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ORIGINAL RESEARCH

Risk Factors for MAFLD and Advanced Liver Fibrosis in Adult-Onset Craniopharyngioma Patients: A Cross-Sectional Study

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Purpose: To investigate the prevalence of and risk factors for metabolic dysfunction-associated fatty liver disease (MAFLD) and advanced liver fibrosis (ALF) in postoperative adult-onset craniopharyngioma (AOCP) patients.

Patients and Methods: This cross-sectional study included 242 postoperative AOCP patients at Huashan Hospital (Shanghai, China). Clinical characteristics were compared between patients with and without MAFLD and ALF. Independent risk factors for MAFLD and ALF were identified using binary logistic regression analysis.

Results: The prevalence of MAFLD in postoperative AOCP patients was 67.4% (95% CI 61.2–73.0%), and 32.5% (95% CI 25.8–40.0%) of patients with MAFLD were diagnosed with ALF. Body mass index (BMI) was independently associated with MAFLD (OR = 1.51, 95% CI 1.33–1.72, P < 0.001). In patients with MAFLD, hypertension (OR = 2.33, 95% CI 1.04–5.20, P = 0.040), glycated hemoglobin (HbA1c) (OR = 1.34, 95% CI 1.01–1.78, P = 0.044), daily hydrocortisone dose (OR = 1.08, 95% CI 1.01–1.15, P = 0.026), and insulin-like growth factor-1 (IGF-1)(OR = 0.99, 95% CI 0.97–0.99, P = 0.011) were independently associated with the presence of ALF.

Conclusion: MAFLD is a common comorbidity in postoperative AOCP patients and is associated with a high risk of ALF. MAFLD is closely related to BMI, while ALF is significantly associated with hypertension, HbA1c levels, IGF-1 levels, and daily hydrocortisone dose. Strategies such as controlling weight gain, maintaining optimal blood glucose and blood pressure levels, appropriate hormone replacement, and avoiding excessive glucocorticoid use should be implemented to prevent and delay the onset and progression of MAFLD and ALF.

Keywords: craniopharyngioma, adult-onset, hypopituitarism, metabolic dysfunction-associated fatty liver disease, advanced liver fibrosis

Introduction

Craniopharyngiomas are rare, low-grade tumors of the sellar/parasellar region, with an annual incidence of 1.3–3 per million persons and a bimodal age distribution, peaking in children aged 5–14 years and adults aged over 50 years.[1–3] Since the tumors are pathologically benign, patients with craniopharyngiomas generally have a favorable long-term survival rate after surgery, with a 10-year survival rate exceeding 80%.[1,4,5] However, due to the damage caused by tumors and surgery to surrounding structures such as the hypothalamus-pituitary and optic apparatus, survivors usually experience long-term multisystem comorbidities, leading to a low quality of life, increased risk of death, and burden of disease.[6–10]

Nearly 90% of craniopharyngioma patients require long-term hormone replacement therapy due to postoperative hypopituitarism.[6,7,11] In addition to endocrine abnormalities, these patients often present with a worse metabolic profile compared to the general population.[7,9,12] Obesity affects nearly half of patients in some studies,[7,9] and the standardized incidence ratio for type 2 diabetes mellitus (T2DM) has been reported to be 4.4–5.6.[8,13] These metabolic disorders are primarily attributed to damage to critical hypothalamic structures and their regulatory functions.[14,15] Specifically, damage to the ventromedial hypothalamus (VMH) and arcuate nucleus, key regions for regulating appetite signaling, leads to

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hyperphagia. Additionally, hypothalamic injury results in reduced sympathetic nervous system activity, lowering resting metabolic rate and overall energy expenditure. This is compounded by increased parasympathetic activity, which promotes hyperinsulinemia and fat storage.[14,15] In addition, hormone deficiencies along with inappropriate replacement therapy especially excessive cortisol, and reduced activity due to visual impairment are also associated with an increased risk of metabolic syndrome.[5,12,15]

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of liver disorders characterized by excessive fat accumulation in the liver, ranging from simple steatosis, nonalcoholic steatohepatitis (NASH) to liver fibrosis and cirrhosis.[16] Advanced liver fibrosis(ALF) in NAFLD is associated with increased risks of liver-related complications and death.[17,18] With insulin resistance playing a key role in its pathogenesis, NAFLD is closely associated with metabolic disorders including obesity, dyslipidemia, and diabetes.[16,19] Hence, in recent years, some experts have proposed renaming it as metabolic dysfunction-associated fatty liver disease (MAFLD) to better reflect its metabolic nature, improve clinical utility, and reduce stigma.[20,21] In addition to metabolic disorders, hormone abnormalities can also cause hepatic steatosis.[22] Previous studies have reported that the prevalence of NAFLD in patients with hypopituitarism, particularly growth hormone deficiency (GHD), is significantly higher than in the general population,[23,24] and NAFLD in these patients tends to progress rapidly.[24,25] Given the coexistence of metabolic and hormonal abnormalities, patients with craniopharyngiomas, especially those who have undergone surgery, are likely at high risk for NAFLD. Two studies have shown that the prevalence of NAFLD in survivors of childhood-onset craniopharyngioma is 47%–50%,[26,27] with nearly one-third of cases diagnosed within 1 year after surgery.[27] However, the prevalence and risk factors of MAFLD in adult-onset craniopharyngioma (AOCP) patients remain largely unexplored. In this study, we investigated a cohort of Chinese AOCP patients who had undergone surgery treatment to determine the prevalence of and risk factors for MAFLD and ALF.

Subjects and Method

Subjects

The objective of this study was to estimate the prevalence of MAFLD in postoperative AOCP patients and the prevalence of ALF in those diagnosed with MAFLD. Based on previous studies[26–28] and preliminary data, the expected prevalence of MAFLD was set at 50% and the prevalence of ALF was 30%. To ensure the reliability and precision of the prevalence estimate, the margin of error (δ) was set at 10%. The confidence level was set at 95%, corresponding to a Z-value of 1.96. The sample size was calculated using the formula for estimating a proportion: $n = \frac{Z_{\alpha/2}^2 \times p \times (1-p)}{\delta^2}$. The sample size required for postoperative AOCP patients presented with MAFLD was 81, and for postoperative AOCP patients was 162.

We recruited patients with postoperative craniopharyngioma admitted to the Department of Endocrinology of Huashan Hospital (Shanghai, China) between January 2020 and January 2022. Eligibility criteria included being 18 years of age or older at the time of diagnosis and having at least one follow-up visit after 3 months of surgery. A computer-based search of medical records identified 1244 records with a diagnosis of craniopharyngioma, of which 836 were duplicates. Among the remaining 408 records, 31 patients were excluded due to childhood-onset craniopharyngioma, 2 due to inconsistent histopathological diagnoses, 24 due to lack of surgical resection, and 109 due to absence of follow-up data after 3 months of surgery or absence of abdominal ultrasound. Ultimately, 242 adult-onset craniopharyngioma patients were included. The flowchart of patient inclusion and exclusion is presented in Figure 1.

Informed consent was obtained from all participants. The study was approved by the Institutional Review Board of Huashan Hospital, Fudan University.

Data Collection

Data on demographic characteristics, anthropometric measurements, tumor characteristics and treatment of craniopharyngioma, postoperative endocrine functions, and metabolic parameters were collected from the medical records.

Tumor characteristics included location, size, pathological subtypes, and recurrence. Location was classified as intrasellar, suprasellar, or both intra- and suprasellar. Tumor size was recorded using the maximum tumor diameter based on preoperative MRI or computed tomography. Pathological subtypes included adamantinomatous and papillary

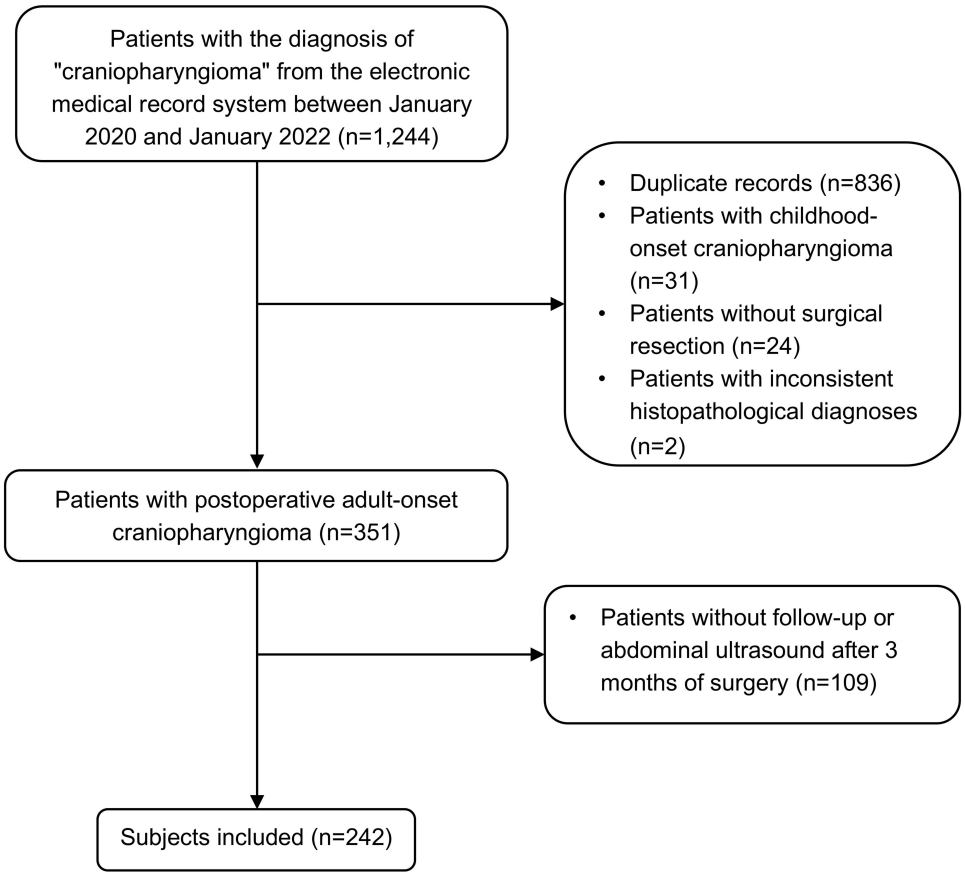

Figure 1 Flowchart of subjects included in this study.

variants. Surgical methods included endoscopic surgery or craniotomy, and the degree of resection was categorized as complete or incomplete based on the surgical report.

Pituitary hormone deficiencies were diagnosed based on clinical presentation, hormone levels, and pituitary function tests when necessary. Central Adrenal Insufficiency (CAI) was diagnosed if the basal serum cortisol level was <3 μg/dL or peak cortisol level was <18.1 μg/dL in the insulin tolerance test or ACTH stimulation test. Central hypothyroidism was defined by free thyroxine (FT4) levels below the reference range with low or normal thyroid-stimulating hormone (TSH) levels.

In men, central hypogonadism was defined by low serum testosterone levels along with low gonadotropin levels. In premenopausal women, identified by oligomenorrhea or amenorrhea combined with low serum estradiol levels and low or normal follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. In postmenopausal women, when serum FSH and LH levels were within the premenopausal range. Insulin tolerance test was not performed to detect GHD in this study but serum IGF-1 level was measured and reduced IGF-1 was defined as serum IGF-1 below the age and gender specific reference range. For the diagnosis of central diabetes insipidus (CDI), clinical presentation, urine-specific gravity, urine and serum osmolality, serum sodium levels, and the need for desmopressin treatment were comprehensively evaluated. Patients presented with hypopituitarism were further investigated for hormone replacement therapy.

The MAFLD was defined based on a consensus proposed by a panel of experts from 22 countries in 2020,[21] and the diagnostic process is illustrated in Figure 2. Patients with MAFLD were further assessed for ALF risk using the Liver Fibrosis Index-4 (FIB-4), a widely recommended non-invasive scoring system for initial screening for ALF in MAFLD.[28,29] FIB-4 was calculated according to the formula: FIB-4 = (age [years] × AST [U/L]) / (PLT [10^9/L] × √ALT [U/L]), with a FIB-4 score ≥1.3 indicating ALF otherwise non-ALF.[30–32]

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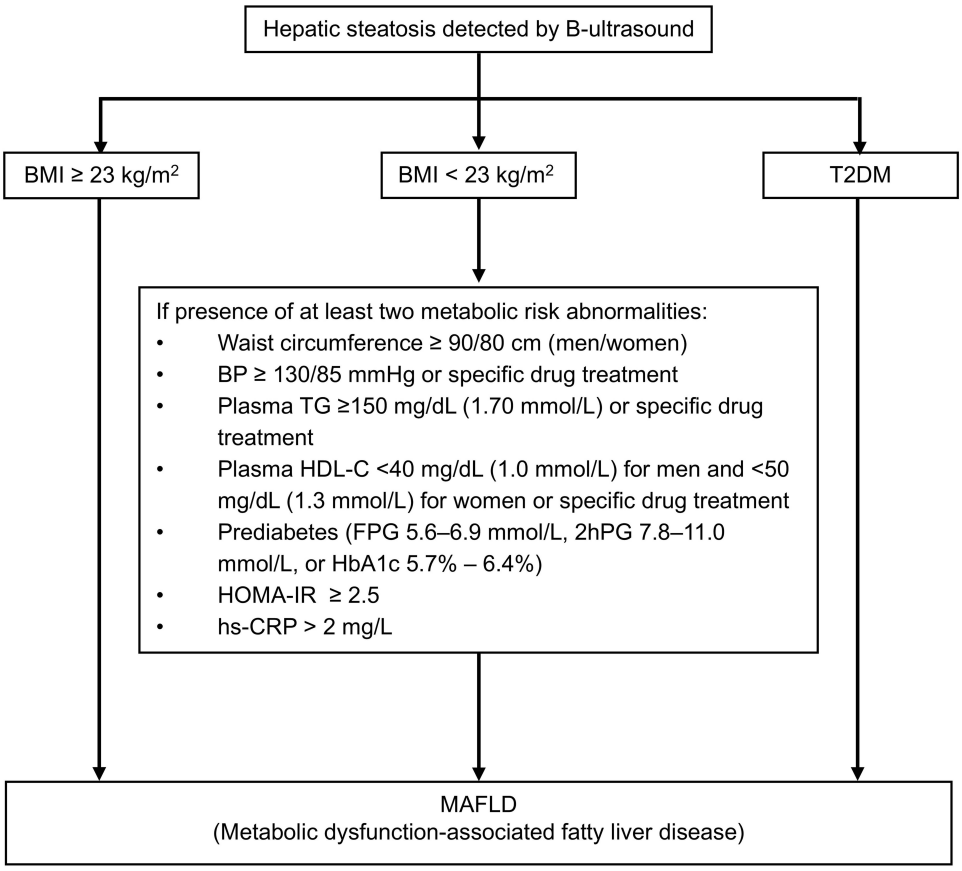

Figure 2 Flowchart for the diagnosis of MAFLD.
Abbreviations: BMI, body mass index; T2DM, type 2 diabetes mellitus; BP, blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; FPG, fasting blood glucose; 2hPG, 2-hour postprandial blood glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance index; hs-CRP, high-sensitivity C-reactive protein.

In addition, other metabolic diseases, including T2DM, dyslipidemia, hypertension, and hyperuricemia, were assessed. According to the criteria of the Working Group on Obesity in China, overweight was defined as a BMI between 24 and 28 kg/m², and obesity was defined as a BMI of ≥28 kg/m².[33]

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS 27.0), with a two-sided P-value < 0.05 considered statistically significant. Multiple imputation was employed to handle missing data. For continuous variables, normality was assessed using the Shapiro–Wilk test. Variables conforming to a normal distribution were expressed as means ± standard deviations (SDs), otherwise reported as medians (interquartile ranges). Categorical variables were presented as frequencies and percentages. Comparisons between groups for continuous variables were performed using Student's t-test for data that met the assumptions of normality and homogeneity of variances; otherwise, the Mann–Whitney U-test was used. For categorical variables, Chi-square tests or Fisher's Exact tests were used as appropriate.

Demographic characteristics, anthropometric measurements, tumor characteristics and treatment modalities of craniopharyngioma, presence, and treatment of hypopituitarism, and metabolic parameters were compared between the MAFLD and non-MAFLD groups, as well as between the ALF and non-ALF groups. Multivariable logistic regression analyses were conducted to identify risk factors for MAFLD and ALF. We calculated the VIF for each predictor variable to identify potential multicollinearity issues. A VIF value greater than 10 indicates severe multicollinearity, while values below 5 are considered acceptable.

Results

Clinical Characteristics and Risk Factors for MAFLD

In this study, we investigated 242 postoperative AOCP patients, of whom 127 (52.5%) were male. The median age at follow-up of the patients was 44 years, with a range from 19 to 78 years. Among the 242 patients, hepatic steatosis was detected in 163 patients based on abdominal ultrasound, all of whom met the diagnostic criteria for MAFLD, despite the lack of waist circumference and high-sensitivity C-reactive protein (hs-CRP) data. Thus, the prevalence of MAFLD was 67.4% (95% CI 61.2–73.0%). Clinical features were compared between the MAFLD and non-MAFLD groups, with results presented in Tables 1–3. The proportion of male patients was significantly higher in the MAFLD group than in the non-MAFLD group (57.1% vs 43.0%, $P = 0.041$), and the postoperative follow-up was longer [12 (6,18) vs 8 (4,14) months, $P = 0.023$]. However, there was no significant difference in age or preoperative duration. The recurrence, size, location, pathological subtype, and extent of tumor resection of craniopharyngiomas as well as surgical approach showed no significant difference between the two groups (Table 1).

As expected, the prevalence of metabolic syndrome (MetS) was significantly higher in patients with MAFLD compared to those without MAFLD (58.3% vs 20.3%, $P < 0.001$). The prevalence of hypertension and blood pressure levels were comparable between the two groups. Median BMI in MAFLD patients was 26.9 (range 20.8–41.0) kg/m^2 and much higher than that in non-MAFLD group [23.4 (range17.0–31.0) kg/m^2, $P < 0.001$]. Among glucose metabolism parameters, fasting plasma glucose (FPG), 2-hour postprandial glucose (2hPG), glycated hemoglobin (HbA1c), fasting insulin (FINS), and homeostasis model assessment of insulin resistance (HOMA-IR) were all significantly higher in the MAFLD group. Triglycerides (TG) and uric acid (UA) levels were significantly higher in the MAFLD group, while high-density lipoprotein cholesterol (HDL-C) was lower, but there were no significant differences in total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) levels between the two groups. Liver function indices showed that aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were significantly higher in the MAFLD group, while albumin (Alb) levels were similar between the groups (Table 2).

Regarding pituitary function, the prevalence of hypogonadism was higher in the MAFLD group compared to the non-MAFLD group, but this difference was significant only in the female subgroup (98.6% vs 84.4%, $P = 0.006$). There was

Table 1 Demographic and Tumor Characteristics of Patients With and Without MAFLD and ALF

Variables	Total (N = 242)	non-MAFLD (N = 79)	MAFLD (N = 163)	*P*	non-ALF (N = 110)	ALF (N = 53)	*P*
Gender, male (%)	127(52.5)	34(43.0)	93(57.1)	0.041	63(57.3)	30(56.6)	0.936
Age at follow-up, years	44(32, 56)	44(31, 58)	44(33, 55)	0.455	40(30, 50)	54(41, 61)	<0.001
Preoperative duration, months	21(13, 39)	18(9, 36)	22(14, 40)	0.098	24(15, 41)	20(13, 38)	0.659
Postoperative follow-up, months	11(6, 16)	8(4, 14)	12(6, 18)	0.023	12(6, 18)	12(6, 17)	0.323
Recurrent craniopharyngioma, n (%)	52(21.8)	18(22.8)	34(21.3)	0.787	21(19.6)	13(24.5)	0.476
Tumor location, n (%)				0.841			0.352
Suprasellar	119(49.2)	37(46.8)	82(50.3)		57(51.8)	25(47.2)	
Intrasellar	11(4.5)	4(5.1)	7(4.3)		3(2.7)	4(7.5)	
Both intra-/suprasellar	112(46.3)	38(48.1)	74(45.4)		50(45.5)	24(45.3)	
Tumor size, mm	28(22, 34)	27(21, 33)	29(22, 35)	0.690	29(22, 35)	27.5(21, 33)	0.353
Pathologic subtype, n (%)				0.730			0.310
Papillary	67(27.7)	23(29.1)	44(27.0)		27(24.5)	17(32.1)	
Adamantinomatous	175(72.3)	56(70.9)	119(73.0)		83(75.5)	36(67.9)	
Extent of surgery, n (%)				0.195			0.261
Gross total resection	181(74.8)	55(69.6)	126(77.3)		88(80.0)	38(71.7)	
Incomplete resection	61(25.2)	24(30.4)	37(22.7)		22(20.0)	15(28.3)	
Surgical approach, n (%)				>0.99			0.665
Endoscopic endonasal approach	235(97.1)	77(97.5)	158(96.9)		106(96.6)	51(96.2)	
Transcranial approach	7(2.9)	2(2.5)	5(3.1)		4(3.4)	2(3.8)	

Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; ALF, advanced liver fibrosis.

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Table 2 Metabolic Characteristics and Parameters of Patients With and Without MAFLD and ALF

Variables	Total (N = 242)	Non-MAFLD (N = 79)	MAFLD (N = 163)	*P*	Non- ALF (N = 110)	ALF (N = 53)	*P*
MetS, n (%)	111(45.9)	16(20.3)	95(58.3)	<0.001	63(57.3)	32(60.4)	0.707
BMI category, n (%)				<0.001			0.850
Normal weight	71(29.3)	47(59.5)	24(14.7)		15(13.6)	9(17.0)	
Overweight	97(40.1)	25(31.6)	72(44.2)		49(44.5)	23(43.4)	
Obese	74(30.6)	7(8.9)	67(41.1)		46(41.8)	21(39.6)	
Classification of glucose metabolism, n (%)				<0.001			0.342
Normal	129(53.3)	53(67.1)	76(46.6)		52(47.3)	24(45.3)	
IFG/IGT	48(19.8)	18(22.8)	30(18.4)		23(20.9)	7(13.2)	
T2DM	65(26.9)	8(10.1)	57(35.0)		35(31.8)	22(41.5)	
Reduced HDL-C, n(%)	156(64.5)	36(45.6)	120(73.6)	<0.001	84(76.4)	36(67.9)	0.252
Elevated TG, n (%)	177(73.1)	38(48.1)	139(85.3)	<0.001	96(87.3)	43(81.1)	0.300
Hypertension, n (%)	60(24.8)	16(20.3)	44(27.0)	0.255	22(20.0)	22(41.5)	0.004
Hyperuricemia, n (%)	109(45.0)	21(26.6)	88(54.0)	<0.001	62(56.4)	26(49.1)	0.381
BMI (kg/m^2)	26.0(23.7, 29.1)	23.4(20.8, 25.3)	26.9(25.4, 30.2)	<0.001	26.8(25.4, 30.2)	27.1(25.6, 29.3)	0.887
DBP (mmHg)	77(71, 85)	74(70, 85)	78(71, 84)	0.127	78(71, 84)	78(71, 84.5)	0.912
SBP (mmHg)	121(110, 128)	120(108, 125)	121(111, 129)	0.155	121(109, 128)	125(112, 133)	0.038
FPG (mmol/L)	4.7(4.4, 5.2)	4.6(4.3, 4.9)	4.8(4.5, 5.5)	<0.001	4.8(4.5, 5.2)	4.9(4.5, 5.8)	0.638
2hPG (mmol/L)	7.1(5.9, 9.1)	6.8(5.3, 8.6)	7.5(6.2, 9.6)	0.003	7.5(6.0, 9.2)	7.4(6.4, 10.8)	0.169
FINS (mU/L)	9.4(5.4, 16.7)	5.2(3.9, 8.2)	12.2(7.6, 20.3)	<0.001	12.8(8.5, 18.0)	11.2(6.0, 28.0)	0.505
HbA1c (%)	5.6(5.3, 6.2)	5.5(5.2, 5.9)	5.8(5.4, 6.5)	<0.001	5.6(5.3, 6.2)	6.1(5.6, 6.9)	0.001
HOMA-IR	1.97(1.12, 3.57)	1.11(0.71, 1.78)	2.72(1.60, 5.12)	<0.001	2.73(1.84, 4.02)	2.66(1.24, 6.36)	0.505
TG (mmol/L)	2.05(1.42, 3.10)	1.37(0.96, 2.12)	2.34(1.78, 3.33)	<0.001	2.36(1.78, 3.38)	2.30(1.77, 3.05)	0.755
TC (mmol/L)	5.01(4.22, 5.66)	5.06(4.22, 5.61)	4.98(4.23, 5.7)	0.722	4.92(4.25, 5.66)	5.07(4.25, 5.66)	0.714
HDL-C (mmol/L)	0.97(0.78, 1.29)	1.28(0.91, 1.57)	0.89(0.74, 1.1)	<0.001	0.88(0.73, 1.16)	0.91(0.75, 1.06)	0.984
LDL-C (mmol/L)	2.93(2.26, 3.54)	3(2.53, 3.64)	2.88(2.17, 3.46)	0.125	2.9(2.17, 3.53)	2.76(2.13, 3.4)	0.685
UA (mmol/L)	0.38(0.31, 0.44)	0.33(0.27, 0.40)	0.40(0.34, 0.46)	<0.001	0.40(0.34, 0.46)	0.40(0.34, 0.45)	0.606
Alb (g/L)	43(41, 45)	43(41, 44)	43(41, 45)	0.488	-	-	-
ALT (U/L)	28(18, 47)	21(14, 34)	31(20, 52)	<0.001	-	-	-
AST (U/L)	25(19, 36)	23(17, 30)	27(20, 43)	<0.001	-	-	-

Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; ALF, advanced liver fibrosis; MetS, metabolic syndrome; BMI, body mass index; IFG/IGT, impaired fasting glucose/ impaired glucose tolerance; T2DM, type 2 diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; DBP, diastolic blood pressure; SBP, systolic blood pressure; FPG, fasting plasma glucose; 2hPG, 2-hour plasma glucose; FINS, fasting insulin; HbA1c, glycated hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine transaminase.

no significant difference in the rate of sex hormone replacement therapy. The prevalence of CAI in the MAFLD group was significantly higher than that in the non-MAFLD group (93.9% vs 83.5%, $P = 0.010$), but the rates of glucocorticoid replacement therapy and daily hydrocortisone dose were similar between the two groups, with the median dose of 20 mg/day. Hypothyroidism was more prevalent in the MAFLD group (92.6% vs 83.5%, $P = 0.029$), but no significant difference was found in the rate of levothyroxine (L-T4) use. Free thyroxine (FT4) levels were significantly lower in the MAFLD group compared to the non-MAFLD group (11.90 pmol/L vs 14.20 pmol/L, $P = 0.003$), while free triiodothyronine (FT3) levels were similar. Insulin-like growth factor 1 (IGF-1) levels were not significantly different between the groups, but the prevalence of reduced IGF-1 was higher in the MAFLD group (52.1% vs 35.4%, $P = 0.015$). Prolactin (PRL) levels were significantly lower in patients with MAFLD compared to those without MAFLD [17.16 (8.27, 41.8) vs 27.84(11.8, 51.12) ng/mL, $P = 0.026$]. The prevalence of central diabetes insipidus (CDI) was also higher in the MAFLD group, though the difference was not statistically significant (84.7% vs 74.7%, $P = 0.061$) (Table 3).

The results of the multivariable logistic regression analysis for risk factors associated with MAFLD are presented in Table 4. After adjusting for age, postoperative follow-up duration, gender, PRL, FT4, CAI, reduced IGF-1, as well as hypogonadism, BMI (OR = 1.51,95% CI1.33–1.72, $P < 0.001$) was independently associated with MAFLD.

Table 3 Endocrine Functions and Treatment in Patients With and Without MAFLD and ALF

Variables	Total (N = 242)	Non-MAFLD (N = 79)	MAFLD (N = 163)	*P*	Non- ALF (N = 110)	ALF (N = 53)	*P*
Hypogonadism, n (%)	227(93.8)	69(87.3)	158(96.9)	0.008	107(97.3)	53(100.0)	0.717
Male	120(94.5)	31(91.2)	89(95.7)	0.384	61(96.8)	30(100.0)	>0.999
Female	107(93.0)	38(84.4)	69(98.6)	0.006	46(97.9)	23(100.0)	>0.999
Sex steroid replacement, n (%)	113(56.8)	34(55.7)	79(57.2)	0.887	59(55.1)	20(39.2)	0.625
Male	86(71.7)	25(80.6)	61(68.5)	0.250	44(72.1)	17(56.7)	0.592
Premenopausal female	27(34.2)	9(30.0)	18(36.7)	0.629	15(39.5)	3(27.3)	>0.999
CAI, n (%)	219(90.5)	66(83.5)	153(93.9)	0.010	100(90.9)	53(100.0)	0.023
Glucocorticoid replacement, n (%)	210(95.9)	63(95.5)	147(96.1)	>0.999	95(95.0)	52(98.1)	0.665
Daily hydrocortisone dose, mg	20(20)	20(20)	20(20)	0.579	20(15, 20)	20(20)	<0.001
Hypothyroidism, n (%)	217(89.7)	66(83.5)	151(92.6)	0.029	100(90.9)	51(96.2)	0.340
L-T4 replacement, n (%)	214(98.6)	66(100.0)	148(98.0)	0.556	98(98.0)	50(98.0)	>0.999
Reduced IGF-1, n (%)	113(46.7)	28(35.4)	85(52.1)	0.015	55(50.0)	30(56.6)	0.429
CDI, n (%)	197(81.4)	59(74.7)	138(84.7)	0.061	91(82.7)	47(88.7)	0.323
FT3, pmol/)	4.11(3.29, 4.94)	3.99(3.36, 5.03)	4.14(3.28, 4.90)	0.770	4.25(3.34, 4.98)	3.85(2.96, 4.68)	0.045
FT4, pmol/L	12.49(9.59, 15.05)	14.2(10.3, 16.6)	11.9(9.42, 14.2)	0.003	12.00(9.76, 15.05)	11.2(8.28, 13.66)	0.077
IGF-1, μg/L	87.0(61.0, 117.0)	85.5(63.0, 132.0)	87.6(58.2, 109.0)	0.179	96.0(70.7, 113.0)	63.5(47.4, 87.6)	<0.001
PRL, ng/mL	20.44(8.99, 44.90)	27.84(11.8, 51.12)	17.16(8.27, 41.80)	0.026	17.76(8.99, 43.29)	16.7(4.66, 34.56)	0.099

Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; ALF, advanced liver fibrosis; CAI, central adrenal insufficiency; L-T4, levothyroxine; IGF-1, insulin-like growth factor 1; CDI, central diabetes insipidus; FT3, free triiodothyronine; FT4, free thyroxine; PRL, prolactin.

Table 4 Multivariate Regression Analysis of Risk Factors for MAFLD

Variables	OR	95% CI	*P*	VIF
Age at follow-up, years	0.99	0.97–1.02	0.651	1.09
Postoperative follow-up, months	1.04	1.00–1.09	0.064	1.80
Female	0.83	0.39–1.74	0.613	1.25
BMI (kg/m^2)	1.51	1.33–1.72	<0.001	1.11
PRL, ng/mL	1.00	0.99–1.01	0.576	1.28
FT4, pmol/L	0.97	0.90–1.05	0.475	1.08
Reduced IGF-1	0.57	0.27–1.20	0.139	1.11
CAI	3.48	0.75–16.07	0.111	1.17
Hypogonadism	2.70	0.80–9.11	0.109	1.20

Abbreviations: OR, odds ratio; CI, confidence interval; VIF, variance inflation factor; BMI, body mass index; PRL, prolactin; FT4, free thyroxine; IGF-1, insulin-like growth factor 1; CAI, central adrenal insufficiency.

ALF in Patients with MAFLD

Among the 163 patients with MAFLD, ALF was diagnosed in 53 based on the FIB-4 score (FIB-4 ≥ 1.3), with a proportion of 32.5% (95% CI 25.8–40.0%). The median FIB-4 score was 1.73 in the ALF group and 0.81 in the non-ALF group. AST levels in the ALF group were significantly higher than those in the non-ALF group [39(24, 77) vs 25 (19, 36) U/L, $P < 0.001$]. Among the 53 patients with ALF, 13(24.5%) and 6(11.3%) had AST above two and three times the upper limit of the reference range. However, there was no significant difference in ALT and albumin (Alb) levels between the two groups (Table 5).

Further comparisons of clinical characteristics were made between the ALF and non-ALF groups, with results detailed in Tables 1–3. The ALF group was significantly older than the non-ALF group [54(41, 61) vs 40(30, 50) years, $P < 0.001$]. No significant differences were found in gender, preoperative and postoperative durations, recurrence of craniopharyngioma, tumor location, size, or pathological subtype between the two groups (Table 1). The prevalence of hypertension was significantly higher in the ALF group compared to the non-ALF group (41.5% vs 20.0%; $P = 0.004$).

Table 5 Liver Function Indices in Patients With and Without ALF

Variables	Non- ALF (N = 110)	ALF (N = 53)	*P*
FIB-4	0.81(0.61, 0.98)	1.73(1.48, 2.30)	<0.001
ALT (U/L)	31(19, 52)	37(21, 56)	0.214
ALT≥ULN, n (%)	37(33.6)	23(43.4)	0.226
ALT≥2ULN, n (%)	13(11.8)	10(18.9)	0.226
ALT≥3ULN, n (%)	3(2.7)	5(9.4)	0.114
AST (U/L)	25(19, 36)	39(24, 77)	<0.001
AST≥ULN, n (%)	20(18.2)	25(47.2)	<0.001
AST≥2ULN, n (%)	3(2.7)	13(24.5)	<0.001
AST≥3ULN, n (%)	1(0.9)	6(11.3)	0.005
Alb (g/L)	43(41, 45)	42(40, 46)	0.251

Abbreviations: ALF, advanced liver fibrosis; FIB-4, fibrosis index-4; AST, aspartate aminotransferase; ALT, alanine transaminase; Alb, albumin; ULN, upper limit of normal.

Although the prevalence of T2DM and prediabetes was similar, HbA1c levels were higher in the ALF group [6.1(5.6, 6.9) vs 5.6(5.3, 6.2) %, $P = 0.001$]. However, no significant differences were observed in other glucose metabolism parameters (FPG, 2hPG, FINS, HOMA-IR) between the two groups. Additionally, no significant differences were found in BMI, TG, TC, LDL-C, HDL-C, and UA between the two groups (Table 2).

All patients with ALF had hypogonadism, the prevalence of which was 97.3% in patients with non-ALF. The rate of sex hormone replacement was lower in the ALF group compared to the non-ALF group, although the difference was not significant (39.2% vs 55.1%; $P = 0.625$). The prevalence of CAI was significantly lower in the non-ALF group compared to the ALF group (90.9% vs 100%; $P = 0.023$). Although there was no significant difference in the rate of glucocorticoid replacement, the average daily hydrocortisone dose was significantly higher in the ALF group than in the non-ALF group, which was 20.66 mg and 16.63 mg respectively [20(20, 20) vs 20(15, 20) mg, $P < 0.001$]. No differences were observed in the prevalence of hypothyroidism and rate of L-T4 use between the two groups, but FT3 and FT4 levels in the ALF group were lower than those in the non-ALF group (Table 3). IGF-1 levels were significantly lower in the ALF group compared to the non-ALF group [63.5 (47.4, 87.6) vs 96.0 (70.7, 113.0) μg/L; $P < 0.001$]. No differences were observed in PRL levels or the prevalence of CDI between the groups (Table 3).

To identify the risk factors for ALF in patients with MAFLD, we performed multivariable logistic regression analysis, including factors with significant differences ($P < 0.05$) between the groups and adjusting for postoperative follow-up duration and gender. The results are presented in Table 6. The analysis revealed that hypertension (OR = 2.33, 95% CI 1.04–5.20; $P = 0.040$), HbA1c (OR = 1.34, 95% CI 1.01–1.78; $P = 0.044$), daily hydrocortisone dose (OR = 1.08, 95% CI 1.01–1.15; $P = 0.026$), and IGF-1 (OR = 0.99, 95% CI 0.97–0.99; $P = 0.011$) were independently associated with the presence of ALF in MAFLD patients.

Table 6 Multivariate Regression Analysis of Risk Factors for ALF

Variables	OR	95% CI	*P*	VIF
Postoperative follow-up, months	1.00	0.97–1.04	0.988	1.08
Male	1.07	0.49–2.04	0.872	1.08
Hypertension	2.33	1.04–5.20	0.040	1.05
HbA1c	1.34	1.01–1.78	0.044	1.10
Daily hydrocortisone dose, mg	1.08	1.01–1.15	0.026	1.18
IGF-1, μg/L	0.99	0.97–0.99	0.011	1.21
FT3, pmol/L	0.91	0.72–1.14	0.154	1.05

Abbreviations: OR, odds ratio; CI, confidence interval; VIF, variance inflation factor; HbA1c, glycated hemoglobin A1c; IGF-1, insulin-like growth factor 1; FT3, free triiodothyronine.

Discussion

In this cross-sectional study, we found that the prevalence of MAFLD in postoperative craniopharyngioma patients was 67.4%, which is significantly higher than the recently reported prevalence of 32.9% general Chinese adult population.[34] The prevalence of advanced fibrosis has been reported to be 0.9–2% in the general population and 6–19% in patients with T2DM patients and MAFLD.[28] In our study, 32.5% of AOCP patients with MAFLD were at risk of ALF. Previous investigations of MAFLD in craniopharyngioma patients have been limited to small-scale studies and case reports and predominantly focused on pediatric-onset cases.[26,27,35,36] Hoffmann et al reported a 50% prevalence of MAFLD in 19 children with treated craniopharyngiomas, with approximately one-third presenting with severe fatty liver.[26] Another study involving 75 patients with childhood-onset craniopharyngiomas showed that 68% had transaminase abnormalities, and 47% were confirmed to have fatty liver by imaging.[27] A pediatric patient with craniopharyngioma was reported to be diagnosed with MAFLD two years after surgery, developed advanced cirrhosis three years later, and eventually died of liver failure.[35] Similarly, Dai et al described a child with recurrent craniopharyngioma who developed advanced cirrhosis seven years after being diagnosed with MAFLD one year post-surgery.[35] Our findings in this study, together with those from previous studies above, indicated that MAFLD is a significant comorbidity in craniopharyngioma patients and tends to progress rapidly, which warrants adequate attention in the management of patients with craniopharyngioma.

MAFLD is considered a hepatic manifestation of metabolic syndrome and is closely associated with obesity, insulin resistance, and dyslipidemia.[19,20] Additionally, hormone deficiencies have been implicated in MAFLD pathogenesis. The prevalence of MAFLD in patients with hypopituitarism due to various causes has been reported to range from 50.5% to 77%.[37–39] Consistently, in our cohort, patients with MAFLD exhibited worse metabolic profiles and higher frequencies of pituitary hormone deficiencies. However, multivariate regression analysis indicated that only BMI was independently associated with MAFLD, while pituitary function was not. A previous study at our center had shown that approximately 40% of AOCP patients got significant weight gain (>5%) after a median follow-up of 12 months after surgery,[40] and after a longer median follow-up of 100 months, this ratio is up to 65%.[9] This weight gain is mainly related to hypothalamic damage, which leads to impaired regulation of appetite and energy metabolism, with patients experiencing overeating and reduced energy expenditure.[15,41] Therefore, active measures should be taken to control postoperative weight gain in AOCP patients to reduce the risk of related metabolic complications such as MAFLD.

In patients with fatty liver disease, the presence of advanced liver fibrosis is associated with a higher risk of liver-related morbidity and all-cause mortality.[28,42] Early identification and prevention of ALF are thus crucial for MAFLD management. Liver biopsy is the "gold standard" for diagnosing ALF, but its invasiveness and high cost mean that it is not widely used in clinical practice. Some non-invasive scoring models based on serum indicators have demonstrated good diagnostic value. The Fibrosis-4 (FIB-4) index, in particular, is widely recommended for initial ALF screening in MAFLD patients, with FIB-4 $\geq$ 1.3 and FIB-4 $\geq$ 2.67 indicating moderate and high risk, respectively,[28–31] and FIB-4 $\geq$ 1.3 is associated with high risk of liver cancer.[32] In our study, no patients underwent liver biopsy; hence, FIB-4 was used to assess ALF risk. The results showed that 32.5% of MAFLD patients had an intermediate to high risk of ALF. However, this proportion may be underestimated, as some patients were taking enzyme-lowering drugs. Therefore, further studies employing more accurate methods, such as vibration-controlled transient elastography (VCTE) or magnetic resonance elastography (MRE), are needed to assess ALF prevalence.

Multivariate logistic regression analysis revealed that HbA1c was positively correlated with ALF, consistent with previous findings in patients with NAFLD.[43–45] Alexopoulos et al demonstrated that each 1% increase in mean HbA1c was associated with a 15% higher likelihood of advancing to a higher fibrosis stage.[45] Compared with patients with HbA1c $\leq$ 5.4%, HbA1c level of 6.5–7.4% group was significantly associated with advanced fibrosis.[44] A prospective study in Japan showed that reducing HbA1c levels were associated with improved liver fibrosis, independent of age, sex, and BMI.[43] Hyperglycemia is known to promote hepatic fibrosis through multiple mechanisms, including inducing hepatic stellate cell proliferation[46] and stimulating the expression of connective tissue growth factor (CTGF), a key molecule in liver fibrosis progression.[47] Therefore, well-controlled glycemia may help to slow the progression of liver fibrosis in craniopharyngioma patients.

In a cross-sectional study of 5362 participants, researchers also used an FIB-4 to assess the severity of liver fibrosis in patients with MAFLD and found that both normotensive and prehypertensive patients were more likely to have a low fibrosis risk when compared with hypertensive patients.[48] A prospective study based on liver biopsy also demonstrated that hypertension was an independent predictor of worsening fibrosis.[49] Consistent with these findings, our study suggested that hypertension is an independent risk factor for ALF in AOCP patients. In addition to insulin resistance, the overactivation of the renin-angiotensin-aldosterone system (RAAS) in hypertensive patients is believed to contribute to liver fibrosis progression.[50–52] Angiotensin II (AngII), the primary effector of RAAS signaling, promotes a pro-oxidant and pro-inflammatory environment by inhibiting liver mitochondrial function, triggering oxidative stress, activating pro-inflammatory factors such as TNF-α and IL-6, and activating hepatic stellate cells.[53,54]

In our study, ALF was independently associated with IGF-1 levels (OR = 0.99, $P = 0.011$). Several studies have shown that GH/IGF-1 deficiency or loss of function is closely related to MAFLD. Nishizawa et al reported that the prevalence of MAFLD in adult patients with growth hormone deficiency (GHD) was significantly higher than that in age-, sex-, and BMI-matched populations (77% vs 12%), with the severity of fatty liver independently and negatively correlated with serum GH levels.[39] Moreover, recombinant human GH (rhGH) replacement therapy in GHD patients has been shown to reduce serum liver enzyme and fibrosis marker concentrations and significantly improve steatohepatitis.[55,56] Studies revealed that GH and IGF-1 prevent and delay the development of MAFLD through a variety of mechanisms including increasing insulin sensitivity, decreasing liver fatty acid uptake and synthase,[57] inhibiting liver inflammatory response, oxidative stress,[58] and inhibiting liver fibrosis by reducing collagen production and inducing hepatic stellate cells senescence.[59,60] However, since over 90% of circulating IGF-1 is synthesized in the liver, chronic liver diseases, including MAFLD, may lead to decreased GH receptor expression, GH resistance, and reduced hepatic IGF-1 synthesis, thereby lowering IGF-1 levels.[61] This suggests a potential bidirectional relationship between low IGF-1 levels and ALF. Further prospective studies are needed to determine whether low IGF-1 is a major determinant of ALF in postoperative AOCP patients.

Additionally, our study found that the daily hydrocortisone dose was negatively associated with ALF in patients with MAFLD. Few studies have explored the relationship between adrenal insufficiency and its related replacement therapy with MAFLD. One study involving 39 patients with Cushing's disease in sustained biochemical remission and 79 patients who had undergone surgery for non-functional pituitary adenoma showed that the average daily dose of hydrocortisone was positively correlated with the fatty liver index, and patients with fatty liver had a significantly higher daily hydrocortisone dose than those without (21.05 ± 5.9 mg vs 17.9 ± 4.4 mg, $P = 0.01$).[62] Excess glucocorticoids promote insulin resistance and increase adipose tissue lipolysis while decreasing hepatic fatty acid β-oxidation, leading to hepatic fat accumulation.[63] Notably, in patients with adrenal insufficiency receiving oral glucocorticoid replacement, glucocorticoids first enter the portal vein system, resulting in direct liver exposure to higher glucocorticoid levels, which may exacerbate hepatic steatosis.[64] However, evidence regarding the impact of glucocorticoids on steatohepatitis and liver fibrosis remains limited and controversial. Adenovirus-mediated overexpression of the glucocorticoid receptor (subtype β) has been shown to increase TNF-α levels and shift macrophages to the M1 phenotype, which are associated with hepatic inflammation and fibrosis.[63,65] Ahmed supposed that local cortisol in the liver of patients with steatohepatitis may inhibit inflammation and delay disease progression.[66] Therefore, the effects of different glucocorticoid doses on liver fibrosis in MAFLD patients need to be further studied.

Based on our findings in this research, regular screening and evaluation of MAFLD and ALF are recommended for postoperative AOCP patients. Given the lack of effective treatments for MAFLD, strategies such as controlling weight gain, maintaining an optimal level of blood glucose and blood pressure, appropriate hormone replacement, and avoiding excessive glucocorticoids should be prioritized to prevent and delay MAFLD onset and progression.

Some limitations of our study should be acknowledged. First, the diagnosis of hepatic steatosis was based on ultrasound, which is less sensitive in obese patients and those with severe hepatic steatosis, and the results may be influenced by the examiner and equipment. Second, ALF was assessed using the non-invasive FIB-4 model, which has varying sensitivity and specificity at different cut-off points. Additionally, patients taking enzyme-lowering drugs were not excluded, potentially leading to an underestimation of ALF prevalence. Finally, as a single-center cross-sectional study, our design inevitably introduces selection bias and precludes the direct determination of causal relationships

between MAFLD and ALF and their associated risk factors. Future multi-center, prospective studies employing more accurate assessment methods are warranted.

Conclusion

MAFLD is a significant comorbidity in postoperative AOCP patients and has a high risk of ALF. The presence of MAFLD is closely related to BMI, while ALF is significantly associated with hypertension, HbA1c levels, IGF-1 levels, and daily hydrocortisone dose.

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Disclosure

The authors report no conflicts of interest in this work.

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