Percutaneous Transhepatic Flexible Ureteroscope-Guided Frequency-Doubled Dual Pulse ND:YAG Laser Lithotripsy for Refractory Choledocholithiasis

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Technical advance

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Abstract

Objectives

To evaluate the safety and efficiency of percutaneous transhepatic flexible ureteroscope-guided frequency-doubled dual pulse ND:YAG laser lithotripsy (PTFU-FREDDY) for refractory choledocholithiasis.

Methods

From December 2017 to October 2018, 24 refractory choledocholithiasis patients with large common bile duct stones, anatomic variations, multiple stones or stones at difficult locations (impacted, above a biliary stricture) were admitted to two centers. Four patients were considered intolerant to surgery or [endoscopic retrograde cholangiopancreatography](#) (ERCP), and 2 had ERCP failure, the others refused. All patients underwent PTFU-FREDDY. Clinical success rate, recurrence of calculus, laser safety, and related complications, such as fever, haematoma, and local thermal damage were recorded.

Results

Patients' mean age was 66.0 ± 12.1 (43-89) years. Sex ratio was 1:1.2 (male: female). The mean diameter of stones was 21.8 ± 2.4 mm. All stones were successfully broken and pushed into the duodenum. The mean lithotripsy frequency and procedure time of Bilirubin stones was higher than cholesterol stones, and the mixed were in middle $P < 0.01$. One patient (4.2%) had haemobilia, requiring immediate transarterial embolisation with 100mg 300-500um gelatin sponge particles. No pancreatitis, sepsis, or serious local thermal damage, such as bile duct perforation, was observed. The rates of Grade A/B of fever, abdominal pain, nausea, and vomiting were 12.5%, 12.5%, 8.3%, and 4.2% during follow-up, respectively. The recurrence was none at the endpoint of 12 months.

Conclusion

PTFU-FREDDY is a safe and effective alternative treatment for refractory choledocholithiasis, especially when traditional treatments fail or are difficult to perform.

Key Points

- Percutaneous transhepatic flexible ureteroscope-guided frequency-doubled dual pulse ND:YAG laser lithotripsy was a safe and effective alternative treatment for refractory choledocholithiasis.
- The mean lithotripsy frequency for FREDDY of different types of common bile duct stones were different.
- The lithotripsy model of 120 mJ single pulse and 5 Hz of FREDDY was enough for most common bile duct stones.

Introduction

The common bile duct stones (CBDS) are present in 10%-20% of individuals with symptomatic cholecystolithiasis¹. Clinical presentations that warrant investigation for CBDS include right upper quadrant or epigastric pain, especially if accompanied with jaundice and/or fever. In patients with acute pancreatitis, CBDS should also be considered, because gallstones or intrahepatic stones also move to the CBD². Laparoscopic duct exploration³ and ERCP¹, supplemented by endoscopic papillary balloon dilation with prior sphincterotomy⁴, mechanical lithotripsy or cholangioscopy⁵, are considered to be the first-line treatments with high success rates in moving CBDS. In patients in whom the previously described techniques failed or are difficult, percutaneous transhepatic balloon dilation (PTPBD)⁶ or combination with basket retrieval⁷ is considered an alternative. Regardless of the type of method, the procedure may be difficult to perform in patients with large CBDS, anatomic variation, multiple stones, and stones at difficult locations (impacted, above a biliary stricture)⁸. With the widespread use of laser lithotripsy for urinary calculus⁹, Himanshu Verma et al. first reported a novel technical method, flexible ureteroscope-guided laser lithotripsy to successfully remove the CBDS after other methods failed¹⁰. The present study first tried to combine PTPBD with novel laser lithotripsy-frequency-doubled dual pulse ND:YAG laser lithotripsy (FREDDY)¹¹ to manage these complicated cases, considering that it could shorten lithotripsy time, improve stone removal rate, and help avoid unnecessary surgeries. This study aimed to evaluate the efficacy and safety of PTPBD combined with FREDDY, which were renamed as percutaneous transhepatic flexible ureteroscope-guided frequency-doubled dual pulse ND:YAG laser lithotripsy (PTFU-FREDDY), for removal of refractory CBDS in patients with large CBDS(>15mm), anatomic variations, multiple stones, and lesions at difficult locations (impacted, above a biliary stricture).

Materials And Methods

Patients

This retrospective observational study was approved by the ethics committee of the Second Hospital of Shandong University. At the beginning of this retrospective analysis, the patients who could be contacted provided written informed consent; patients who could not provide informed consent were excluded from the study.

The inclusion criteria were as follows: trans-abdominal ultrasound combined with enhanced computed tomography (CT) or magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS)-confirmed CBDS(Fig 1); refractory CBDS including large CBDS, anatomic variations, multiple stones or stones at difficult locations (impacted, above a biliary stricture); patients between 18 and 90 years old; the Karnofsky performance score is no less than 70.

Exclusion criteria were severe as follows: coagulation disorder (prothrombin time prolonged more than 6s) that was difficult to correct; cachexia or other serious organ disorders with life expectancy of <3 months; concurrent multiple intrahepatic calculi; pregnancy or Breast-Feeding Women.

The study analysed a total of 106 patients with CBDS who were admitted to two centers from December 2017 to October 2018. Refractory CBDS was detected in 30 patients, of these, 5 patients concurrent multiple intrahepatic calculi. Of the residual 25 patients, one was diagnosed with local advanced gastric carcinoma whose life expectancy was considered to be less than 3 months who accepted biliary drainage alone. Therefore, there were 24 eligible patients.

Procedure

PTFU-FREDDY

Pre-procedural preparations included the administration of sensitive antibiotics (levofloxacin or cephalosporin) and intravenous anaesthesia (dexmedetomidine or fentanyl). Percutaneous transhepatic biliary access was obtained, preferably through right-sided access, and a 12Fr sheath (Olympus, Japan) was used with a safety wire through the ampulla(Fig 2A). After dilation of the papilla with a 40mm x 10mm balloon(Blat, France), the 9.8Fr flexible ureteroscope (Olympus, Japan) with an U100plus laser fiber (W.O.M, German) in its biopsy hole was inserted into the bile duct tree through the 12-F sheath(Fig 2B). The flexible ureteroscope was maneuvered until its terminal end was against the CBDS (Fig 2C). Laser lithotripsy at 120 mJ single pulse and 5 Hz was chosen to break the stone under the scope, although the setting of 160 mJ and 10 Hz was more efficient for stiff and large stones(Fig 2D). During laser lithotripsy, the bile was replaced by a saline solution, because fluid was required for the generation of shock waves, and plasma was formed by the 532-nm laser (Fig 2E). Repeat lithotripsy was performed until all fragments were small enough (mostly <6 mm) to get through the papilla. The access site was flushed again through the sheath to ensure all small fragments flowed to the duodenum. Repeat scope check and cholangiography were performed to ensure all stones were pushed into the duodenum and no residual calculi were left. A 10.2-F external drainage catheter was placed into the CBD through the existing access to prevent pancreatitis and reserve a channel for repeat PTPBD when residual calculi occurred, and was removed if no residual calculi were observed during the repeat cholangiography 1 week later(Fig 2F).

Concurrent gallbladder stones

For concurrent gallbladder stones, patients were treated with routine PTFU-FREDDY to deal with CBD stones, followed by a 1 week later percutaneous transcyst access PTFU-FREDDY, which was performed as before.

Stone analysis

The diameter of stone was determined according to the cholangiography imaging, combined with contrast CT or MRCP when difficult. Stone chemical and structural analyses were performed using the Attenuated Total internal Reflectance Fourier Transform Infrared spectroscopy (ATR-FTIR, Spectrum 100 equipped with an attenuated total reflection sampling universal accessory, Perkin-Elmer, USA). The reflectance mode was selected.

Post-procedural management

Liver-protecting drugs and the second generation cephalosporin antibiotics, might be changed according to susceptibility testing, were administered for 1 week. Oral ursodeoxycholic acid (250 mg, Losan Pharma GmbH, Germany) was recommended for all patients after the procedure. The prescribed dose was 250 mg three times a day⁶. Routine analysis of blood, liver function, and serum amylase was performed. One week after the procedure, repeat cholangiography via the existing drainage catheter was performed, and the catheter was removed when no residual calculi were present; otherwise, a repeat PTPBD was performed. Somatostatin (3mg q12h) was continually recommended to prevent choleperitonitis for at least 24 hours from 1 h before the drainage catheter was removed¹². During repeat cholangiography, if the contrast agent overflows to the enterocoelia, access coil embolisation was recommended to prevent choleperitonitis.

Follow-up

All patients were generalizational followed for 1 year at 3-month intervals and underwent clinical assessment, physical examination, laboratory test, and imaging evaluation (Fig 3). For pure cholesterol stones, ultrasound was the first choice, and MRCP was recommended. Complete absence of CBDS was the optimal result and referred to as technical success, and the secondary result was medical success, which was defined as the absence of symptoms regardless of the presence or absence of residual stones.

Statistical analysis

All statistical analyses were performed using SPSS Statistics 24×0 (IBM, USA). Categorical variables were presented as number and percentage. The normal distribution of continuous variables was evaluated by Kolmogorov-Smirnov test. Continuous data with normal distribution were expressed as

mean±standard deviation; if with non-normal distribution, data were expressed by the median and range. Paired t-tests were used to compare the indices at 1 week and 1 month after PTPBD with those before the procedure. A *P*-value <0.05 was considered statistically significant.

Results

Population information

Among the consecutive 106 patients with CBDS admitted during the study period, 24 patients were included, and the other patients underwent conventional PTPBD, ERCP or laparoscopic common bile duct exploration and stone extraction. Sex ratio was 1:1.2 (male: female), and the mean age was (66.0±12.1, 43-89) years. Among all patients, 4 were considered intolerant to ERCP or surgery because of cardiopulmonary insufficiency, anaesthesia contraindication, upper gastrointestinal stenosis, acute pharyngitis or tonsillitis. Two patients had ERCP failure because of impacted stones with anatomic variation, and the other 18 refused ERCP or surgery. The mean diameter of the biggest stone was (21.8±2.4) mm, which was determined according imaging or cholangiography. The reasons for stones difficult to removal included smaller common bile duct/stone diameter ratio (29.2%), strictures distal to the stones(20.8%), large diameter(20.8%), impacted stone(16.7%) and anatomic variations(12.5%). The demographic and baseline clinical characteristics are presented in Table 1.

Lithotripsy

All patients underwent PTFU-FREDDY. The most common laser lithotripsy model (18/24,75%) was 120 mJ single pulse and 5 Hz. The mean frequency of Cholesterol, mixed, Bilirubin and all types stones were 776.2, 956.5, 1550.4 and 1240.5 (*P*<0.01), respectively. The mean procedure time in Cholesterol, mixed, Bilirubin and all types stones were 65.0±9.2 min, 82.5±3.5 min, 104±13.8 min, 94.3±20.5 min (*P*<0.05). Complete stone fragmentation using PTFU-FREDDY was achieved in all 24 patients. Treatment information is shown in Table 2.

Laboratory test changes

The changes in the laboratory data pre- and post-intervention are shown in Table 3. Alanine transaminase, total bilirubin (TBIL), and white blood cell (WBC) count normalised after the procedure. There was no significant statistical difference in the serum amylase and haemoglobin levels before and after the procedure (*P*>0.05).

Complication

All complications details per SIR standards are shown in Table 4. One patient had haemobilia, because of the formation of bile duct and hepatic artery fistula during the 12-F 35-cm-long sheath insertion into the intrahepatic bile duct. Immediate transcatheter arterial embolisation was performed with 100mg 300-500um gelatin sponge particles (Gelpart; Nippon Kayaku, Tokyo, Japan). No other major complications, such as bile duct or duodenum perforation and procedure-related perioperative death, occurred.

According to the SIR guidelines, the occurrence rate of Grade A/B complications of fever, abdominal pain, nausea, and vomiting were 12.5% (3/24), 12.5% (3/24), 8.3%(2/24), and 4.2%(1/24), respectively. Pancreatitis severer than Grade C was not observed, and only one patient had increased amylase levels at 3 days after the procedure with normal imaging findings, which normalised after somatostatin treatment. No cholangitis and stone recurrence was observed at the endpoint of 12 months.

Discussion

Complete stone removal by using traditional, less invasive methods such as [endoscopic Retrograde Cholangiopancreatography](#)(ERCP), endoscopic papillary balloon dilation (EPBD), and percutaneous transhepatic balloon dilation (PTPBD) were challenging in refractory choledocholithiasis, especially when CBDS bigger than 15mm was impacted. The authors showed their experiences of the advantages of combination of FREDDY and PTPBD to manage these complicated cases and verified its efficacy and safety in the present study.

European Society of Gastrointestinal Endoscopy (ESGE) recommended stone extraction for all patients with CBDS, symptomatic or not, who were fit enough to tolerate the intervention¹³. Multiple studies showed that larger stones were inversely correlated with successful biliary clearance during ERCP¹⁴. Biliary sphincterotomy with a balloon dilation time of 30 s could significantly increase stone extraction and reduce the frequency of post-ERCP pancreatitis^{15,16}. Mechanical bile stone lithotripsy on difficult bile duct stones could produce around 90% successful rate with minimal complications.^{17,18} But a randomized study showed that Mechanical lithotripsy had a significantly lower stone clearance rate in the first session compared with laser lithotripsy (63% vs. 100%; *P*< 0.01)¹⁹. Extra-corporeal shock wave lithotripsy (ESWL) also could be an alternative in difficult common bile duct stones (DCBDS), with a success rate greater than 90%, and a recurrence rate of 20% over a median follow-up of 4 years²⁰. stenting for immediate and definitive stone treatment²¹, papillary large balloon dilation²²

In 1986, Hochberger et al. reported performing the first successful endoscopic retrograde laser lithotripsy in humans using a flash lamp-pulsed millisecond meodymium:YAG laser.²³ With the development of microsecond-pulsed dye laser systems that allowed the formation of plasma-induced shock waves, laser lithotripsy has become a commonly accepted modality for the treatment of difficult CBDS.

Most studies on laser lithotripsy for CBDS removal involved endoscopic guidance, but sometimes it might be difficult to perform this procedure. Himanshu Verma et al. reported a case of a 91-year-old woman with a medical history of gallstone ileus and prior ERCP who experienced several failed treatments,¹⁰ such as ERCP with spyglass cholangioscopy, Holmium laser lithotripsy, and cholangioscopy with percutaneous transhepatic cholangiography access to help position the stone for laser lithotripsy, for removing large CBDS; finally, the stone was successfully removed through percutaneous transhepatic cholangiography combined with flexible ureteroscope-guided laser lithotripsy.

The present study presented experience of percutaneous transhepatic flexible ureteroscope-guided FREDDY laser lithotripsy for refractory choledocholithiasis with a technical successful rate of 100%, low incidence of haemobilia which need correction, and absence of other Grade C or severer procedure-related adverse effects, such as perioperative death or intestinal and bile duct perforation.

The percutaneous access to the biliary tree was established by a 12-F 35-cm-long sheath, which was specifically suitable for the flexible ureteroscope to get through. One laser-related instrument complication was ureteroscope damage, which occurred during the initial application of the technique. Accurate positioning, complete view of the working area, and close coordination of ureteroscope and laser were useful to avoid this.

The selected pulse energy usually was 120 mJ, and the pulse frequency was 5 Hz. Higher energy and frequencies could crush the stones more efficiently, but these could shorten the service life. The usual selection was enough, except for stiff cholelithiasis. In addition to impact stones,²⁴ the composition of choledocholithiasis was another influencing factor of lithotripsy. In this study, the ratio of bilirubin stones was significantly higher than usual,²⁵ which usually require more lithotripsy frequency or higher energy and pulse frequency because of its rigidity.

For refractory choledocholithiasis, in the present study, none pancreatitis occurred. The main reason for this might be the smaller size of stones after lithotripsy, and a small-sized balloon might be capable of pushing the stones into the duodenum.

Although several studies have shown that endoscopic sphincterotomy plus balloon dilation was safe and effective for large CBDS removal, owing to the improvements of laser technology, more and more endoscopists preferred lithotripsy plus balloon dilation.²⁶⁻²⁸ Peroral cholangioscopy-guided lithotripsy achieved a technical success rate of 80%-86% in a single procedure, and was significantly more likely indicated for stones ≤ 30 mm in size than for stones with >30 mm in size.^{29,30} In the present study, no CBDS had a size of ≥ 30 mm, and the technical success rate was 100%. However, there were no cases of recurrence at 1 year, indicating that the PTFU-FREDDY was better than the simple PTPBD procedure we reported before,³¹ and ERCP alone,⁵ similar to choledochoscopy-guided laser lithotripsy,³² but with less complications. Digital single-operator cholangioscopy with electrohydraulic and laser lithotripsy is also effective in removing difficult biliary stones,³³ but the procedural injury is larger than that of PTFU-FREDDY. A 10-year retrospective study showed that multiple CBDS (≥ 2), cholesterol stone, and sharp bile duct angulation ($<145^\circ$) are associated with recurrent CBDS after cholecystectomy.³⁴ To prevent recurrence, ursodesoxycholic acid was administered in this study,⁶ and a prospective cholelithiasis-related bile acid metabolomics have been initiated in multiple centers.

Large difficult CBDS also can be managed either by open surgery or laparoscopically with comparable and acceptable outcomes and without the need for multiple ERCP sessions due to their related morbidities.³⁵ Open choledocostomy was considered to be more suitable for stone clearance than a T-tube.³⁶

For concurrent gallbladder and CBD stones, Liu et al. introduced a novel technique, which they referred to as sequential percutaneous transhepatic balloon dilation (PTBD) and percutaneous transhepatic extraction and balloon dilation (PTEBD).³⁷ In the present study, patients were treated with routine PTFU-FREDDY, followed by percutaneous transcyst access PTFU-FREDDY.

Recently, a retrospective analysis study reported the outcomes of percutaneous transhepatic biliary laser lithotripsy for intrahepatic cholelithiasis,³⁸ which achieved a 100% success rate in fragmenting the target stones. Eleven (92%) out of the 12 patients had successful first pass extraction of target stone fragments, and two patients (2/12; 17%) required repeat lithotripsy. In this study, the authors exclude the CBDS with concurrent multiple intrahepatic cholelithiasis, considering that it was difficult to ensure complete intrahepatic calculi fragmentation and discharge. In the following research, these patients would be prioritized for admission and treatment, and a special report would be presented.

The limitation of this study includes its small sample size and retrospective nature. More prospective, multicenter, randomised controlled trials are necessary to confirm the results of this study.

In conclusion, PTFU-FREDDY is a safe and efficient alternative treatment for refractory choledocholithiasis, especially when traditional treatments are difficult to perform or failed.

Declarations

Acknowledgements

Wei Wang, Wujie Wang, Yongzheng Wang and Yuliang Li had full access to all the data in the study. They took responsibility for the integrity of the data and the accuracy of the data analysis. The authors thank the patients and institutions involved in this study.

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Declarations of interest

The authors who have taken part in this study declare that they do not have anything to disclose regarding conflicts of interest concerning this manuscript.

Author contributions

Study concept and design: Wang Wei, Wang Wujie and Li Yuliang; study supervision and guarantor of the article: Wang Yongzheng and Li Yuliang; data collection: Wang Wei, Wang Wujie, Tian Shilin, Jia Yunming and Wang Yongzheng; statistical analysis: Shao Chunhuan; data analysis and interpretation: Wang Wei, Shao Chunhuan and Li Yuliang; report drafting, review, and approval: Wang Wei, Wang Wujie, Jia Yunming, and Li Yuliang; drafting the first version of the manuscript: Wang Wei and Wang Wujie; critical revision of the manuscript for relevant intellectual content: Wang Yongzheng, and Li Yuliang; approval of the submitted final draft: Wang Wei, Wang Wujie, Tian Shilin, Shao Chunhuan, Jia Yunming, Wang Yongzheng and Li Yuliang.

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Tables

Table 1. Baseline characteristics of the study participants

Characteristics	Total (N=139170)			Male (N=78176)			Female (N=60994)			
	MAFLD (N=36306)	Non- MAFLD (N=102864)	<i>P</i> - value	MAFLD (N=27684)	Non-MAFLD (N=50492)	<i>P</i> - value	MAFLD (N=8622)	Non-MAFLD (N=52372)	<i>P</i> - value	<i>P</i> - value [†]
Age (years)	47±19	42(21)	<0.001	45±18	43±22	<0.001	54±19	41(20)	<0.001	<0.001
Gender, male (%)	27684 (76.3)	50492 (49.1)	<0.001	-	-	-	-	-	-	-
BMI (Kg/m ²)	26.18 ±3.41	22.27(3.69)	<0.001	26.35±3.24	23.05±3.43	<0.001	25.59 ±3.70	21.48(3.35)	<0.001	<0.001
Waist circumference (cm)	89±9	78(12)	<0.001	91±9	82±10	<0.001	84±9	73(9)	<0.001	<0.001
Systolic pressure (mmHg)	130±24	117(22)	<0.001	130±22	121±21	<0.001	132±28	112(21)	<0.001	<0.001
Diastolic pressure (mmHg)	81±15	72(14)	<0.001	82±15	75±15	<0.001	78±16	69(13)	<0.001	<0.001
Fasting glucose (mmol/L)	5.5±1.0	5.1(0.7)	<0.001	5.5±1.0	5.2±0.6	<0.001	5.6(1.0)	5.1(0.6)	<0.001	<0.001
Total cholesterol (mmol/L)	5.02±1.22	4.64(1.16)	<0.001	4.98±1.20	4.68±1.13	<0.001	5.13±1.30	4.61(1.18)	<0.001	<0.001
Triglyceride (mmol/L)	2.04±1.43	1.10(0.72)	<0.001	2.12±1.50	1.26±0.83	<0.001	1.79(1.13)	0.97(0.58)	<0.001	<0.001
HDL-C (mmol/L)	1.20±0.36	1.47(0.45)	<0.001	1.15±0.32	1.34±0.39	<0.001	1.35(0.39)	1.60(0.43)	<0.001	<0.001
LDL-C (mmol/L)	3.30±1.07	2.83(1.05)	<0.001	3.29±1.03	2.97±1.03	<0.001	3.32(1.14)	2.70(1.04)	<0.001	0.001
Albumin (g/L)	47±4	47(4)	<0.001	48±4	47±3	<0.001	46±4	46(3)	<0.001	<0.001
Total bilirubin (μmol/L)	12.3±5.9	12.2(5.8)	0.002	12.8±6.1	13.3±6.3	<0.001	10.8±4.7	11.3(5.0)	<0.001	<0.001
ALT (U/L)	32±24	18(13)	<0.001	35±26	22±15	<0.001	24±16	15(8)	<0.001	<0.001
AST (U/L)	24±10	20(7)	<0.001	25±10	22±8	<0.001	22±8	19(6)	<0.001	<0.001
BUN (mmol/L)	5.1±1.6	4.9(1.7)	<0.001	5.2±1.6	5.2(1.7)	0.024	5.0(1.7)	4.6(1.6)	<0.001	<0.001
Creatinine (μmol/L)	73±19	66(23)	<0.001	77±15	78(15)	<0.001	56(12)	56(12)	0.059	<0.001
Uric acid (μmol/L)	393±121	313±115	<0.001	414±110	368(96)	<0.001	323(89)	268(73)	<0.001	<0.001
WBC (×10 ⁹ /L)	6.55(1.97)	5.89±1.85	<0.001	6.64±1.96	6.09±1.88	<0.001	6.29±1.94	5.71(1.79)	<0.001	<0.001
RBC (×10 ¹² /L)	5.09(0.62)	4.77±0.70	<0.001	5.20±0.49	5.12±0.50	<0.001	4.60±0.44	4.49(0.43)	<0.001	<0.001
Hemoglobin (g/L)	155(18)	144±22	<0.001	159±14	157±13	<0.001	138±11	134(12)	<0.001	<0.001
Platelet count (×10 ⁹ /L)	211(75)	210±73	<0.001	207±72	200±69	<0.001	226±82	219(76)	<0.001	<0.001
HCT (%)	45.8(4.8)	43.1±6.0	<0.001	46.8±3.6	46.3±3.7	<0.001	41.5±3.3	40.6(3.3)	<0.001	<0.001
MS (%)	19310 ±53.2	10340 ±10.1	<0.001	14013(50.6)	5675(11.2)	<0.001	5297(61.4)	4665(8.9)	<0.001	<0.001
Dyslipidemia (%)	29027 ±80.0	42854 ±41.7	<0.001	22600(81.6)	24797(49.1)	<0.001	6427(74.5)	18057(34.5)	<0.001	<0.001
Hyperuricemia (%)	16325 ±45.0	17314 ±16.8	<0.001	13605(49.1)	13175(26.1)	<0.001	2720(31.5)	4139(7.9)	<0.001	<0.001

[†]The *P*value were calculated from the comparison between the group of Male with MAFLD (27684) and Female with MAFLD (8622).

Data were described by medians (interquartile range) and proportions (%). *P*-values were derived from Mann-Whitney U test or chi-square test.

MAFLD, Metabolic dysfunction-associated fatty liver disease; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; WBC, white blood cell count; RBC, red blood cell count. HCT, hematokrit; MS, metabolic syndrome.

Table 2. Proportions of abnormal metabolic features and elevated liver enzymes among 139170 participants

Characteristics	Total (N=139170)			Non-obese subjects (N=97079)				
	With MAFLD (n [%]) (N=36306)	Without MAFLD (n [%]) (N=102864)	<i>P</i> - value	Non-obese with MAFLD (n [%]) (N=11143)	Non-obese without MAFLD (n [%]) (N=85936)	<i>P</i> - value	Obese with MAFLD (n [%]) (N=25163)	<i>P</i> - value [†]
Elevated waist circumference	23038(63.5)	18840(18.3)	<0.001	3337(29.9)	8238(9.6)	<0.001	19701(78.3)	<0.001
Elevated systolic pressure	18610(51.3)	25477(24.8)	<0.001	4999(44.9)	18163(21.1)	<0.001	13611(54.1)	<0.001
Elevated diastolic pressure	13487(37.1)	14824(14.4)	<0.001	3334(29.9)	10158(11.8)	<0.001	10153(40.3)	<0.001
Elevated triglyceride	23574(64.9)	20044(19.5)	<0.001	7182(64.5)	14143(16.5)	<0.001	16392(65.1)	0.204
Reduced HDL-C	10042(27.7)	12336(12.0)	<0.001	3046(27.3)	9301(10.8)	<0.001	6996(27.8)	0.359
Elevated fasting glucose	17165(47.3)	21259(20.7)	<0.001	5347(48.0)	15835(18.4)	<0.001	11818(47.0)	0.073
Elevated total cholesterol	15287(42.1)	28121(27.3)	<0.001	4885(43.8)	22537(26.2)	<0.001	10402(41.3)	<0.001
Elevated LDL-C (mmol/L)	16386(45.1)	25543(24.8)	<0.001	5114(45.9)	19641(22.9)	<0.001	11272(44.8)	0.052
Elevated ALT	15426(42.5)	11443(11.1)	<0.001	3816(34.2)	8032(9.3)	<0.001	11610(46.1)	<0.001
Elevated AST	3443(9.5)	2593(2.5)	<0.001	774(6.9)	1963(2.3)	<0.001	2669(10.6)	<0.001

[†]The *P*-value were calculated from the comparison between the group of Obese with MAFLD (25163) and Non-obese with MAFLD (11143).

Data were described by proportions (%). *P*-values were derived from chi-square test.

Elevated waist circumference: ≥90 cm for men and ≥80 cm for women. Elevated systolic pressure: ≥130 mm Hg. Elevated diastolic pressure: ≥85 mm Hg. Elevated triglyceride: ≥1.70 mmol/L. Reduced HDL-C: < 1.0 mmol/L. Elevated fasting glucose: ≥5.6 mmol/L. Elevated total cholesterol: ≥5.2 mmol/L. Elevated LDL-C: ≥3.4 mmol/L. Elevated ALT: > 35IU/L. Elevated AST: > 40IU/L.

MAFLD, Metabolic dysfunction-associated fatty liver disease; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 3. The prevalence of MAFLD in people with different number of MS components

Number of MS risk components	Total population	People with MAFLD	Prevalence (%)
0	45255	1471	3.3
1	36339	5218	14.4
2	27926	10307	36.9
3	18353	10758	58.6
4	9033	6685	74.0
5	2264	1867	82.5

MAFLD, Metabolic associated fatty liver disease; MS, metabolic syndrome.

Table 4. Results of binary logistic regression of MAFLD and the tested variables

Variable	<i>P</i> -value	OR	95 % CI of OR
Age (years)	0.015	1.018	1.001-1.033
BMI (Kg/m ²)	0.000	1.476	1.320-1.660
Waist circumference (cm)	0.006	1.057	1.017-1.102
ALT (U/L)	0.009	1.023	1.002-1.043
Triglyceride (mmol/L)	0.000	1.776	1.238-2.257
Fasting glucose (mmol/L)	0.000	1.403	1.116-1.839
Uric acid (μmol/L)	0.001	1.003	1.001-1.006
Platelet count (×10 ⁹ /L)	0.014	1.004	1.000-1.007

OR, odds ratio; CI, confidence interval; MAFLD, Metabolic associated fatty liver disease; BMI, body mass index; ALT, alanine aminotransferase.

Figures

Figure 1

Preoperative computed tomography shows a common bile duct stone (white arrow).

Figure 2

The flexible ureteroscopy-guided FREDDY laser lithotripsy procedure. A. Cholangiography with diluted contrast reveals large common bile duct stones (CBDS) (white arrow). B. A long guidewire was inserted into the duodenum as a protective measure, and the sphincter of Oddi was dilated with a 10×40-mm balloon through another guidewire. C. The flexible ureteroscope was inserted along the guidewire. D. A laser fiber was attached to the stone surface, and the working model used had a setting of 120 MJ and 5 Hz. E. The CBDS was broken into small fragments and washed by mixture of water and contrast or pushed into the duodenum with a balloon. F. Repeat endoscopy and cholangiography were performed to ensure that no calculi residual was present. After the endoscopy examination, the percutaneous sheath was removed and a 10·2F was inserted into the bile duct, and repeat cholangiography was performed.

Figure 3

A repeat computed tomography scan at 3 months later showed no calculi at the same level (white arrow).