Spotting the Red Flags: Screening and Risk Strat Like a Pro

CMEO Podcast Transcript

Conan Tu, MD, MBA, DACD, BC-ADM:

Hello, I'm Dr. Conan Tu. Thank you for joining us for *The Glow-Up Era of Metabolic Dysfunction-Associated Steatohepatitis (MASH) Management*. This initiative is sponsored by an educational grant from Novo Nordisk Incorporated. You will notice the asterisk there because we need to define “glow-up” for older physicians like me who really are not up to date with the lingo. In modern slang, glow-up means dramatic positive change, and we are here to change your knowledge about MASH management. This is the first of four CMEO Snacks in the series. Today's episode will address screening and risk stratification for metabolic dysfunction-associated steatotic liver disease **(**MASLD) and MASH.

Again, I'm Conan Tu. I'm the Regional Chief of Adult Primary Care for Optum, New York and New Jersey. I am an adult internal medicine physician by training and I'm also board certified in diabetology. I'm located in Bethpage, New York, and I'm very pleased to be joined today by my esteemed colleague, Dr. Arun Jesudian, who I will ask to introduce himself. Welcome, Dr. Jesudian.

Arun B. Jesudian, MD:

Thank you very much, Dr. Tu. I am happy to be here. I am Dr. Arun Jesudian. I'm Associate Professor of Clinical Medicine and Director of Liver Quality and Inpatient Liver Services at New York Presbyterian Hospital and Weill Cornell Medicine in New York City.

Conan Tu, MD, MBA, DACD, BC-ADM:

Awesome. Your perspective and my perspective are slightly different. I'm more on the primary care and diabetes side and you are more on the specialty side. So, we're going to get a really great viewpoint from yourself and myself on the different aspects of MASLD and MASH management as the patient goes through the diagnostic and treatment pathway. So, thank you very much for joining me. We're looking forward to our discussion. Here is our learning objective for today's program. After participating in this activity, learners should be better able to identify best practices for optimal screening, identification and risk stratification of patients at high risk for MASH with fibrosis. To set the stage for our discussion, let's start with a few fundamental definitions. Dr. Jesudian, would you please do the honors?

Arun B. Jesudian, MD:

Yes, happy to. Let's start by defining what MASLD and MASH are. MASLD is metabolic dysfunction-associated steatotic liver disease, what we used to call nonalcoholic fatty liver disease. This is new nomenclature that really focuses on the steatosis, the fat in the liver, and this is defined by a patient who has fat in their liver, steatosis in greater than or equal to 5% of their hepatocytes, their liver cells. Importantly, MASLD does not really involve significant alcohol consumption. So, these are patients who have minimal alcohol consumption and also they do not have other etiologies of liver disease and specifically of liver steatosis. Some of those that you might need to exclude are things like medications that cause steatosis in the liver, so, for example, steroids or tamoxifen, HIV, lipodystrophy.

MASLD is extremely common. Fat in the liver in absence of alcohol or secondary causes is prevalent in about 30% of adults worldwide, and that prevalence is expected to increase as we see more and more obesity and type 2 diabetes and metabolic syndrome in general. When there is inflammation and liver cell damage in addition to the fat, that's when a patient has gone on to develop MASH or metabolic dysfunction-associated steatohepatitis. This is important because these patients can progress and develop fibrosis or scarring of their liver. Ultimately, they could develop the final stage of scarring of their liver cirrhosis and be at risk of major liver-related outcomes like decompensated cirrhosis, requiring a transplant, or developing liver cancer, hepatocellular carcinoma. It's important to appreciate that MASLD is often asymptomatic and often discovered incidentally during routine labs in patients at risk. Those patients with metabolic syndrome would be a good example of who's at risk. To round out our discussion, there are a couple of other types of steatotic liver disease that are worth mentioning.

Patients are allowed to drink more alcohol than a minimal amount, but also have metabolic syndrome and MASLD-type features. If you have the combination of those two, this is when you can diagnose a patient with MetALD, or metabolic dysfunction and alcohol-associated liver disease. These are patients who have hepatic steatosis. They have at least one metabolic risk factor and moderate alcohol consumption. We often talk about alcohol consumption in terms of grams of alcohol per day. This could be 20-50 grams a day for a female or 30-60 grams a day for a man. This results from a combination of metabolic dysfunction and moderate alcohol consumption. So, this represents a spectrum between MASLD-predominant and alcohol-predominant disease.

Certain patients have alcohol-associated liver disease, or ALD. These are patients who are drinking heavily, greater than 50 grams of alcohol a day for women or 60 grams a day for men. Remember, a standard drink contains about 14 grams of alcohol. So, that's how you can figure out how many units that is for your patients, but these are patients with alcohol-associated liver disease who really don't have much of the metabolic syndrome at play. Their steatotic liver disease is the consequence of their heavy alcohol consumption.

Conan Tu, MD, MBA, DACD, BC-ADM:

Got you. Thank you very much, Dr. Jesudian. In my practice as a primary care physician and also a diabetologist, taking care of patients with pre-diabetes and diabetes, I've been following the guidelines and starting to screen my patients a little bit more and I am absolutely shocked with the incidents of MASLD and MASH in my patients. I wanted to share a little bit about guidelines that I use for screening patients, those that are at risk for whom we should really be applying the new MASLD and MASH screening guidelines.

Let's go over the American Association for Steatotic Liver Disease (AASLD) guidelines about the risk factors and things that we should be really looking at for our patients and then thinking the next step about whether or not they should be screened for fatty liver disease. The first criteria is excess adiposity. That can simply be a mildly elevated body mass index (BMI) in non-Asian patients that would be greater than 25, which is considered overweight. In Asians, it would be a BMI greater than 23. That is not a very high BMI at all. Or they could have central obesity. So, they could have a low BMI, but it's all packed right in the middle. Think of the typical “dad bod” or the typical apple-shaped person. The BMI doesn't have to be significantly high and the body habitus can be measured based on waist circumference.

Then another criterion aside from adiposity would be having a disorder of glucose metabolism that could be either prediabetes or type 2 diabetes or it could be somebody being treated for hyperglycemia with the normal sugar in the normal range, but if they're getting there due to treatment. Another criterion would be

hypertriglyceridemia or another criterion is high-density lipoprotein (HDL) that is low. The final criteria would be hypertension or elevated blood pressure or even normal blood pressure that is being treated. So, these are the five basic criteria that we would use. If you think about it, that's like most of our patients. So, as a primary care doctor, I am screening a lot of my patients more and more. As I said before, I am absolutely surprised as to how many people I am finding who have MASLD or even MASH based on simple screening. We'll talk about the screening in the future.

Then in clinical practice there are even those patients I don't think might be at risk for MASLD or MASH but we find incidental findings on computed tomography (CT) scan of the abdomen or ultrasound of the abdomen, where a patient is reported to have excess fatty buildup or heterogeneous liver morphology. Those are all things that we need to think about. Then we always send them to Dr. Jesudian for further workup.

Arun B. Jesudian, MD:

Yes, I couldn't agree with you more that it is so common in any health care setting to see patients with these metabolic features that you just went through who are clearly at risk for a variety of metabolic-associated diseases. I think we have become very good at looking at blood glucose and hemoglobin A1C and lipids and blood pressure, and perhaps what sometimes gets forgotten or overlooked is the liver disease aspect of this, the MASLD and potential MASH. I think it's important to understand that patients usually have no symptoms from this disease or at least no specific symptoms. Just as you mentioned, it's something that we have to actively screen for.

We do have to look at, say, their liver enzymes or if they have any imaging of their liver where we might identify some fat that could then cause us to take the next step and really look into the existence of MASLD or MASH and how severe that might be in an individual patient. But we see so many patients with metabolic risk factors and we should be thinking about the potential for having MASLD or MASH and screening that population in primary care settings, in diabetes practices like your own, endocrinology offices, anywhere where these patients are seeking care. When we identify that, we can certainly then help that patient by risk stratifying them. That's some of what we'll talk about over the course of this discussion.

Conan Tu, MD, MBA, DACD, BC-ADM:

Yes. I wanted to point out also that primary care physicians typically have a very holistic attitude towards their patients where they're trying to treat all of their medical conditions that they might be at risk for or might be diagnosed with actively. Sometimes you get patients who are so-called healthy who come in and then they think that everything is fine and are like, "Oh, yeah, I just have a ‘dad bod’. It's normal. All my buddies have it." But then when you dig a little bit deeper, you can find some diagnoses that might be so overt to help maybe push the needle and put a seed in the patient's head that a little bit of lifestyle modification now can go a very long way towards preventing future disease and not only MASLD and MASH but further development of hypertension, further development of dyslipidemia, and further development of dysglycemia. I think that for many primary care practitioners (PCPs) it will resonate to find any excuse to help begin the lifestyle modification process and at least put that little seed in their brain so that they need to think about it and it helps the PCP think about screening their patient population a little bit better too.

Arun B. Jesudian, MD:

Absolutely.

Conan Tu, MD, MBA, DACD, BC-ADM:

Let's take a look at a case study so that we can maybe really drill this home for a lot of other people. By the way, this case we're going to start here in the first webinar is going to continue throughout the other three programs that we're doing. Let's go with a hypothetical patient named Mr. B. He's a 61-year-old gentleman who works in the utilities field as a crew chief and he presents for a routine follow-up visit. He feels well. He has no specific complaints. He denies fatigue, abdominal pain, parities, and jaundice. There are no liver complaints. His history is typical for most people with his presentation in the middle age. He has type 2 diabetes, dyslipidemia, and hypertension. He's overweight a little bit, with a BMI of 29.1. He drinks an occasional glass of wine with dinner, so no excess alcohol intake. His current medications are metformin, valsartan, and hydrochlorothiazide. So, these are all pretty typical treatment modalities for patients with his conditions. His physical exam is unremarkable, aside from the fact that he is a little bit on the heavy side. Let's go next to his lipids and his liver function studies. His aspartate aminotransferase (AST) is 28. His alanine aminotransferase (ALT) is 36, both in the normal range. Alkaline phosphatase is 100, total bilirubin is 1, albumin is 4. Platelets are 110,000. All that is pretty routine. Low-density lipoprotein (LDL) is 130, HDL is 36, triglycerides are 235, hemoglobin A1C is 7.1. So, that's not terrible at all.

Before we discuss this case further, let's get everybody involved. We're just going to level set a little bit. We haven't gone through the steps for risk stratification. We just want to make sure that we see if everybody is really an expert at this or really is here to learn. So, which of the following is the first step for risk stratification? We have five choices here. The first choice could be Fibrosis-4 (FIB-4) calculation, the second choice is liver biopsy, the third choice is magnetic resonance elastography, the fourth choice is ultrasound transient elastography, and the fifth choice is “I don't know.” Be honest here. We're all here to learn. This is completely anonymous. We just want to find out what your basic knowledge is and how great of a job we did teaching you. The correct answer is the first choice, FIB-4 calculation. It's non-invasive and very inexpensive. As long as patients have had routine blood work, then you can calculate a FIB-4. Dr. Jesudian, why don't you tell our audience a little bit more about the screening?

Arun B. Jesudian, MD:

Yes. This is a very widely available score. It's one of the non-invasive tests that can help you estimate the likelihood that your patient with MASLD or MASH has advanced fibrosis. Advanced fibrosis is a level of scarring of the liver that either is cirrhosis, stage 4 scarring or nearing that, stage 3 or so. Those are patients you'd really want to look into more deeply in terms of their actual level of fibrosis. You would want to consider them for therapy to help arrest the fibrosis that they've progressed or potentially even cause progression of that fibrosis as you treat their underlying MASH or MASLD. That's something that we will continue to discuss over the course of these series of discussions. As you can see here, the FIB-4 score involves some basic information, some basic blood tests that are really sent all over the place. It's not a specialized type of test that's only available in certain centers. It incorporates the patient's age, their liver enzymes, ALT and AST, and their platelet count. Why is the platelet count important? Because as patients develop more advanced fibrosis, certainly cirrhosis, they could be

at risk of developing portal hypertension, backup of blood flow that causes enlargement of their spleen, and thrombocytopenia or low platelets.

So, using that information, a FIB-4 calculator, you could find that online or some of the electronic medical record systems have this integrated in them. You can then see a score that gives you an assessment of your patient's fibrosis through this non-invasive estimation. Scores less than 1.3 are very reassuring. This rules out advanced fibrosis pretty effectively. Whereas scores greater than 2.67 are relatively predictive of advanced fibrosis. That's certainly someone who you would want to look into more closely in terms of how much fibrosis they actually have. I think of it as a good initial branch point in someone with MASLD and MASH to tell you how concerned you should be about this person's liver, how much fibrosis they have at this point in time. Again, it's available to you as long as you're sending liver enzymes and you know the patient's age and you can send a complete blood count (CBC) and get a platelet count.

Conan Tu, MD, MBA, DACD, BC-ADM:

Excellent. Thank you very much. I do want to point out one caveat. In my organization, we recently started building in MASLD screening with FIB-4s. In our DMR, we use Epic as many other clinicians do. So, to your point, it was quite easy. Even when the score doesn't automatically calculate, for whatever reason, you can simply enter FIB-4 and then it would come out. But there is a little bit of a caveat because the accuracy diminishes as the patient gets older. In our organization, over the age of 65, the cutoff for us goes up to 2.0. So, we use that just to help maintain the utility of that calculation. Is that about what you would recommend?

Arun B. Jesudian, MD:

That's a good point. I think that that makes good sense. I'm glad you brought that up.

Conan Tu, MD, MBA, DACD, BC-ADM:

Excellent. So, let's go back to our gentleman, Mr. B. So, Mr. B's calculation comes out at 2.59. Despite all of his transaminases being normal, despite his platelet count being normal, well, his platelet count was a touch flow, 2.59 is a pretty significantly high reading for somebody who might not overtly have struck us as a patient with liver disease. So, when this 2.59 comes into play and then the low risk would be under 1.3 and then the high risk would be greater than 2.7. So, he falls into this intermediate category. What do you think the next step should be, Dr. Jesudian?

Arun B. Jesudian, MD:

This is certainly someone I would be concerned about having advanced fibrosis based off of that FIB-4. It's not absolutely above that cutoff of 2.67, but it is a pretty high FIB-4. What I would say about patients like this is that clearly he is at risk for having MASLD or MASH and he did have lower platelets, and we shouldn't be falsely reassured by his transaminases as AST and ALT being normal because that's often the case. They don't have to be elevated in patients who have MASLD or MASH. In my line of work, I see a lot of patients with cirrhosis. What happens with cirrhosis is that as fibrosis develops and progresses. There's more and more scar tissue in the liver, which means there are less and less healthy hepatocytes or liver cells. That's where AST and ALT come from. So, patients with cirrhosis oftentimes will have normal liver enzymes because they really don't have as many hepatocytes left over to generate higher than normal transaminase levels.

So, it's possible that he could have compensated cirrhosis. Compensated cirrhosis is by definition asymptomatic. Patients often don't know that they have it, and this high FIB-4 could be a tip off about that. Another piece of information that would be helpful is if he's ever had any imaging of his liver or if you get an ultrasound; it would be helpful to see if he has steatosis in his liver. Certainly, I would pretty much expect this in him because he has metabolic risk factors. He has a high FIB-4 score. If you take him at his word, that he is not really drinking in excess, then we do have some additional non-invasive fibrosis assessments that are more accurate than a FIB-4.

You saw them on that question that you answered, some of the options there. We have transient elastography or an ultrasound-based liver stiffness measurement. Stiffer livers have more scar tissue in them and that's how elastography or liver stiffness measurement works. There is magnetic resonance imaging (MRI) with elastography that is a more sophisticated test. It's not as widely available as an ultrasound-based elastography, which is often found in offices or with a small machine that doesn't require a big infrastructure to support it. There are other serum-based tests that are more accurate than a FIB-4, send-out tests like the ELF, or the enhanced liver fibrosis score.

So, in general, if you see a high FIB-4 and you want to know with more certainty what this gentleman's fibrosis degree is or how concerned you should be about advanced fibrosis or cirrhosis, you could then choose a second non-invasive test. There's always liver biopsy available, usually reserved for if you might be entertaining two different liver diseases, for example. Maybe you're worried he has an autoimmune hepatitis based on some antibodies or serologies you sent. That's when a liver biopsy could be helpful, but we can find out a lot about fibrosis assessment through noninvasive testing.

Conan Tu, MD, MBA, DACD, BC-ADM:

Yes. I wanted to point out that recently, the U.S. Food and Drug Administration (FDA) published new guidelines regarding research trials involving therapeutics, and they recently said that liver biopsies were not required and that noninvasive testing was equivalent. So, the accuracy seems to be pretty good at determining fibrosis score without having to stick a needle in a vascular organ and all the risks that are associated with that. I think people can rest assured in choosing a noninvasive test and feeling reasonably comforted that it is an accurate approximation of fibrosis.

Arun B. Jesudian, MD:

I just mentioned a number of different noninvasive tests or fibrosis assessments in terms of introducing them to you, but in the next program you're going to hear about them in much more detail.

Conan Tu, MD, MBA, DACD, BC-ADM:

I wanted to also point out that the FIB-4 calculation is simply a tool. It has been validated based on extensive research studies, and the FIB-4 calculation is used in all of the current clinical trials studying therapeutics as well. One of the recent big trials that was published just a couple of months ago, the ESSENCE trial, enrolled thousands of patients with fibrosis and they had either F-2, F-3, or F-4 fibrosis. These patients, all in the average FIB-4 score, just over 1.3. So, once it meets that threshold for significance, 1.4 or 2.5, it doesn't necessarily correlate with the severity of fibrosis. As long as they meet that criteria for significance, it is incumbent to go the next step for some noninvasive testing to quantify that fibrosis level.

Arun B. Jesudian, MD:

I think it's such an important point. FIB-4 is a great test in that it's easy and it's widely available. It's not a perfect test. We've seen in some of our clinical trials of MASH therapeutics where the criteria for entry involve a biopsy where patients have stage 2 or 3 fibrosis, moderate or advanced fibrosis that some of them have a FIB-4 that's close to 1.3 or lower than you would expect. That's just important for us to be aware of, but it's still to this day the best initial triage or risk stratification test in terms of it being so widely available and in terms of it generally being good for being able to tell you, as a clinician, who you are worried about having advanced fibrosis or who you are less worried about having advanced fibrosis.

In this case, this gentleman ends up getting an abdominal ultrasound that demonstrates, again, as we would expect, hepatic steatosis, so fat in his liver. He doesn't have any focal liver lesions. That's important because patients, particularly those who have cirrhosis, stage 4 fibrosis, but also we think patients who have advanced fibrosis or stage 3 fibrosis, can be at risk of developing liver cancer or hepatocellular carcinoma. So, it's important to know that on the ultrasound you're not seeing any hepatoma or lesion that could make you concerned for liver cancer. Also, you don't see anything else in terms of structural liver problems. Bile ducts aren't dilated. You don't see any evidence of decompensated liver disease like ascites fluid in the abdomen. But this is a very common ultrasound that you might see where the echogenicity of the liver, that's what the radiologist would refer to it as, is increased. That's what happens when you have abnormal amounts of fat in the liver. So, in patients with metabolic risk factors and who get an ultrasound and you see increased echogenicity or fat, that's certainly someone you want to evaluate further for MASLD or MASH.

A FIB-4 is a good risk stratification–type test to send. Fatty livers, if you're looking at an ultrasound of a fatty liver versus one that's normal, what you really see in the liver tissue is that the fatty liver is going to look brighter or whiter and that is the increased echogenicity, and that's what happens when there's fat inside of the liver as opposed to a normal or a non-existent amount of fat in a normal liver. So, maybe we can transition to speaking a bit about risk stratification in the patient with MASLD and that is regardless of your practice setting, especially early on. We're going to talk about non-invasive testing in much more detail in the next session, but we want to introduce you to this concept of risk stratification. If you're in primary care or a non-gastrointestinal (GI) or hepatology–type practice, what you really want to do is identify patients at risk, so those patients who have metabolic risk factors, those patients who have steatosis on imaging, and then start to risk stratify them in terms of who might have advanced fibrosis.

Just as we've been talking about, the FIB-4 is such a great test for this because it just involves liver enzymes, a platelet count, and patient age. It's easy to calculate, or your electronic medical record might even calculate it for you. That less than 1.3 reassures you that this is a patient who's at lower risk of having advanced fibrosis, but they still need to be periodically reassessed in terms of their MASLD or MASH and whether it could be progressing. So, repeating that FIB-4 every 1-2 years in patients with diabetes or those with two or more metabolic risk factors is important. You might space that out a bit if you have a patient without diabetes or with fewer than two metabolic risk factors. But if that FIB-4 is high, like in our gentleman, or particularly if it's above 2.67, that's a patient you really should consider referring to a gastroenterologist or hepatologist and/or yourself getting another more accurate non-invasive test. We mentioned the types of elastography, ultrasound-based, MRI-based, or sending a proprietary serum test like the enhanced liver fibrosis score.

Again, you're going to hear much about this in the next session, but this is just how a general risk assessment would go. You identify patients at risk and then you send a FIB-4 to give you an idea of how likely they are to

have advanced fibrosis or even cirrhosis. I won't go into too much detail beyond that point, but that's the beginnings of a risk stratification for this type of patient.

Conan Tu, MD, MBA, DACD, BC-ADM:

Well, that's about all the time that we have today. I'd like to thank you, Dr. Jesudian, for your expert perspectives on how risk stratification can be optimized for MASLD and MASH. I'd also like to thank you, our audience, for participating. Before we close, I'd like to offer two SMART goals, actual items that are specific, measurable, attainable, relevant. These timely action items can be applied to the care of your patients in your own practice. First, focus on risk stratification for patients rather than just screening for MASLD and MASH and increase the number of patients assessed in your practice over the next 3-6 months. Then, evaluate ultrasound findings of FIB-4 calculations to identify patients with fibrosis, including those with less obvious risk factors. Again, increase the number of patients assessed in your practice over the next 3-6 months. Those patients who really are at higher risk or surprise you and have more fibrosis, definitely refer them to a hepatologist for further management and care.

To receive credit for this activity, please complete the evaluation and the post-test. Again, please check out the following three Snack activities in this series. Thank you and have a great day.

