CLINICAL PRACTICE GUIDANCE 2021

A Practice Guidance of
Metabolic Associated Fatty Liver Disease (MAFLD)
By Hepatology Society, Dhaka, Bangladesh
For Primary Healthcare Physicians of Bangladesh

Published by:

Hepatology Society Dhaka, Bangladesh
House No. 64, Road No. 8/A, Mirza Golam Hafiz Road
Dhanmondi R/A, Dhaka- 1209

A Practical Guidance of Metabolic Associated Fatty Liver Disease (MAFLD) by Hepatology Society, Dhaka, Bangladesh for Primary Healthcare Physicians of Bangladesh

Shahinul Alam[1], Tanvir Ahmad[2], Golam Mustafa[3], Golam Azam[4], Saiful Islam[5], Asma Helen Khan[5], M Motahar Hossain[6], Kamrul Millat[7], Mobin Khan[8]

Summary

Metabolic associated fatty liver disease (MAFLD) is the most common cause of liver disease worldwide and affects nearly one third of Bangladeshi population. The purpose of this document is to increase awareness and understanding of the disease among primary healthcare physicians of Bangladesh and thereby assist them in improving the diagnostic process and patient care by providing evidence-based information at primary level. The guidance will provide an approach to the identification of MAFLD in general practice, the distinction between simple steatosis and non-alcoholic steatohepatitis (NASH), and the management of these two conditions at an early stage. NASH is more common in the presence of diabetes, obesity and metabolic syndrome, and is more likely to progress to cirrhosis if these conditions co-exist. Cirrhosis may be complicated by liver failure or hepatocellular carcinoma (HCC). HCC has also been described in NASH without cirrhosis. Assessment and treatment of features of the metabolic syndrome may reduce associated cardiovascular mortality. Numerous agents have been evaluated, but weight loss remains the important effective treatment for MAFLD.

Keywords

MAFLD - Metabolic associated fatty liver disease, NASH - Non-alcoholic steato-hepatitis, Bangladesh.

ARTICLE INFORMATION:

1. Professor and Corresponding author, Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka. e-mail: shahinul67@yahoo.com.
2. Assistant Registrar, Department of Medicine, Kurmitola General Hospital, Dhaka.
3. Professor, Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka.
4. Associate Professor, Department of Gastroenterology, Hepatobiliary and Pancreatic Disorder, BIRDEM, Dhaka.
5. Research Assistant, Bangabandhu Sheikh Mujib Medical University, Dhaka.
6. Ex-Consultant, Department of Gastroenterology, Square Hospital Ltd, Dhaka.
7. Medical Officer, Cumilla Medical College Hospital, Cumilla.
8. Ex Professor and Founder Chairman, Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka.

Introduction

Metabolic associated fatty liver disease (MAFLD) formerly known as non-alcoholic fatty liver disease (NAFLD)) has risen in prevalence to alarming levels, placing an enormous burden on individuals and health care systems (1). The term NAFLD was first coined by Ludwig et al. to describe a cohort of patients with a liver disease that histologically mimicked alcoholic fatty liver disease in patients without a history of significant alcohol intake and has been used until recently (2). MAFLD includes both non-alcoholic steato-hepatitis (NASH), involving ballooning, lobular inflammation and fibrosis, and simple steatosis (non-NASH). This distinction is important, as simple steatosis is unlikely to lead to liver related complications, whereas NASH may lead to increased fibrosis and cirrhosis, and its complications. The difficulty lies in trying to decide whether abnormal liver functions tests (LFTs) are due to simple steatosis, NASH without fibrosis, NASH with severe fibrosis or cirrhosis, or another cause of hepatitis altogether. The cornerstone of management of MAFLD is to differentiate NASH from simple steatosis, stratify the risk factors for progression, referral to specialty centre and follow up at primary care level.

Epidemiology

A recent systematic review and meta-analysis of MAFLD prevalence from an Asian context comprising > 13,044,518 individuals suggested that the prevalence of MAFLD in this region is 29.62% (3). Nationwide community ultrasound-based study from Bangladesh of 2782 participants observed that the overall prevalence of MAFLD was 33.86% with no difference between urban and rural populations suggesting that Bangladesh has one of the highest rates of MAFLD in South Asia (4). Several studies of Bangladesh between 2009 to 2019 at tertiary care hospital found the prevalence of NASH in NAFLD to be 31.11% to 64%. That could be translated to assume the prevalence of NASH at general population to be 10.53 – 21.67 % (5,6,7,8,9,10). Hepatology Society Dhaka, Bangladesh predicted that the prevalence of NASH is about 12-17% in Bangladesh (11).

Definition and diagnosis of MAFLD

NAFLD, which is a diagnosis of exclusion rather than one of inclusion, is highly heterogeneous and can negatively influence clinical decision making. To address these issues, APASL approved a more appropriate nomenclature for the disease and that is "metabolic associated fatty liver disease" or MAFLD (12). The diagnosis of MAFLD is based on (figure 1) –

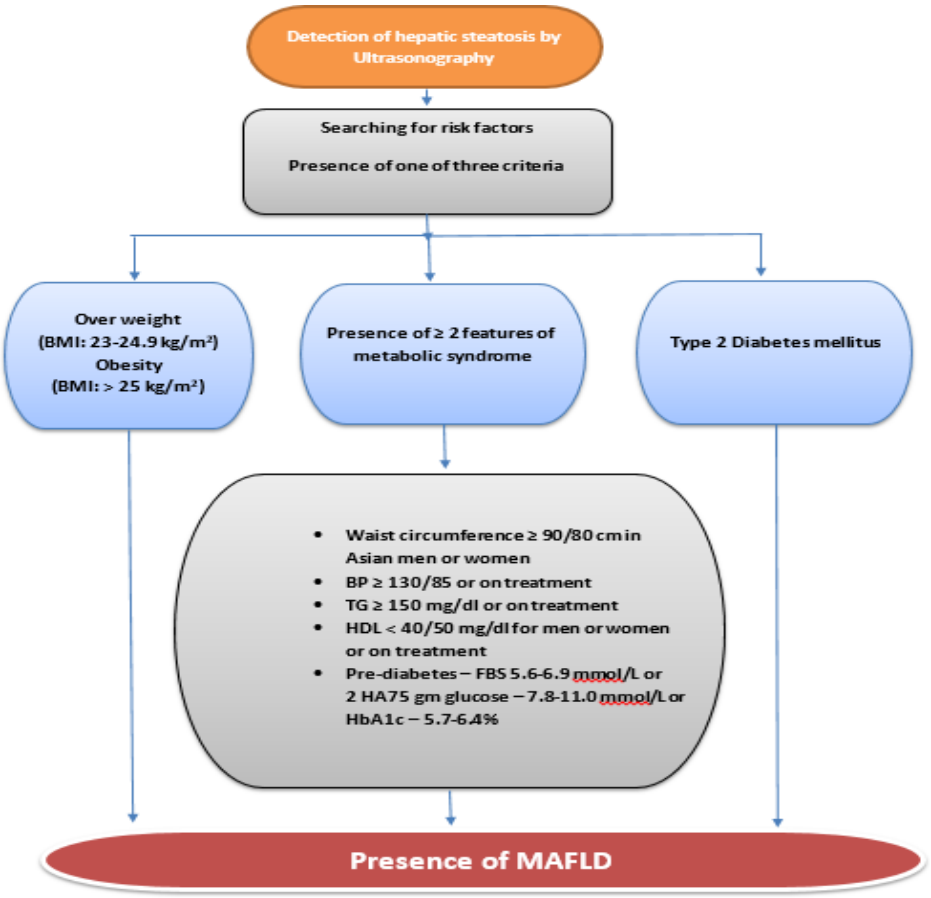


Figure 1: Algorithm to diagnose MAFLD

- The detection of liver steatosis (liver histology, non-invasive biomarkers or imaging) together with the presence of at least one of three criteria:
    - Overweight (BMI: 23.0-24.9 kg/m^2) or obesity (BMI>25.0 kg/m$^{2)}$ according Asian criteria
    - Type 2 diabetes mellitus (T2DM) or
    - Presence of two or more features of metabolic syndrome (MSy):

- Waist circumference ≥ 90/80 cm in men and women.
- Blood pressure ≥ 130/85 mmHg or on specific drug treatment.
- Plasma triglyceride ≥ 150 mg/dl or specific drug treatment
- Plasma HDL-cholesterol < 40 mg/dl for men or < 50 mg/dl for women or specific drug treatment.
- Prediabetes (i.e., fasting glucose level 100 to 125 mg/dl (5.6 to 6.9 mmol/L) or 2-hour post-load glucose levels 140-199 mg/dl (7.8 to 11.0 mmol/L or HbA1C 5.7% to 6.4%.

Natural history of MAFLD

Simple steatosis appears to be a relatively benign condition, although it may progress to NASH over time rarely (figure 2). Cardiovascular disease (CVD) followed by liver failure and cancer are the main causes of death in MAFLD (12). When MAFLD occurs in the presence of other features of the metabolic syndrome (MSy) mortality rises(13). The MSy is a clustering of cardiovascular risk factors related to reduced insulin sensitivity.

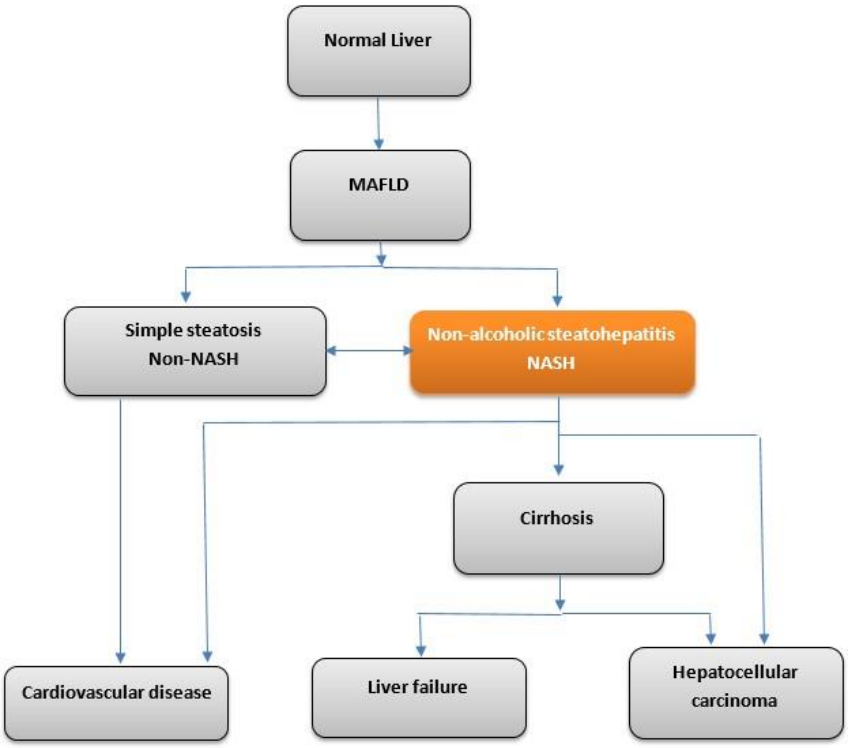


Fig.2: Natural history of MAFLD

In addition to its association with cardiovascular complications, MAFLD can lead to liver related morbidity and mortality. The risk of developing cirrhosis is higher in the presence of NASH, which is more likely in the presence of the following features (14):

- Type 2 diabetes mellitus (T2DM)
- obesity (body mass index [BMI] >30 kg/m_2)
- Age more than 50 years
- Serum aminotransferases (ALT or AST) more than two times the upper limit of normal.

NASH cirrhosis probably accounts for the vast majority of what was previously described as 'cryptogenic cirrhosis'. In one series, 70% of patients with cryptogenic cirrhosis had risk factors for fatty liver disease (15). In the US, NASH is an increasingly common indication for liver transplantation (16). Concerning comparisons with other liver diseases, in a prospective cohort study, the yearly cumulative incidence of HCC was 2.6% in MAFLD-cirrhosis during a median follow-up of 3.2 years. This was comparable with a reported 4% incidence in a chronic hepatitis C-cirrhotic population over the same time (17). Hepatocellular carcinoma has also been reported in NASH without cirrhosis, particularly in association with the MSy (18).

Risk factors for MAFLD

Risk factors for MAFLD in Asians are similar to that of Western population (Table I).

Table I: Risk factors for MAFLD

Major risk factor
• **Overweight/obesity**
• **Type 2 diabetes mellitus**
• **Dyslipidaemia**
• **Hypertension**
• **Metabolic syndrome**
• **Dietary factors: High-calorie diets rich in saturated fats and cholesterol, soft drinks high in fructose, highly processed foods**
• **Sedentary lifestyle or sedentary occupation, low level of physical activity**

Recommendations

- Population who are at-risk such as patients with overweight or obesity, type 2 diabetes mellitus and metabolic syndrome should be screened by ultrasonography for MAFLD.
- Patients with MAFLD should be assessed for metabolic syndrome and be treated accordingly.
- Utrasound should be the primary diagnostic tool for detection of fatty liver

MAFLD and other liver disease

Since MAFLD is no longer a diagnosis of exclusion and is based on the presence of metabolic dysfunction, it is now possible to diagnose its coexistence with other liver diseases such as alcoholic liver disease, chronic hepatitis B virus infection, chronic hepatitis C virus infection-genotype 3, primary biliary cholangitis, and primary haemochromatosis, especially in Asian populations. Moreover, meeting the criteria for a diagnosis of MAFLD plus one and more other less frequent alternative causes of fatty liver should be diagnosed, e.g., long-term use of steatogenic medications or Wilson disease (12)

Recommendations

- MAFLD frequently does coexist with other liver diseases.
- Treatment of MAFLD and other concomitant liver diseases should be given as per the recommendations for each of the diseases.

Evaluation of MAFLD at primary healthcare level

Patients with obesity, diabetes mellitus or MSy who are at high risk of developing MAFLD should be assessed by ultrasonography. Further evaluation is needed to assess the severity of MAFLD.

Recommendations

- Patients with MAFLD should be evaluated by
    - ALT
    - AST
    - AST/ALT ratio and
    - Platelet count
- If the baseline investigations are normal, it should be repeated at intervals of 2-3 years (12).

Management of MAFLD at primary healthcare level

The cornerstone of managing MAFLD is achieving weight control and reduction in cardiovascular risk factors such as smoking, diabetes, hypertension and dyslipidaemia. Hence, lifestyle modification including dietary change, weight loss, and structured exercise intervention remains the first-line management for this condition.

Diet and lifestyle changes

Lifestyle intervention programs and weight loss can achieve reductions in liver fat content, resolution of steatohepatitis and fibrosis and improve a patients' quality of life. A recent study showed an improvement in liver histology (steatohepatitis) in 58% of those achieving > 5% and in 90% of those achieving weight loss of > 10%, respectively. Only the latter demonstrated an improvement in fibrosis stage (in 45%) (19). The overall aim of lifestyle intervention should be for gradual weight loss (up to 1 kg/week) with a hypocaloric diet (500–1000 kcal deficit). There is no strong evidence to support a particular dietary approach for the resolution of MAFLD. However, patients may be advised to take low-carbohydrate, low fat and Mediterranean-type diet (12).

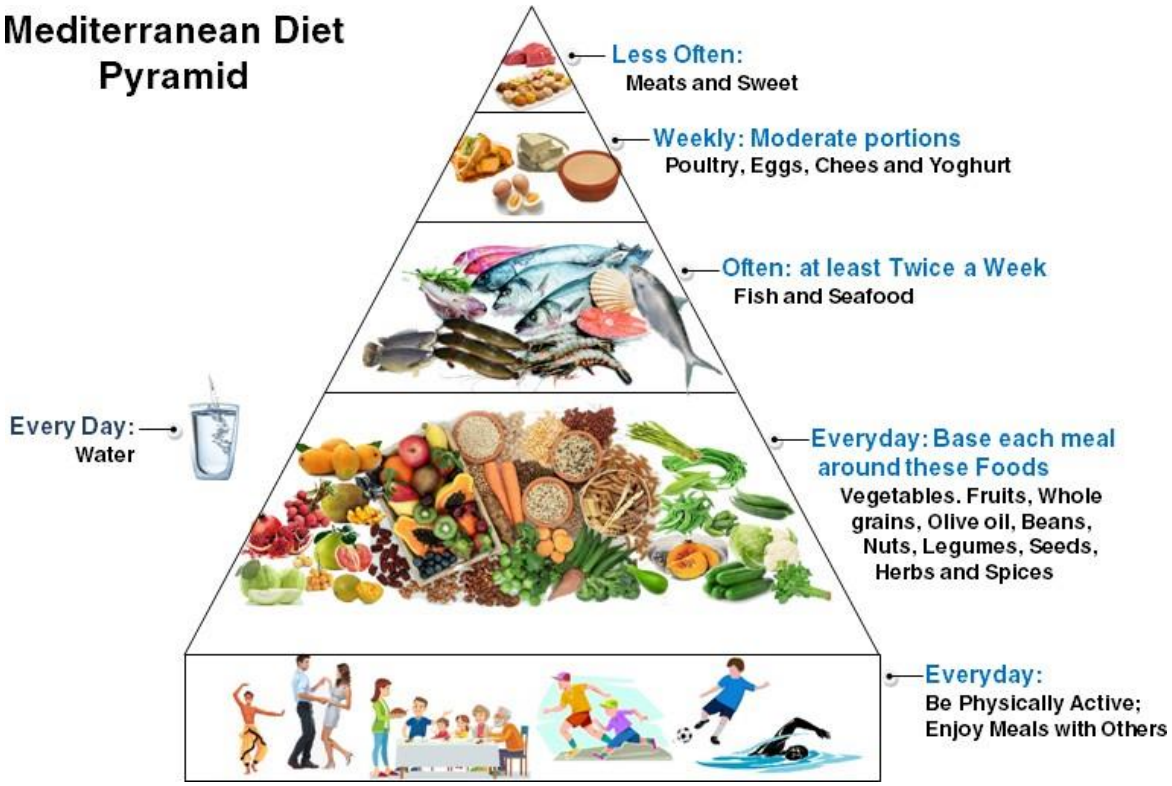


Figure 3: Mediterranean type diet

Exercise

For the general adult population, 30 min/day of moderate-intensity exercise for ≥ 5 days/week or a total of ≥ 150 min/week or vigorous-intensity exercise for ≥ 20 min/day on ≥ 3 days/week (≥ 75 min/week) (20) are recommended.

Recommendations

- Lifestyle change towards a healthy diet and structured physical activity programs are recommended for MAFLD.
- Patients without steatohepatitis or fibrosis should receive counselling for a healthy diet and physical activity and no pharmacotherapy for their liver disease.
- Both overweight/obese and non-obese MAFLD can benefit from weight loss. In the former, a 7–10% weight loss is the target of most lifestyle interventions and results in improvement of liver enzymes and histology.

- Dietary recommendations include energy restriction and exclusion of MAFLD-mediating components (sugar, sweetened, large amount of rice, food and beverages high in fructose etc.). A Mediterranean type diet is advisable.
- Combined diet/exercise strategies are more effective in normalization of liver enzymes levels, reducing liver fat and improving histology.
- All forms of exercises reduce liver fat and should be tailored based on patient preferences to ensure long-term adherence (12).

Follow up MAFLD patients at GP level

Normalization of liver function tests (LFTs) associated with mild weight loss may be an encouraging sign.

Recommendations

- All MAFLD patients with initial derangement of liver function tests should be assessed at least 6-monthly by ALT, AST and platelet count.

When to refer for specialist management

Referral for specialist management should be undertaken whenever there is a suspicion of severe disease, whether at initial assessment or at any time during monitoring.

Recommendations

A patient with MAFLD should be referred, if he or she is having -

- Uncontrolled high-risk factors
- Raised ALT
- Altered AST/ALT ratio
- Thrombocytopenia
- Ultrasonographic evidence of chronic liver disease
- Pregnancy

- Coexisting other liver disease –
    - Chronic hepatitis B infection
    - Chronic hepatitis C infection
    - Autoimmune hepatitis
    - Wilson disease

Key point

- Metabolic associated fatty liver disease is increasingly common, and will have a significant impact on morbidity and mortality in a growing number of Bangladeshi populations.
- Patients with overweight / obesity or T2DM or MSy should be assessed by ultrasonography to diagnose MAFLD.
- Patients with MAFLD should be evaluated by LFTs and for MSy.
- MAFLD patients should be referred to specialist if there are deranged LFTs and uncontrolled metabolic factor(s).
- Weight reduction via caloric restriction and regular exercise are important tools for intervention.
- Primary healthcare physicians can play a vital role in identifying patients at risk of MAFLD, and encouraging initiation and maintenance of appropriate lifestyle changes.

Further reading

The Asian Pacific association for the study of liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease.
Available at: https://doi.org/10.1007/s12072-020-10094-2.

References

1. Wong MC , Huang JL , George J , Huang J , Leung C , Eslam M , et al. The changing epidemiology of liver disease in the Asia-Pacific region. Nat Rev Gastroenterol Hepatol. 2019;(16:57-73).

2. Ludwig J , Viggiano TR , McGill DB , Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc. 1980;(55:434–438).

3. Li J , Zou B , Yeo YH , Feng Y , Xie X , Lee DH. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999–2019: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2019;(4: 389–398).

4. Alam S , Fahim SM , Chowdhury MAB , Hassan MZ , Azam G , Mustafa G , et al. Prevalence and risk factors of non-alcoholic fatty liver disease in Bangladesh. JGH Open. 2018;(2: 39-46).

5. Mollic KU. Correlation between Liver Histology with Sonological Grading and Elastography in Nonalcoholic Fatty Liver Disease. 2009. MD Thesis. Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

6. Bosunia ZH. Evaluation of Serum Ferritin as an Independent Predictor of Non-alcoholic steatohepatitis (NASH). 2013. MD Thesis. Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

7. Alam SKME. Biochemical Scoring System for Diagnosing Non-alcoholic Steatohepatitis. 2013. MD Thesis. Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

8. Anam MK. Validation of the BARD (BMI, AST ratio, DMt2) Scoring System for Detection of Fibrosis in Patients with Nonalcoholic Fatty Liver Disease. 2016.MD Thesis. Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

9. Islam MS. Association of Single Nucleotide Polymorphism in Patients Like Phopholipase Domain Containing 3 Gene at 148 Positions with Histological Severity of Non alcoholic Fatty Liver Disease. 2016. MD Thesis. Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

10. Quayyum AA. Clinicopathological and Histological Features Variation in Nonalcoholic Fatty Liver Disease Patients in Relation to Insulin Resistance. 2019. MD Thesis. Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

11. Hepatology Society Dhaka, Bangladesh. 2nd International NASH Day. 2019. A brochure publised on NASH day. http://www.hepatolsocietybd.org/uploads/2/6/7/8/26786438/nash_brochure.pdf.

12. Eslam M , Sarin SK , Wong VW , Fan JG , Kawaguchi T , Ahn SH , et al. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hepatology International. 2020;(14:889-919).

13. Gami AS , Witt BJ , Howard DE. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. Journal of American College of Cardiology. 2007;(49:403).

14. Iser D , Ryan M. Fatty liver Disease: A practical guide for GPs. Australian Family Physician. 2013;(6:444-447).

15. Caldwell SH , Oelsner DH , Lezzoni JC. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. Hepatology. 1999;(29:664).

16. Bugianesi E , Leone N , Vanni E. Expanding the natural history of non-alcohoic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. Gastroenterology. 2002;(123:134-140).

17. Ascha MS , Hanouneh IA , Lopez R , Tamimi TAR , Feldstein AF , Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology. 2010;(51:1972-1978).

18. Ertle J , Dechene A , Sowa JP , Pendorrf V , Herzer K , Kaiser G , et al. Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. International journal of cancer. 2011;(128:2436-2443).

19. Vilar-Gomez E , Martinez-Perez Y , Calzadila-Bertot L , Torres-Gonzalez A , Gra-Oramas B , Gonzalez-Fabian L. Weight loss throuh lifestyle modification significantly reduce features nonalcoholic steatohepatitis. Gastroenterology. 2015;(149:367-378).

20. Garber CE , Blissmer B , Deschenes MR , Franklin BA , Lamonte MJ , Lee I-M , et al. Quantity and quality of exercise for developing and and maintaingn cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Medicine & Science in Sports & Exercise. 2011;(43:1334-1599).

BANGABANDHU INTERNATIONAL NASH DAY
JUNE 10, 2021

Observance of International NASH Day 2021
by Hepatology Society, Dhaka, Bangladesh

WEBINAR

Clinical Practice Guidance of Metabolic Associated Fatty Liver Disease (MAFLD) for General Practitioners

DATE:
June 10, 2021, Thursday

TIME:
9.30 pm to 11.00 pm

CHAIRPERSON

PROF. MOBIN KHAN
President
Hepatology Society, Dhaka, Bangladesh

MODERATOR

PROF. MD. SHAHINUL ALAM
General Secretary
Hepatology Society, Dhaka, Bangladesh

DR. MD. GOLAM AZAM
Secretary, Scientific Affairs
Hepatology Society, Dhaka, Bangladesh

KEYNOTE SPEAKER

DR. TANVIR AHMED
MD (Hepatology)
Kurmitola General Hospital

PANEL OF EXPERTS

PROF. ABU SAYEED
Vice President
Hepatology Society, Dhaka, Bangladesh

PROF. MD. GOLAM MUSTAFA
Professor, Dept. of Hepatology
Bangabandhu Sheikh Mujib Medical University

PROF. SHOHAEL MAHMUD ARAFAT
Chairman, Dept. of Internal Medicine
Bangabandhu Sheikh Mujib Medical University

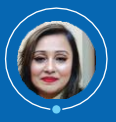
DR. MD. MOTAHAR HOSSAIN
Ex. Consultant
Dept. of Gastroenterology
Square Hospital Ltd.

PROF. MD. AKMAT ALI
Professor, Dept. of Hepatology
Ad-Din Women's Medical College Hospital

DR. MD. FEROZ AMIN
Associate Professor
Dept. of Endocrinology and Metabolism, BIRDEM

DR. S.K.M. NAZMUL HASAN
Asst. Professor (Hepatology)
Shahid Syed Nazrul Islam Medical College, Kishoreganj

DR. MOHAMMAD HARUN OR RASHID
Asst. Professor (Hepatology)
Colonel Malek Medical College, Manikgonj



DR. SHAYLA NASRIN PhD
Nutritionist, Dept. of Nutrition
Institution of Child & Mother Health

DR. MD. KAMRUL ANAM
MD (Hepatology)
Sheikh Russel National Gastroliver Institute & Hospital

DR. MD. SAIFUL ISLAM ALIN
MD (Hepatology)
Bangabandhu Sheikh Mujib Medical University

Hepatology Society
Dhaka, Bangladesh.

LIVE
Doctor tv

Please scan the
QR code for registration
WEBINAR ID: 897 7198 3685

EXECUTIVE COMMITTE

President	:	Prof. Mobin Khan
Vice President	:	Prof. Md. Abu Sayeed
General Secretary	:	Prof. Dr. Md. Shahinul Alam
Secretary of Scientific Affairs	:	Dr. Md. Golam Azam
Treasurer	:	Prof. Dr. Md. Golam Mostafa
Members	:	Prof. Nooruddin Ahmad
		Dr. M. Motahar Hossain
		Dr. Md. Mahbubul Alam
		Dr. Saiful Islam

Hepatology Society Dhaka, Bangladesh
House No. 64, Road No. 8/A, Mirza Golam Hafiz Road
Dhanmondi R/A, Dhaka- 1209