal cancers (26). In the present study, higher CD147 levels were observed in diabetic patients with cancer, although only a marginal association was noted in the obese group. In the present study, ROC curve analysis suggested that plasma CD147 may have predictive utility for 10-year cancer risk in non-obese patients with T2DM, whereas plasma PCSK9 may serve as a predictive biomarker for 10-year cancer risk in obese patients with T2DM. The anti-CD147 antibody improves the effects of chemoradiation therapy in certain cancer treatments (28). Overexpression of CD147 has been associated with unfavorable clinical outcomes in cancer patients, suggesting possible relevance in tumor biology. Individuals with concomitant obesity and diabetes exhibited elevated circulating PCSK9 concentrations relative to non-diabetic individuals. In the present study, higher circulating PCSK9 levels were observed in patients with cancer, obesity and diabetes. Emerging evidence has suggested possible associations between PCSK9 and cancer-related outcomes in experimental and clinical studies and experimental studies have shown that PCSK9 inhibition can improve cancer-related outcomes and tumor behavior (29,30). Tumor-induced lipoprotein cholesterol has been reported to promote tumor growth through PCSK9 activation, which is associated with elevated LDL cholesterol levels (31). However, LDL cholesterol levels were not increased in patients with cancer in the present cohort, indicating that the association between PCSK9 and cancer prevalence may not be mediated by dyslipidemia. Instead, PCSK9 may influence cancer progression through alternative mechanisms, such as modulation of proprotein convertase substrates, including matrix metalloproteinases (32). Notably, PCSK9 demonstrated superior predictive performance for cancer risk among patients with obesity and diabetes compared with CD147 and CyPA. The apparent discrepancy between the Cox regression and ROC analyses likely reflects the different statistical objectives of these approaches. Multivariate Cox regression evaluates independent associations after adjustment for covariates, whereas ROC analysis assesses the discriminatory performance of biomarkers within specific subgroups. Therefore, although PCSK9 did not remain independently associated with cancer risk in the overall adjusted Cox model, it demonstrated relatively better discriminatory performance in obese patients with T2DM, suggesting potential subgroup-specific discriminatory performance that warrants further validation.

In the present study, plasma CyPA levels were associated with the BMI. Consistent with the current findings, Kumar *et al* (16) reported elevated CyPA concentrations in obese individuals, irrespective of diabetes status. Overexpression of CyPA has been linked to adverse clinical outcomes in several pathological conditions, including congestive heart failure, pancreatitis, brain injury and cancer (32-35). In the present cohort, lower plasma CyPA levels were observed among deceased patients with obesity and diabetes; however, this difference did not reach statistical significance. Furthermore, CyPA concentrations did not differ according to cancer status in these patients.

This study had several methodological limitations that warrant consideration. First, the sample size was determined by the available cohort during the study period rather than by a priori power calculations. Although the overall cohort was sufficient for exploratory analyses, the relatively small number of cancer events and subgroup stratification may have limited statistical precision and reduced the ability to detect modest associations. Furthermore, the limited number and heterogeneous distribution of cancer types prevented cancer site-specific analyses. Because the biological relevance of CD147 and PCSK9 may vary across different malignancies, the present findings should be interpreted cautiously and considered exploratory and hypothesis-generating. In addition, detailed oncologic information, including tumor stage, metastatic status, recurrence and treatment response, was not consistently available in this cohort. Second, missing baseline biomarker data were minimal (<5%) and were handled by listwise deletion. Although this approach was unlikely to have substantially influenced the main findings, a minor degree of bias cannot be excluded. Third, only 23 cancer events occurred among the 141 patients with type 2 diabetes during the 10-year follow-up period. Further stratification by obesity status reduced both the subgroup sample sizes and the number of events, resulting in wide confidence intervals and limited statistical precision. Although baseline smoking status, statin use and renal function were available for evaluation, detailed information on metformin and other glucose-lowering medications, including treatment duration, dosage and changes during follow-up, was not comprehensively available. In addition, the small numbers of cases across heterogeneous cancer types precluded reliable cancer site-specific analyses. Given the limited number of events, including all potentially relevant covariates in the multivariate Cox regression models, would have increased the risk of overfitting. Therefore, only a limited set of clinically relevant covariates was included. Residual confounding cannot be excluded and the phenotype-specific subgroup findings should be interpreted cautiously as exploratory and hypothesis-generating. Fourth, this was a single-center observational cohort study based on patients with available follow-up data; therefore, potential selection bias remains possible. In addition, the imbalance in baseline age distribution and the relative homogeneity of the study population may limit the generalizability of the present findings. Future large-scale, multicenter prospective studies incorporating larger and more diverse populations, together with detailed cancer-related clinical information, are needed to validate these findings and further clarify the clinical relevance of these biomarkers across different cancer types.

Despite these limitations, this study has several important strengths. To our knowledge, this is one of the first studies to simultaneously evaluate plasma CD147, CyPA and PCSK9 in relation to long-term cancer risk in patients with T2DM. With up to 10 years of follow-up, the present findings revealed phenotype-specific predictive associations, suggesting that CD147 may have greater predictive value in non-obese patients, whereas PCSK9 may have greater predictive value in obese patients with T2DM. These findings provide a foundation for future biomarker-based cancer risk stratification and precision medicine in patients with type 2 diabetes.

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**Availability of data and materials**

The data generated in the present study may be requested from the corresponding author.

**Authors' contributions**

LCT, CSL and SLS contributed to the conception and experimental design. CLK completed the data analysis. LCT and CLK drafted the manuscript. CSH and YSC performed data analysis and literature searches. LCT, CSL, CLK and SLS contributed to the drafting and revision of the manuscript. CSL and SLS checked and confirmed the authenticity of all the raw data. All authors have read and approved the final manuscript.

**Ethics approval and consent to participate**

This study was approved by the IRB of CCH (Changhua, Taiwan; approval nos. 071228 and 161220). All patients provided written informed consent to participate in this study.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**References**

1. Carstensen B, Jørgensen ME and Friis S: The epidemiology of diabetes and cancer. Curr Diab Rep 14: 535, 2014.
2. Li Y, Luo J, Bao K, Wei Q, Wang X, Chen J, Zhang T, Wang F and Zhu Y: Association of age at diagnosis of type 2 diabetes mellitus with the risks of the morbidity of cardiovascular disease, cancer and all-cause mortality: Evidence from a real-world study with a large population-based cohort study. Diabetes Res Clin Pract 217: 111870, 2024.
3. Lawler T, Hibler E, Walts ZL, Giurini L, Steinwandel M, Lipworth L, Murff HJ, Zheng W and Warren Andersen S: Associations of diabetes and mortality among colorectal cancer patients from the southern community cohort study. Br J Cancer 131: 1050-1059, 2024.
4. Rawshani A, Rawshani A and Gudbjörnsdottir S: Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med 377: 300-301, 2017.
5. Petersen SE, Sanghvi MM, Aung N, Cooper JA, Paiva JM, Zemrak F, Fung K, Lukaschuk E, Lee AM, Carapella V, *et al*: The impact of cardiovascular risk factors on cardiac structure and function: Insights from the UK Biobank imaging enhancement study. PLoS One 12: e0185114, 2017.
6. Nigro P, Pompilio G and Capogrossi MC: Cyclophilin A: A key player for human disease. Cell Death Dis 4: e888, 2013.

7. Kirk P, Wilson MC, Heddle C, Brown MH, Barclay AN and Halestrap AP: CD147 is tightly associated with lactate transporters MCT1 and MCT4 and facilitates their cell surface expression. EMBO J 19: 3896-3904, 2000.
8. Coughlin SS, Calle EE, Teras LR, Petrelli J and Thun MJ: Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol 159: 1160-1167, 2004.
9. Pan WH, Lee MS, Chuang SY, Lin YC and Fu ML: Obesity pandemic, correlated factors and guidelines to define, screen and manage obesity in Taiwan. Obes Rev 9 (Suppl 1): S22-S31, 2008.
10. Taghizadeh N, Boezen HM, Schouten JP, Schröder CP, Elisabeth de Vries EG and Vonk JM: BMI and lifetime changes in BMI and cancer mortality risk. PLoS One 10: e0125261, 2015.
11. Tu SH, Chen C, Hsieh YT, Chang HY, Yeh CJ, Lin YC and Pan WH: Design and sample characteristics of the 2005-2008 nutrition and health survey in Taiwan. Asia Pac J Clin Nutr 20: 225-237, 2011.
12. Amann T, Maegdefrau U, Hartmann A, Agaimy A, Marienhagen J, Weiss TS, Stoeltzing O, Warnecke C, Schölmerich J, Oefner PJ, *et al*: GLUT1 expression is increased in hepatocellular carcinoma and promotes tumorigenesis. Am J Pathol 174: 1544-1552, 2009.
13. Yang XM, Bian H and Chen ZN: CD147/Basigin: From integrative molecular hub to translational therapeutic target. Adv Sci (Weinh) 13: e18884, 2026.
14. Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, Wolff AC and Brancati FL: Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: A systematic review and meta-analysis. JAMA 300: 2754-2764, 2008.
15. Arsenault BJ, Pelletier-Beaumont E, Alméras N, Tremblay A, Poirier P, Bergeron J and Després JP: PCSK9 levels in abdominally obese men: association with cardiometabolic risk profile and effects of a one-year lifestyle modification program. Atherosclerosis 236: 321-326, 2014.
16. Kumar J, Badade ZG and Rai S: Study of cyclophilin-A, high sensitivity C-reactive protein, and malondialdehyde in obese and nonobese type 2 diabetes mellitus patients. MGM J Med Sci 5: 159-163, 2018.
17. Leander K, Mälarstig A, Van't Hooft FM, Hyde C, Hellénius ML, Troutt JS, Konrad RJ, Öhrvik J, Hamsten A and de Faire U: Circulating proprotein convertase subtilisin/Kexin type 9 (PCSK9) predicts future risk of cardiovascular events independently of established risk factors. Circulation 133: 1230-1239, 2016.
18. Xiao Y, Peng C, Huang W, Zhang J, Gao Y, Kim JH, Yeoh EK and Su X: Circulating proprotein convertase subtilisin/Kexin type 9 (PCSK9) concentration and risk of cardiovascular events-systematic review and meta-analysis of prospective studies. Circ J 81: 1150-1157, 2017.
19. Tóth Š, Fedačko J, Pekárová T, Hertelyová Z, Katz M, Mughees A, Kuzma J, Štefanič P, Kopolovets I and Pella D: Elevated circulating PCSK9 concentrations predict subclinical atherosclerotic changes in low risk obese and non-obese patients. Cardiol Ther 6: 281-289, 2017.
20. Hasan H, Attlee A, Raigangar V, Madkour M and Awadallah S: Proprotein convertase subtilisin/kexin type 9 (PCSK9) and metabolic syndrome components among young adult females. Diabetes Metab Syndr 11 (Suppl 1): S337-S341, 2017.
21. Chan DC, Pang J, McQuillan BM, Hung J, Beilby JP, Barrett PH and Watts GF: Plasma proprotein convertase subtilisin kexin type 9 as a predictor of carotid atherosclerosis in asymptomatic adults. Heart Lung Circ 25: 520-525, 2016.
22. Schlegel V, Treuner-Kaueroff T, Seehofer D, Berg T, Becker S, Ceglarek U, Thiery J and Kaiser T: Low PCSK9 levels are correlated with mortality in patients with end-stage liver disease. PLoS One 12: e0181540, 2017.
23. Silbernagel G, Scharnagl H, Kleber ME, Stojakovic T and März W: Circulating proprotein convertase subtilisin-kexin type 9, all-cause mortality, and cardiovascular mortality: The ludwigshafen risk and cardiovascular health study. Eur J Prev Cardiol 24: 1095-1101, 2017.
24. Seeger H, Latus J, Kitterer D, Alscher MD, Biegger D, Chen J, Edenhofer I, Wüthrich RP and Segerer S: CD147 expression in peritoneal injury. Clin Exp Nephrol 21: 1097-1104, 2017.
25. Wilson MR, Petrie JE, Shaw MW, Hu C, Oakley CM, Woods SJ, Patel BV, O'Dea KP and Takata M: High-fat feeding protects mice from ventilator-induced lung injury, via neutrophil-independent mechanisms. Crit Care Med 45: e831-e839, 2017.
26. Sato M, Nakai Y, Nakata W, Yoshida T, Hatano K, Kawashima A, Fujita K, Uemura M, Takayama H and Nonomura N: EMMPRIN promotes angiogenesis, proliferation, invasion and resistance to sunitinib in renal cell carcinoma, and its level predicts patient outcome. PLoS One 8: e74313, 2013.
27. Li H, Jiang C, Wu D, Shi S, Liao M, Wang J, Li Y and Xu Z: The prognostic and clinicopathologic characteristics of CD147 and esophagus cancer: A meta-analysis. PLoS One 12: e0180271, 2017.
28. Han JM and Jung HJ: Cyclophilin A/CD147 interaction: A promising target for anticancer therapy. Int J Mol Sci 23: 9341, 2022.
29. Bonaventura A, Grossi F, Carbone F, Vecchié A, Minetti S, Bardi N, Elia E, Ansaldo AM, Ferrara D, Rijavec E, *et al*: Serum PCSK9 levels at the second nivolumab cycle predict overall survival in elderly patients with NSCLC: A pilot study. Cancer Immunol Immunother 68: 1351-1358, 2019.
30. Momtazi-Borojeni AA, Nik ME, Jaafari MR, Banach M and Sahebkar A: Effects of immunization against PCSK9 in an experimental model of breast cancer. Arch Med Sci 15: 570-579, 2019.
31. Huang J, Li L, Lian J, Schauer S, Vesely PW, Kratky D, Hoefler G and Lehner R: Tumor-induced hyperlipidemia contributes to tumor growth. Cell Rep 15: 336-348. 2016.
32. Bassi DE, Fu J, Lopez de Cicco R and Klein-Szanto AJ: Proprotein convertases: 'Master switches' in the regulation of tumor growth and progression. Mol Carcinog 44: 151-161, 2005.
33. Lu GW, Lu DW and Zhang YX: Predictive value of serum cyclophilin A concentrations after acute pancreatitis. Clin Chim Acta 484: 237-245, 2018.
34. Jin HH, Mao TM, Bai ZQ, Chen Y, Ji HL and Jin Y: The 90-day prognostic value of serum cyclophilin A in traumatic brain injury. Clin Chim Acta 484: 258-264, 2018.
35. Jin S, Zhang M and Qiao X: Cyclophilin A: Promising target in cancer therapy. Cancer Biol Ther 25: 2425127, 2024.