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ORIGINAL RESEARCH

Prognostic Implication of Metabolic Syndrome in Patients with Nasopharyngeal Carcinoma: A Large Institution-Based Cohort Study from an Endemic Area

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Objective: Metabolic syndrome has been identified as a prognostic predictor in multiple cancers. This study aimed to evaluate the impact of metabolic syndrome on the clinical outcome of patients with nasopharyngeal carcinoma (NPC) and its mechanism.

Methods: A cohort of 2003 NPC patients with a median follow-up time of 96.3 months (range: 4.1–120.0 months) were enrolled in this analysis. Kaplan–Meier curves and the Log rank test were used to determine the differences in progression-free survival (PFS), cancer specific survival (CSS) and overall survival (OS). Univariate and multivariable analyses were used to identify independent prognostic predictors. Untargeted metabolomics (LC-HRMS) was used to detect the serum metabolic profiles of 10 well-matched patients with or without metabolic syndrome. Differential metabolite-based enrichment analysis and pathway analysis were performed to identify the potential mechanism of metabolic syndrome in NPC.

Results: A total of 171/2003 (8.5%) patients were diagnosed with metabolic syndrome, and these patients tended to be male ($P < 0.001$) and older ($P = 0.003$). Patients with metabolic syndrome had poorer PFS ($P = 0.011$), CSS ($P = 0.003$) and OS ($P = 0.001$) than those without metabolic syndrome. Univariate and multivariable analyses showed that metabolic syndrome was a statistically significant and independent predictor for PFS (HR: 1.34, 95% CI: 1.03–1.75, $P = 0.032$), CSS (HR: 1.53, 95% CI: 1.12–2.08, $P = 0.008$), and OS (HR: 1.50, 95% CI: 1.13–2.00, $P = 0.006$). The serum metabolic profile of patients with metabolic syndrome was distinct from that of patients without metabolic syndrome. A total of 319 differential metabolites [log2(FC)>1 or log2 (FC)<-1] were identified and were significantly involved in D-glutamine and D-glutamate metabolism, and valine, leucine and isoleucine biosynthesis.

Conclusion: Metabolic syndrome can serve as a prognostic predictor and guide a more personalized therapy for NPC patients.

Keywords: nasopharyngeal carcinoma, metabolic syndrome, metabolite, prognosis, survival

Background

Nasopharyngeal carcinoma (NPC), a unique subtype of head and neck cancer, has an extremely unbalanced endemic distribution across the world, with age-standardized rates of 3.0 per 100,000 in China and 0.4 per 100,000 in predominantly white populations.[1] Global cancer data on global cancer showed an estimated 129,079 new NPC cases and 72,987 deaths in 2018.[2] On account of the deep-seated anatomical position and the high radiosensitivity of NPC, radiotherapy has become

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the mainstay treatment for NPC, and combined chemoradiotherapy has been applied to patients with advanced-stage disease.[3] Currently, the tumour-node-metastasis (TNM) staging system is most widely used for formulating treatment strategies and evaluating clinical outcomes in NPC. However, this system does not consider the tumour biological heterogeneity, so prognostic deviation inevitably occurs in NPC patients with the same stage and similar therapies.[4] Therefore, deficiencies in accurate prediction stress the urgent demand to explore better predictors.

Metabolic syndrome, defined by the presence of at least three out of four factors including obesity, hyperglycemia, hypertension and dyslipidemia, is widely recognized as a great challenge for public health.[5] Causality consistently resides between metabolic syndrome and multifarious disorders, such as cardiovascular disease and type II diabetes.[5] Metabolic syndrome represents a cluster of metabolic derangements, and emerging technologies have remarkably enhanced the comprehensive elucidation of its relevant mechanisms by revealing variations in diverse metabolites at specific disease stages.[6,7] In addition, numerous studies have shown an association between metabolic syndrome and various cancers.[8] Importantly, due to its aggressive involvement in multiple malignancies, metabolic syndrome has been shown to serve as a prognostic indicator in various cancers, including breast cancer,[9] gastric cancer,[10] colorectal cancer,[11,12] oesophageal squamous cell carcinoma,[13] prostate cancer,[14] ovarian cancer,[15] renal cancer,[16] etc. Nonetheless, even though a case-control NPC study reported that metabolic disorder increases the carcinogenesis risk,[17] the impact of metabolic syndrome on NPC outcomes and its relevant mechanism remain vastly elusive.

Thus, we performed a retrospective study to meticulously appraise the prognostic efficacy of metabolic syndrome in NPC and adopted untargeted metabolomics to identify a latent mechanism, which will pave a novel path for guiding the personalized therapy of NPC.

Materials and Methods

Patient Population

We conducted this retrospective study of NPC patients treated with radical radiotherapy at Sun Yat-Sen University Cancer Center (SYSUCC, Guangzhou, China) between April 2009 and September 2012. The patient enrolment criteria were as follows: (1) pathological confirmation of NPC; (2) absence of distant metastasis; (3) no previous anticancer treatment; (4) no history of other malignancies; and (5) complete medical history and haematological profiles. Finally, a total of 2003 patients were included in the study.

Pretreatment Evaluation

All enrolled patients underwent routine pretreatment evaluation consisting of complete medical history, physical examination, routine blood test, biochemical analyses, fibre-optic nasopharyngoscopy, histopathological diagnosis, magnetic resonance imaging (MRI) of the nasopharynx and neck, chest radiography, abdominal ultrasonography, and whole-body bone scan using single-photon emission computed tomography (ECT) or 18^{F}-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT). All patients were restaged according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system by two radiation oncologists specializing in head and neck cancer. This study regarding the analysis of anonymous patient data was approved by the Institutional Ethical Review Board of Sun Yat-Sen University Cancer Center, and the requirement to obtain written informed consent was waived by the Ethics Review Board.

Treatment

The primary tumour and the upper area above the caudal edge of the cricoid cartilage of the patients were treated with intensity-modulated radiation therapy (IMRT). Details regarding the radiotherapy techniques used at our centre were provided in a previous study.[4] The prescribed doses were 66–72 Gy (28–33 fractions) to the planning target volume (PTV) of the gross tumour volume of the nasopharynx lesion (GTVnx), and 64–70 Gy (28–33 fractions) to the PTV of the gross tumour volume of the malignant lymph nodes (GTVnd). According to our institutional guidelines during this study period, radiation therapy alone was suggested to patients with stage I disease, concurrent chemoradiotherapy (CCRT) to patients with stage II disease, and CCRT with or without induction/adjuvant chemotherapy (IC/AC) to patients with stage III–IVB disease.

Definition of Metabolic Syndrome

Metabolic syndrome was diagnosed in accordance with the criteria set forth by the Chinese Diabetes Society in 2004,[9] which defines a person as having metabolic syndrome if at least three out of the following four factors as present: (1) obesity: body mass index $\geq$25 kg/m^2; (2) hyperglycemia:

fasting blood glucose ≥6.1 mmol/L and/or 2-hour plasma glucose ≥7.8 mmol/L and/or previously diagnosed diabetes; (3) hypertension: systolic/diastolic blood pressure ≥140/90 mmHg and/or antihypertensive therapy; and (4) dyslipidemia: triglycerides ≥1.7 mmol/L and/or high-density lipoprotein <0.9 mmol/L in men or <1.0 mmol/L in women.

Follow-Up

The primary endpoints included progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS). PFS was calculated as the time from the first day of treatment to the date of disease progression or death from any cause, whichever occurred first; CSS as the time to the date of death owing to cancer; and OS as the time to the date of death from any cause. The patients were examined every three months in the first 2 years, every six months during years 3–5, and annually thereafter. The last follow-up date was November 15, 2019. The follow-up duration was calculated from the first day of treatment to either the day of the last visit or death.

Metabolomics Profiling with LC-HRMS

Blood was collected at the time of diagnosis and centrifuged at 2330 × g for 10 minutes at 4 °C. Subsequently, the serum was separated and stored at −80 °C until analysis. We vortexed the serum samples before extraction. Then, precooled methanol (500 μL), ice water (150 μL) and chloroform (500 μL) were added successively, vortexed for 10 min, and centrifuged at 4 °C and 15,000 rcf for 15 min. The supernatant was placed in a vacuum freeze-drying machine to dry. In the process of sample resolution, after 120 μL of resolution solvent (acetonitrile: water = 4:1, V/V) was added, the mixture was vortexed for 5 min and then centrifuged at 4 °C and 15,000 rcf for 10 min, of which 100 μL of supernatant was removed for liquid chromatography - high resolution mass spectrometry (LC-HRMS) analysis. In addition, an equal volume of supernatant from each sample was mixed as QC samples for quality control.

Pretreatment involving peak extraction, alignment and missing value elimination and filling was carried out based on raw metabolic profile data in Compound Discovery 3.1. Ions with peak intensity RSD>30% in QC samples were removed and the rest were normalized by the sum based on the peak area. The partial least squares discriminant analysis (PLS-DA) model was constructed by SIMCA software (version 13.0, Umetrics, Umea, Sweden). Fold change (FC) analysis was performed to identify differential metabolites with log2(FC)>1 or log2(FC)<-1. R package "ggplot2" was used to perform volcano plot in R 4.03. A hierarchical clustering heatmap based on Student's *t*-test was used to provide intuitive visualization. Enrichment and pathway analysis based on Kyoto Encyclopedia of Genes and Genomes (KEGG) human metabolic pathways (Oct. 2019) were performed to identify differential metabolite-enriched biological processes. MetaboAnalyst5.0 were used to perform this analysis.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for Social Sciences, version 22.0 (SPSS, Inc., Chicago, IL, USA). Categorical variables were compared using the chi-square test or Fisher's exact test. The cumulative survival rates were calculated by the Kaplan–Meier method and the differences were compared by the Log rank test. Univariate and multivariate analyses with a Cox proportional hazards model were used to test independent predictors by backward elimination of confounding variables. Covariates included age, sex, smoking, drinking, family history of cancer, metabolic syndrome, PS score, World Health Organization (WHO) type and TNM stage. All of the tests were two sided and P value <0.05 was considered statistically significant.

Results

Patient Characteristics

The baseline characteristics of the 2003 NPC patients are displayed in Table 1. The median age was 45 years (range, 18–78 years). Among them, 507 (25.3%) patients were female and 1496 (74.7%) were male. According to the 8th AJCC staging system, 11 (5.5%) patients were classified as stage I, 396 (19.8%) as stage II, 935 (46.7%) as stage III, and 561 (28.0%) as stage IV. All of the patients underwent radical radiotherapy, and 1705 (85.1%) patients also received platinum-based chemotherapy.

The median follow-up time was 96.3 months (range: 4.1–120.0 months). A total of 487 (24.3%) patients experienced disease progression, among which 242 (12.1%) and 302 (15.1%) patients developed locoregional recurrence or distant metastasis, respectively. A total of 437 (21.8%) patients died, including 374 (18.7%) patients who died due to cancer. The five-year PFS, CSS, and OS of the entire cohort were 85.9%, 86.1%, and 85.1%, respectively.

Table 1 Baseline Characteristics of 2003 Patients with Nasopharyngeal Carcinoma

Characteristic	No. of Patients (%)
Age, yr	
Median	45
Range	18–78
Sex	
Female	507 (25.3)
Male	1496 (74.7)
Smoking	
No	1284 (64.1)
Yes	719 (35.9)
Drinking	
No	1759 (87.8)
Yes	244 (12.2)
Family history of Cancer	
No	1432 (71.5)
Yes	571 (28.5)
Body mass index	
< 25 kg/m^2	1484 (74.1)
≥ 25 kg/m^2	519 (25.9)
Hyperglycemia	
No	1675 (83.6)
Yes	328 (16.4)
Hypertension	
No	1711 (85.4)
Yes	292 (14.6)
Dyslipidemia	
No	1283 (64.1)
Yes	720 (35.9)
Metabolic syndrome	
No	1832 (91.5)
Yes	171 (8.5)
WHO type	
I	9 (0.4)
II	95 (4.7)
III	1899 (94.8)
T stage*	
T1	331 (16.5)
T2	333 (16.6)
T3	950 (47.4)
T4	389 (19.4)
N stage*	
N0	334 (16.7)
N1	1136 (56.7)
N2	324 (16.2)
N3	209 (10.4)
TNM stage*	
I	111 (5.5)
II	396 (19.8)
III	935 (46.7)
IV	561 (28.0)
PS score	
0	1709 (85.3)
1	288 (14.4)
2	6 (0.3)
Chemotherapy	
No	298 (14.9)
Yes	1705 (85.1)

Note: *According to the 8th AJCC/UICC staging system.
Abbreviations: WHO, World Health Organization; TNM, tumour-node-metastasis; PS, performance status, according to Eastern Cooperative Oncology Group Performance Status.

Correlation of Metabolic Syndrome with Patient Characteristics

For the entire cohort, obesity, hyperglycemia, hypertension and dyslipidemia were present in 519 (25.9%), 328 (16.4%), 292 (14.6%), and 720 (35.9%) of the 2003 patients, respectively. In total, 171/2003 (8.5%) patients were diagnosed with metabolic syndrome (Table 1).

We first analysed the relationship of metabolic syndrome with the clinical characteristics of NPC patients. As shown in Table 2, patients with metabolic syndrome tended to be male (P<0.001) and older (P=0.003) than those without metabolic syndrome. Additionally, there were no significant differences regarding smoking, drinking, family history of cancer, WHO type, T stage, N stage, PS score, TNM stage, and chemotherapy between patients with metabolic syndrome and those without metabolic syndrome.

Prognostic Value of Metabolic Syndrome in NPC

We analysed the effect of metabolic syndrome on NPC patient survival and found that patients complicated with metabolic syndrome had a significantly poorer 5-year PFS (69.0% vs 77.9%, P=0.011), CSS (80.5% vs 86.7%, P=0.003) and OS (78.4% vs 85.7%, P=0.001) than patients without metabolic syndrome (Figure 1).

We then performed univariate analysis to identify prognostic factors for NPC patients and found that metabolic syndrome was significantly associated with PFS (hazard ratio (HR): 1.36, 95% confidence interval (95% CI): 1.06–1.76, P=0.017), CSS (HR: 1.58, 95% CI: 1.18–2.12, P=0.002), and OS (HR: 1.55, 95% CI: 1.18–2.05,

Table 2 Baseline Characteristics of Nasopharyngeal Carcinoma Patients with or without Metabolic Syndrome

Characteristic	Metabolic Syndrome		*P* value†
	With, n (%)	Without, n (%)	
Age			
≤ 45 yr	52 (30.4)	1020 (55.7)	<0.001
> 45 yr	119 (69.6)	812 (44.3)	
Sex			
Female	27 (15.8)	480 (26.2)	0.003
Male	144 (84.2)	1352 (73.8)	
Smoking			
No	100 (58.5)	1184 (64.6)	0.109
Yes	71 (41.5)	648 (35.4)	
Drinking			
No	151 (88.3)	1608 (87.8)	0.839
Yes	20 (11.7)	224 (12.2)	
Family history of cancer			
No	123 (71.9)	1309 (71.5)	0.895
Yes	48 (28.1)	523 (28.5)	
WHO type			
I+II	7 (4.1)	97 (5.3)	0.498
III	164 (95.9)	1735 (94.7)	
T stage*			
T1	22 (12.9)	311 (17.0)	0.093
T2	39 (22.8)	292 (15.9)	
T3	80 (46.8)	870 (47.5)	
T4	30 (17.5)	359 (19.6)	
N stage*			
N0	27 (15.8)	307 (16.8)	0.957
N1	96 (56.1)	1040 (56.8)	
N2	30 (17.5)	294 (16.0)	
N3	18 (10.5)	191 (10.4)	
TNM stage*			
I	6 (3.5)	105 (5.7)	0.436
II	40 (23.4)	356 (19.4)	
III	79 (46.2)	856 (46.7)	
IV	46 (26.9)	515 (28.1)	
PS score			
0	142 (83.0)	1567 (85.5)	0.463
1	29 (17.0)	259 (14.2)	
2	0 (0.0)	6 (0.3)	
Chemotherapy			
No	26 (15.2)	272 (14.8)	0.900
Yes	145 (84.8)	1560 (85.2)	

Notes: †P value was calculated using the chi-square test or Fisher's exact test. *According to the 8th AJCC/UICC staging system.

Abbreviations: WHO, World Health Organization; TNM, tumour-node-metastasis; PS, performance status, according to Eastern Cooperative Oncology Group Performance Status.

P=0.002, Table 3). In addition, patients in the older, male, smoking, WHO type I+II or advanced TNM stage groups had shorter PFS and OS (all *P*<0.05, Table 3), and patients in the older, smoking, WHO type I+II or advanced TNM stage groups had shorter CSS (all *P*<0.05, Table 3).

We finally performed multivariate analysis to determine independent prognostic factors in NPC (Table 4). After adjusting for age, sex, smoking, WHO type and TNM stage, we found that metabolic syndrome was a significant independent predictor for PFS (HR: 1.34, 95% CI: 1.03–1.75, *P*=0.032), CSS (HR: 1.53, 95% CI: 1.12–2.08, *P*=0.008), and OS (HR: 1.50, 95% CI: 1.13–2.00, *P*=0.006). In addition, age, smoking, WHO type, and TNM stage were independent prognostic factors for PFS, CSS, and OS (all *P*<0.05).

Metabolic Profiles of NPC Patients with Metabolic Syndrome

We attempted to discover the metabolic profile features of NPC patients with and without metabolic syndrome. We acquired the metabolite peak intensity data of 10 NPC serum samples using untargeted metabolomics, which matched well with age, sex and TNM stage. The metabolomic profiles of NPC patients with metabolic syndrome were obviously distinct from those of patients without metabolic syndrome, as evidenced by robust PLS-DA models (Figure 2A). A comparison of patients with metabolic syndrome versus those without metabolic syndrome identified 319 differential metabolites, including 255 downregulated metabolites and 64 upregulated metabolites (Figure 2B). A hierarchical clustering heatmap was established to show the top 50 differential serum metabolites (Figure 2C), and we were surprised to discover that some differential metabolites were closely linked.

We then performed enrichment analysis of differential metabolites with matched Human Metabolome Database IDs or KEGG IDs. The analysis results indicated that the differential metabolites were mainly enriched in the pathways of D-glutamine and D-glutamate metabolism, and valine, leucine and isoleucine biosynthesis, which had the highest enrichment ratios (Figure 3). Cancer cells confer poor survival in the absence of glutamine and glutamate is a promising target for cancer therapy.[18] Valine, leucine and isoleucine are branched-chain amino acids that are closely associated with malignant biological processes.[19]

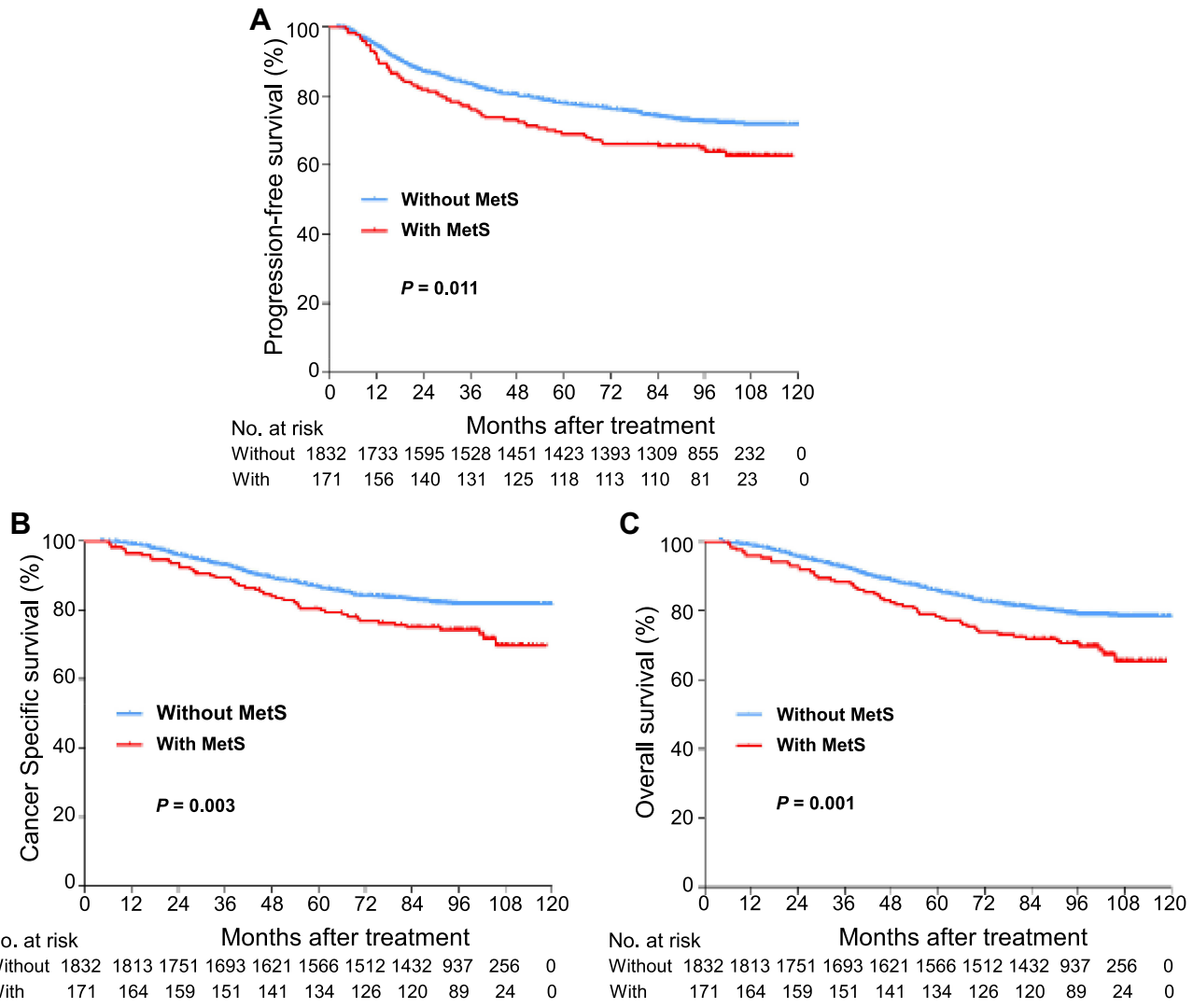

Figure 1 Kaplan–Meier curve analysis of survival probabilities of NPC patients stratified by metabolic syndrome. (**A**) Progression-free survival. (**B**) Cancer specific survival. (**C**) Overall survival.
Abbreviation: MetS, metabolic syndrome.

Discussion

To the best of our knowledge, our study was the first to analyse the largest dataset to evaluate the prognostic value of metabolic syndrome in NPC. Our findings showed that NPC patients complicated with metabolic syndrome had an inferior clinical outcome, which is probably mediated by D-glutamine and D-glutamate metabolism, and valine, leucine and isoleucine biosynthesis. It is of clinical significance to better monitor metabolic derangements before and during antitumor treatment to improve the survival of NPC patients.

Metabolic syndrome is a growing global health problem and is commonly recognized as a risk factor for diabetes and cardiovascular disease.[5] Recently, a growing body of evidence has suggested that metabolic syndrome is associated with an increased risk of tumour occurrence and can serve as an indicator of poor prognosis in a wide variety of cancers.[9–16] In NPC, it has been reported that the single components of metabolic syndrome are associated with survival. Several studies have shown that pretreatment body mass index is a reliable prognostic factor, and NPC patients with overweight/obese status have a favourable clinical outcome.[20–22] Another two studies revealed that overweight/obese do not affect the survival of NPC, but underweight can increase the risk of death and distant metastasis.[23,24] A meta-analysis of nine studies showed that diabetes has no impact on NPC prognosis.[25] However, a recent case-control study showed that patients with diabetes have shorter survival than those

Table 3 Univariate Analysis of Prognostic Factors in Patients with Nasopharyngeal Carcinoma

Variable	Univariate Analysis		
	HR	95% CI	*P* value†
Progression-free survival			
Age (≥45 years vs <45 years)	1.42	1.21–1.68	<0.001
Sex (Female vs Male)	0.81	0.66–0.99	0.037
Smoking (Yes vs No)	1.33	1.12–1.57	0.001
Drinking (Yes vs No)	1.19	0.94–1.51	0.149
Family history of cancer (Yes vs No)	0.84	0.70–1.02	0.071
Metabolic syndrome (With vs Without)	1.41	1.08–1.83	0.012
WHO type (III vs I+II)	0.61	0.45–0.84	0.002
TNM stage (III–IV vs I–II)	2.27	1.80–2.88	<0.001
Cancer-specific survival			
Age (≥45 years vs <45 years)	1.43	1.17–1.76	0.001
Sex (Female vs Male)	0.79	0.62–1.01	0.058
Smoking (Yes vs No)	1.42	1.16–1.75	0.001
Drinking (Yes vs No)	1.12	0.83–1.51	0.464
Family history of cancer (Yes vs No)	0.87	0.69–1.10	0.242
Metabolic syndrome (With vs Without)	1.59	1.17–2.17	0.003
WHO type (III vs I+II)	0.51	0.36–0.72	<0.001
TNM stage (III–IV vs I–II)	3.05	2.21–4.22	<0.001
Overall survival			
Age (≥45 years vs <45 years)	1.60	1.32–1.93	<0.001
Sex (Female vs Male)	0.75	0.59–0.94	0.014
Smoking (Yes vs No)	1.41	1.17–1.70	<0.001
Drinking (Yes vs No)	1.09	0.82–1.44	0.558
Family history of cancer (Yes vs No)	0.86	0.70–1.07	0.181
Metabolic syndrome (With vs Without)	1.60	1.21–2.13	0.001
WHO type (III vs I+II)	0.56	0.40–0.79	0.001
TNM stage (III–IV vs I–II)	2.93	2.18–3.93	<0.001

Note: †P value was calculated using the univariate Cox proportional hazards model.
Abbreviations: WHO, World Health Organization; HR, hazard ratio; 95% CI, 95% confidence interval; TNM, tumour-node-metastasis.

without diabetes.[26] The prognostic value of different lipoproteins in NPC is different, among which high-density lipoprotein and apolipoprotein A-I are favourable prognosticators, while low-density lipoprotein is an indicator of poor prognosis.[27–33] A significant correlation between hypertension and inferior prognosis in NPC has also been reported.[33] The prognostic value of the single components of metabolic syndrome is somewhat controversial. Furthermore, no study has yet evaluated the impact of metabolic syndrome on the survival outcome of NPC patients.

Here, we conducted a retrospective study with a total of 2003 patients and a median follow-up time of 96.3 months to evaluate the effect of metabolic syndrome on the prognosis of NPC. Our findings convincingly suggested that NPC patients complicated with metabolic syndrome had inferior PFS, CSS and OS. Moreover, univariate and multivariate Cox regression analyses showed that metabolic syndrome was a significant and independent prognostic predictor for PFS, CSS, and OS after adjusting for age, gender, smoking, WHO type and TNM stage. Our findings suggest that special and close attention should be given to the management of metabolic derangements before and during antitumor treatment to improve the prognosis and quality of life of NPC patients.

Various potential mechanisms linking metabolic derangements to NPC have been reported. IGF-1 actively participates in malignant biological processes, such as epithelial-mesenchymal transition, cell proliferation and radiosensitivity.[34–38] Lymphoid-specific helicase promotes tumour progression by inhibiting fumarate hydratase transcription and upregulating alpha-KG and citrate levels.[39] Epstein-Barr virus (EBV)-encoded LMP1 modulates aerobic glycolysis by activating the IGF1-mTORC2 and FGFR1

Table 4 Multivariable Analysis of Prognostic Factors in Patients with Nasopharyngeal Carcinoma

Variable	Multivariable Analysis		
	HR	95% CI	*P* value†
Progression-free survival			
Age (≥45 years vs <45 years)	1.32	1.11–1.56	0.001
Smoking (Yes vs No)	1.22	1.03–1.44	0.023
Metabolic syndrome (With vs Without)	1.34	1.03–1.75	0.032
WHO type (III vs I+II)	0.60	0.44–0.83	0.002
TNM stage (III–IV vs I–II)	2.25	1.78–2.85	<0.001
Cancer-specific survival			
Age (≥45 years vs <45 years)	1.29	1.05–1.60	0.016
Smoking (Yes vs No)	1.30	1.06–1.60	0.013
Metabolic syndrome (With vs Without)	1.53	1.12–2.08	0.008
WHO type (III vs I+II)	0.49	0.35–0.70	<0.001
TNM stage (III–IV vs I–II)	3.03	2.19–4.19	<0.001
Overall survival			
Age (≥45 years vs <45 years)	1.45	1.20–1.76	<0.001
Smoking (Yes vs No)	1.27	1.05–1.53	0.016
Metabolic syndrome (With vs Without)	1.50	1.13–2.00	0.006
WHO type (III vs I+II)	0.55	0.39–0.78	0.001
TNM stage (III–IV vs I–II)	2.89	2.15–3.88	<0.001

Note: †P value was calculated using the multivariable Cox proportional hazards model. The following parameters were included in the Cox proportion hazard model by backward elimination: age (≥45 vs <45 years), sex (Female vs Male), smoking (Yes vs No), drinking (Yes vs No), family history of cancer (Yes vs No), metabolic syndrome (With vs Without), WHO type (Type III vs Type I+II), and TNM stage (III–IV vs I–II) as covariates. Only variables significantly related to survival are presented.
Abbreviations: WHO, World Health Organization; HR, hazard ratio; 95% CI, 95% confidence interval; TNM, tumour-node-metastasis.

signalling pathways.[40,41] CPT1A interacts with Rab14 to regulate fatty acid transport and energy production in NPC.[42] Overall, metabolic derangement is regulated by various metabolic pathways. Consequently, we speculate that NPC cells obtain nutrient metabolites from the tumour microenvironment or improve metabolic efficiency by de novo synthesis to compromise clinical outcomes. This conjecture was validated by enrichment and pathway analysis based on 319 differential serum metabolites, which exhibited a great enrichment tendency in D-glutamine and D-glutamate metabolism, and valine, leucine and isoleucine biosynthesis. "Glutamine addiction" has been observed in various cancer entities and is defined as poor cancer cell survival in the absence of glutamine.[43] Glutamine has also been described as an essential activator of mammalian target of rapamycin complex 1 (mTORC1), which is capable of modulating protein translation, cell growth and autophagy.[44] Furthermore, glutaminase converts glutamine into glutamate and the latter is a promising target for cancer therapy.[18] Valine, leucine and isoleucine are branched-chain amino acids, which are essential amino acids preferentially taken up by tumour cells.[45] Branched-chain amino acids offer nitrogen and nutrition for de novo nucleotide synthesis, engage in the activation of signalling pathways and influence the expression of mounting metabolite-derived factors, which meet the inherent demand of cancer proliferation.[19]

Although our study has clear strengths including the large dataset and the availability of complete clinical information of patients, there are some limitations in our design that should be considered when interpreting the findings. First, our study was based on a single centre, and multicentre research should be carried out to further confirm study results. Second, the definition of metabolic syndrome we adopted was based on the criteria set forth by the Chinese Diabetes Society in 2004, so the findings cannot be used for patients diagnosed with metabolic syndrome by other criteria. Third, studies report that metformin and statins have antitumor effects in multiple types of cancers,[46,47] however, we did not exclude the effect of metabolic syndrome drugs, such as metformin and statins, on the survival of NPC.

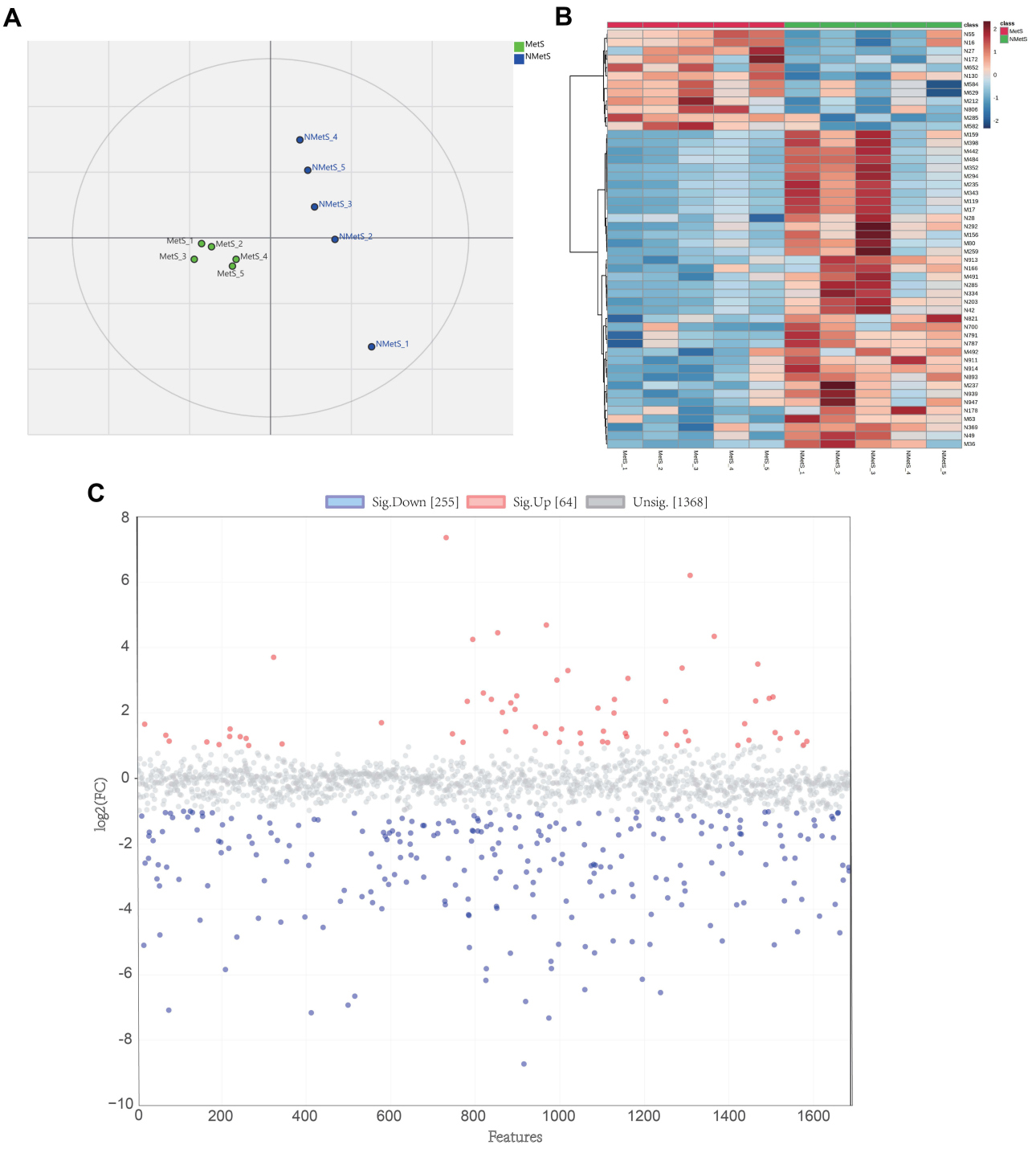

Figure 2 Metabolic profile analysis of NPC patients with and without metabolic syndrome. (**A**) Partial least-squares discrimination analysis (PLS-DA) of the serum metabolomic file of NPC patients in the MetS and NMetS groups (n = 5). Each symbol represents the data of an individual patient. (**B**) Fold change analysis discovering differential serum metabolites, which were identified with a $\log_2$ (FC) of MetS/NMetS > 1 or < −1. (**C**) Heatmap showing the top 50 differential serum metabolites. Differential serum metabolites were identified with $p<0.05$ using Student's *t*-test.
Abbreviations: MetS, metabolic syndrome; NMetS, non-metabolic syndrome.

Conclusions

To the best of our knowledge, this is the first retrospective study to evaluate the effect and potential mechanism of metabolic syndrome on the clinical outcome of NPC patients. We found that NPC patients with metabolic syndrome had inferior survival compared with those without metabolic syndrome. Metabolic syndrome can serve as an independent prognostic indicator and is closely correlated

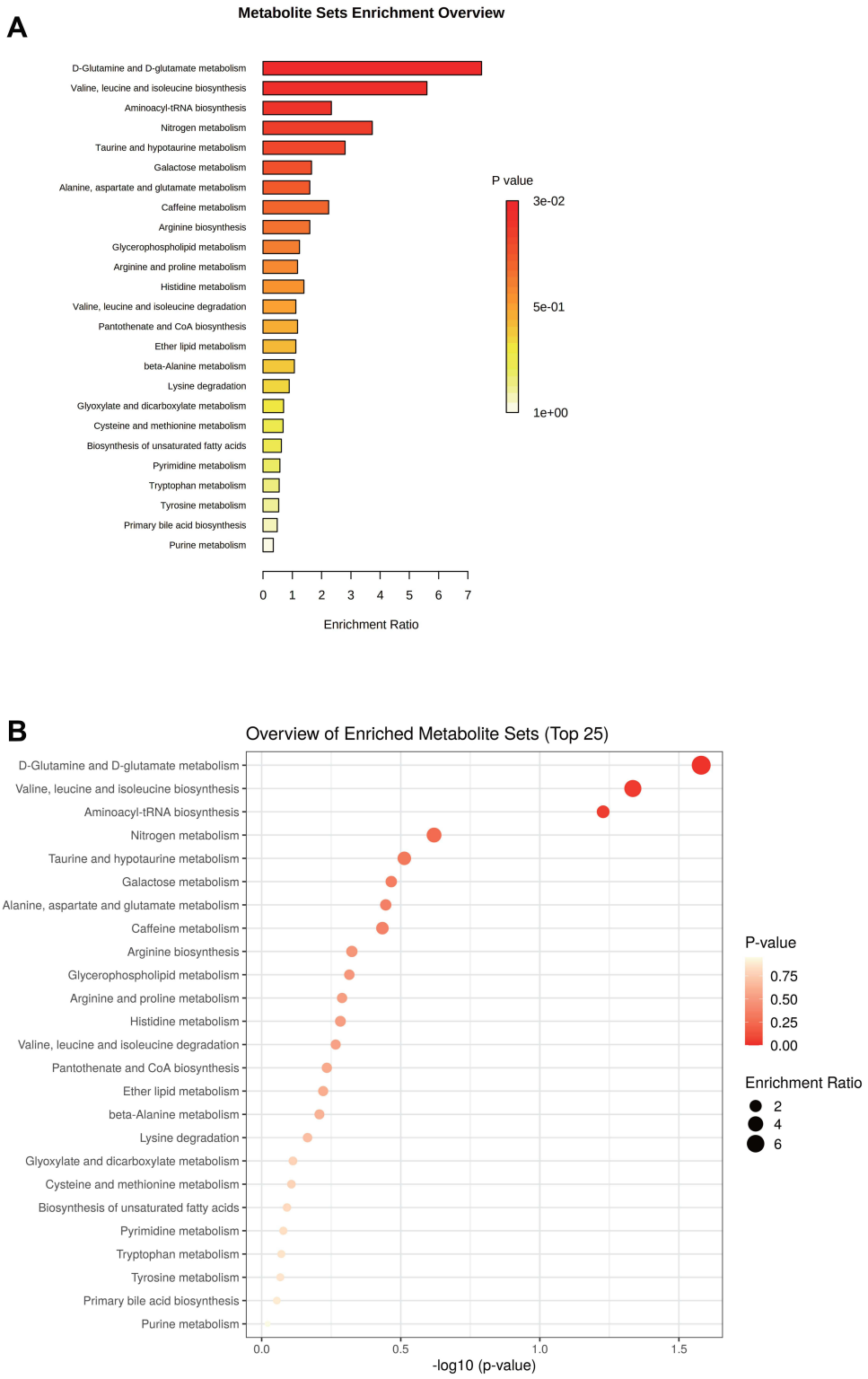

Figure 3 Enrichment and pathway analysis of differential metabolites. (**A**) Bar plot of KEGG pathway analysis of differential metabolites; (**B**) dot plot of KEGG pathway analysis of differential metabolites.

with D-glutamine and D-glutamate metabolism and valine, leucine and isoleucine biosynthesis, which could guide more personalized therapy for NPC patients.

Abbreviations

NPC, nasopharyngeal carcinoma; TNM, tumor-node-metastasis; MRI, magnetic resonance imaging; ECT,

emission computed tomography; 18F-FDG PET/CT, 18F-fluorodeoxyglucose positron emission tomography/computed tomography; AJCC, American Joint Committee on Cancer; IMRT, intensity-modulated radiation therapy; PTV, planning target volume; GTVnx, gross tumor volume of nasopharynx lesion; GTVnd, gross tumor volume of the malignant lymph nodes; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; AC, adjuvant chemotherapy; PFS, disease-free survival; CSS, cancer specific survival; OS, overall survival; LC-HRMS, liquid chromatography - high resolution mass spectrum; PLS-DA, Partial Least Squares Discriminant Analysis; FC, fold change; KEGG, Kyoto Encyclopedia of Genes and Genomes; WHO, World Health Organization; HR, hazard ratio; 95% CI, 95% confidence interval.

Data Sharing Statement

All of the key raw data have been uploaded onto the Research Data Deposit public platform (http://www.researchdata.org.cn) with the approval number RDDA2021001742.

Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki. The study regarding the analysis of anonymous patient data was approved by the Institutional Ethical Review Board of Yat-Sen University Cancer Center, and requirement to obtain written informed consent was waived by the Ethics Review Board.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no potential competing interests.

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