The Daffodil Centre

The Australian Prevention Partnership Centre

Preventing liver cancer: Scoping review on diagnostic technologies for the diagnosis of MASH in MAFLD patients

Authors: Anna Kelly, Dr Joachim Worthington, Dr Emily He, Associate Professor Eleonora Feletto

30 June 2023

A partnership between Cancer Council | The University of Sydney

daffodilcentre.org

The project, review and advisory team included: Dr Joachim Worthington, Associate Professor Eleonora Feletto, Dr Emily He, and Anna Kelly. This report was prepared by Anna Kelly.

Acknowledgements: The team would like to thank Georgia Carney, Professor Karen Canfell and Associate Professor Michael Caruana for their assistance with this report.

We thank the Australian Institute of Health and Welfare and the population-based cancer registries of New South Wales, Victoria, Queensland, Western Australia, South Australia, Tasmania, the Australian Capital Territory and the Northern Territory for the provision of data from the Australian Cancer Database.

This research has been supported by seed funding from The Australian Prevention Partnership Centre. The Prevention Centre is funded by the NHMRC, Australian Government Department of Health, ACT Health, Cancer Council Australia, NSW Ministry of Health, Wellbeing SA, Tasmanian Department of Health, and VicHealth. The Australian Government also contributed through the Medical Research Future Fund. Queensland Health became a financial contributor in 2022. The Prevention Centre is administered by the Sax Institute.

The Australian Prevention Partnership Centre

Suggested citation: The Daffodil Centre. Preventing liver cancer: Scoping review on diagnostic technologies for the diagnosis of MASH in MAFLD patients. Sydney; The Daffodil Centre and The Australian Prevention Partnership Centre. June 2023.

Contents

Definitions and Terminology **4**

Scoping Review **5**

1. Purpose of report **5**

2. Introduction **5**

2.1. Review questions and aims 6

3. Methods **6**

3.1. Search strategy 6

3.2. Eligibility criteria 6

3.3. Types of sources 7

3.4. Study selection 7

3.5. Data extraction 7

4. Key findings **7**

4.1. Search outcomes 7

4.2. Fibrosis-4 (FIB-4) Index for Liver Fibrosis 8

4.3. NALFD Fibrosis Score (NFS) 9

4.4. Enhanced Liver Fibrosis (ELF) Test 10

4.5. PRO-C3-based fibrosis algorithm that included age, presence of diabetes, PRO-C3, and platelet count (ADAPT) 12

5. Discussion **12**

6. Conclusion **14**

References **15**

Appendix **18**

Definitions and Terminology

ADAPT is a non-invasive test which detects liver fibrosis through a PRO-C3-based fibrosis algorithm which measures age, presence of diabetes, PRO-C3, and platelet count.(1)

Body mass index (BMI) is the ratio of a person's weight in kilograms (or pounds) to the square of their height in meters, used as a proxy measure for a person's body size. For most adults, the World Health Organization (WHO) defines a BMI (in kg/m 2) of: ≥ 18.5 to <25 as normal weight; ≥ 25 to <30 as overweight, and ≥ 30 as obese.

Compensated cirrhosis refers to asymptomatic build-up of scar tissue in the liver.

Decompensated cirrhosis refers to the build-up of scar tissue in the liver with at least one complication including ascites, jaundice, variceal haemorrhage, or hepatic encephalopathy.

Enhanced Liver Fibrosis (ELF) is a non-invasive test which detects liver fibrosis by assessing three markers: type III procollagen peptide (PIIINP), hyaluronic acid (HA), and tissue inhibitor of metalloproteinase-1 (TIMP1).(2)

Fibrosis refers to the formation of scar tissue in the liver. It can be further classified into stages: F0, there is no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis; F3, numerous septa without cirrhosis; F4, cirrhosis.

Fibrosis-4 (FIB-4) Index for Liver Fibrosis is a non-invasive test for steatosis or fibrosis based on a patient's platelet count and AST level.(3)

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer diagnosed in Australia.(4)

Metabolic-associated fatty liver disease (MAFLD) is the presence of hepatic steatosis in combination with one or more of the following: overweight/obesity, T2DM, or two or more markers of metabolic dysregulation.

Metabolic-associated steatohepatitis (MASH) refers to the presence of hepatic steatosis with evidence of inflammation and hepatocellular injury the form of ballooning of the hepatocytes, with or without fibrosis, in patients with MAFLD.

Non-alcoholic fatty liver disease (NAFLD) encompasses the entire spectrum of fatty liver disease in individuals without other causes such as significant alcohol consumption, chronic viral hepatitis, hereditary disorders, or use of steatogenic medications.

Non-alcoholic fatty liver disease Fibrosis Score (NFS) is a non-invasive test which detects liver fibrosis in NAFLD patients by assessing a patient's age, hyperglycemia, body mass index, platelet count, albumin, and AST/ALT ratio.(5)

Non-alcoholic steatohepatitis (NASH) refers to the presence of hepatic steatosis with evidence of inflammation and hepatocellular injury in the form of ballooning of the hepatocytes, with or without fibrosis, in patients with NAFLD.

Scoping Review

1. Purpose of report

This report describes the evidence review on diagnostic technologies for the diagnosis of MASH in MAFLD patients, completed to support the *Preventing Liver Cancer: Assessing the benefits of risk assessment for patients with metabolic-associated fatty liver disease* report.(6) It is designed to be a supplement to be read in parallel to that report where further detail is required.

This report contains material previously included in the *Preventing Liver Cancer: Obesity and Alcohol Consumption* report.(7)

2. Introduction

Liver cancer is one of the most rapidly growing cancer types in Australia in terms of both incidence and mortality.(8) Hepatocellular carcinoma (HCC), the most common type of liver cancer,(4) often develops in people with underlying liver disease caused by modifiable risk factors.(9)

Categorised as a build-up of excess fat in the liver, metabolic-associated fatty liver disease (MAFLD), linked to excess body fatness, type 2 diabetes mellitus and/or metabolic abnormalities, is a major risk factor for the development of HCC.(10) Previously, patients with MAFLD were typically diagnosed with non-alcohol fatty liver disease (NAFLD). From 2020, the MAFLD classification was introduced; proponents of the new classification argue that MAFLD better reflects the metabolic nature of the disease.(11)[1]

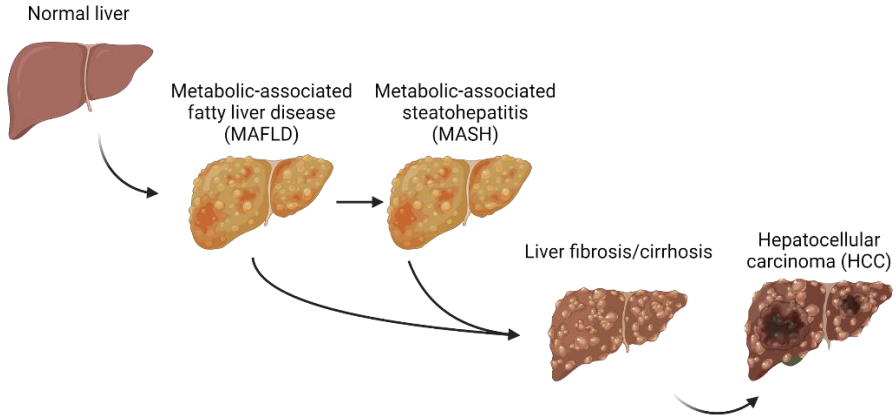
Whilst a benign condition in isolation, the progression of MAFLD to metabolic-associated steatohepatitis (MASH), categorised by inflammation of the liver, can lead to liver scarring (known as fibrosis, or at a later stage, cirrhosis), and a subsequently increased risk of HCC. (10) Patients with MASH are a subgroup of those with MAFLD, and, as with MAFLD and NAFLD, the term 'MASH' has been developed to replace the previous classification of non-alcoholic steatohepatitis (NASH). See Figure 1 for a diagram of the biological pathway of HCC through MAFLD and later MASH.

Risk assessments tools use imaging, biomarkers, and clinical characteristics to diagnose MASH/NASH. This allows patients at elevated risk of HCC to be identified and referred to appropriate HCC surveillance, potentially lessening the burden of screening for those at lower risk.

Given this, the purpose of this review was to identify evidence available from recently published international and national studies on the diagnostic technologies that aim to identify MASH in MAFLD patients.

[1] We will refer to non-MASH MAFLD patients simply as MAFLD patients for convenience; terminology regarding the overlap between MAFLD and MASH patients differs across sources.

Figure 1 – Progression of liver disease to MAFLD, MASH, cirrhosis, and HCC (created with biorender.com)



2.1. Review questions and aims

1. What diagnostic tests are available and in use for the diagnosis of MASH/NASH?
2. How effective are these diagnostic tests for the detection of MASH/NASH?

3. Methods

3.1. Search strategy

A preliminary scope of the literature was conducted to compile a list of currently used and/or on the horizon diagnostic tests for steatohepatitis (see Appendix 1). Expert opinion was sought from a gastroenterologist/hepatologist to identify the tests most relevant in the Australian context. The Fibrosis-4 (FIB-4) Index for Liver Fibrosis, the NALFD Fibrosis Score (NFS) and Enhanced Liver Fibrosis (ELF) Test were identified as the most likely candidates for steatohepatitis screening, based on clinician acceptability and performance.

An electronic literature search was performed in April 2023 using the MEDLINE database to search the national and international literature. Key terms relating to MASH/NASH were paired with terms relating to FIB-4, NFS, or ELF. Complete details are provided in the Appendix 2.

3.2. Eligibility criteria

The eligibility criteria and scope of the review were defined using the “Participant Concept Context” framework.(12) See Appendix 3 for the full study selection criteria.

Participants

As MASH is a relatively new term in the literature, studies based in the NASH population were searched for in addition to studies on MASH. Additionally, as the literature on MASH/NASH in general was scarce, no exclusions were made based on participant demographics.

Concept

To be included, studies needed to report on the sensitivity or specificity of the test, or the area under the receiver operating characteristic curve (AUC). Sensitivity measures the true positive rate in the positive population, specificity measures the true negative rate in the negative population, and the AUC indicates the overall diagnostic accuracy of a test across values of the discrimination threshold. Confidence intervals, measures of heterogeneity, and

p-values were included when available. The data were collected as reported in the original study.

Context

The searches were limited to human studies written in English. There were no specific exclusion criteria based on cultural/sub-cultural factors, geographic location, racial or gender-based interests or details about the setting. Data was extracted from relevant studies to a sufficient level of evidence to answer the research questions, with a focus on recency and relevance to the Australian MASH/MAFLD population.

3.3. Types of sources

Conference abstracts, letters, editorials, and narrative reviews were excluded. All other source types were considered, with systematic reviews, meta-analyses, and pooled analyses identified as the preferred source type. Preprints were included.

3.4. Study selection

Following the search, all identified citations were collated and duplicates removed. Titles and abstracts were screened by one reviewer (AK) for assessment against the inclusion criteria. Potentially relevant articles were retrieved in full and assessed in detail.

3.5. Data extraction

The following information was extracted from relevant studies:

- Study information (title, author, year published, study type, # of studies, study types included, and literature search date for systematic reviews, location)
- Participant information (total # participants, participant type, participant age)
- Information on outcome (outcome type, outcome measure)
- Data (estimates, confidence intervals, heterogeneity, p-values etc.)
- Quality assessment information
- Funding information
- Key conclusions

A formal critical appraisal and risk of bias assessment were not performed as this was outside the scope of this report.

4. Key findings

4.1. Search outcomes

The electronic literature search identified 336, 215, and 70 potentially relevant records on FIB-4, NFS and ELF, respectively (as shown in Appendix 2). After the removal of duplicates and studies that did not meet the inclusion criteria, data was extracted from 12 studies. This included eight studies which reported on the FIB-4 index, six studies which reported on the NFS and six which provided estimates on the ELF test. This also included one study on the PRO-C3-based fibrosis algorithm ADAPT, which was not searched for in the original electronic literature search but identified by JW as a diagnostic tool that may be on the horizon.

Of the 12 studies, five were systematic reviews with meta-analyses,(2,13–16) and seven were cross-sectional studies.(1,17–21)

The characteristics of included studies are presented in Table 1.

Table 1. Characteristics of included studies

Diagnostic Test	Author (year)	Study Type	Literature search to[2]	Participant type	Measures reported	Outcome(s)
FIB-4, NFS	Contreras et al. (2023) (13)	MA	Jan 2022	NAFLD adult patients in cohort and cross-sectional studies	AUC, SE, SP	NASH
FIB-4, NFS	Castellana et al. (2021) (14)	MA	Dec 2020	NAFLD patients in observational studies	SE, SP	AF (F ≥ 3)
FIB-4, NFS	Sun et al. (2016) (15)	MA	NR	NAFLD adult patients in observational studies	SE, SP	AF (F ≥ 3)
FIB-4, NFS	Singh et al. (2020) (17)	CSS	NR	Patients with Type-2 Diabetes and NAFLD in the USA	SE, SP	AF (F ≥ 3)
FIB-4, ELF	Younossi et al. (2023) (18)	CSS	NR	NAFLD adult patients in the USA	AUC, SE, SP	SF (F ≥ 2)
FIB-4, NFS, ELF	Anstee et al. (2019) (19)	CSS	NR	NASH patients, aged between 18 and 70, from 26 countries	SE, SP	AF (F ≥ 3)
FIB-4, NFS	Ismaiel et al. (2021) (16)	MA	Nov 2019	NASH adult patients in observational and case-control studies	AUC	NASH, F stages
ELF	Vali et al. (2020) (2)	MA	Dec 2019	NAFLD adult patients in observational studies	SE, SP	SF (F ≥ 2), AF (F ≥ 3)
ELF	Guillaume et al. (2019) (20)	CSS	NR	NAFLD adult patients from tertiary care centers in France	SE, SP	AF (F ≥ 3)
ELF	Sanyal et al. (2023) (22)	CSS	NR	NAFLD adult patients in the USA	AUC	SF (F ≥ 2), AF (F ≥ 3) and C
ELF	Seko et al. (2023) (21)	CSS	NR	NAFLD patients in Japan	AUC	F stages
ADAPT	Nielsen et al. (2021) (1)	CSS	NR	NAFLD patients, aged between 18 and 75	SE, SP	NASH

NR; not relevant/not retrieved, MA; meta-analysis, CSS; cross-sectional study, AUC; area under the curve, SE; sensitivity, SP; specificity, F; fibrosis, SF; significant fibrosis, AF; advanced fibrosis, C; cirrhosis.

4.2. Fibrosis-4 (FIB-4) Index for Liver Fibrosis

Study characteristics

Four systematic reviews with meta-analyses,(13–16) and four cross-sectional studies (17–19,22) reported on the sensitivity, specificity or AUC of the FIB-4 index.

Relevant outcomes

Reported sensitivity and specificity of the FIB-4 test in detecting NASH in NAFLD patients was estimated at 57% (SE) and 89% (SP) at a cut-off value ≥3.25,(13) and at 76.4% (SE) and 58.4% (SP) with no cut-off value.(22) Sensitivity and specificity of the test in detecting significant fibrosis (F≥2) in NAFLD patients was estimated in two studies, at 47.4% (SE) and 92.1% (SP) at a 1.45 cut-off,(18) and 65.6% (SE) and 80.6% (SP) with no reported cut-off value.(22) As for advanced fibrosis (F≥3) with a 1.3 cut-off value, sensitivity and specificity was reported at 76% (SE) and 67% (SP) (14) and 84.4% (SE) and 68.5% (SP) in NAFLD patients,(15) and 82% (SE) and 57% (SP) in NASH patients.(19) Sensitivity and specificity measurements at a range of other cut-off values, and for the detection of specific fibrosis stages (e.g., cirrhosis) are listed in Table 2, below.

[2] For studies which included a literature search

Table 2 - FIB-4 results

Author (year)	# Participants	Initial disease stage	Outcome	Measure	Est.	LCI	UCI	Cut-off	I2	P-value
Contreras et al. (2023) (13)	3557	NAFLD	NASH	AUC	0.81	0.77	0.84			
				Sensitivity %	57	39	74	3.25	NR	
				Specificity %	89	77	95			
Castellana et al. (2021) (14)	10,074	NAFLD	Advanced fibrosis (F ≥ 3)	Sensitivity %	76	70	81	1.3	NR	
				Specificity %	67	61	73			
	12,265			Sensitivity %	39	30	49	2.67		
				Specificity %	95	93	96			
Sun et al. (2016) (15)	1,038	NAFLD	Advanced fibrosis (F ≥ 3)	Sensitivity %	84.4	77.2	90.1	1.3	NR	
				Specificity %	68.5	65.4	71.6			
				Sensitivity %	38	30	47	3.25		
				Specificity %	96	95	98			
Singh et al. (2020) (17)	1,157	Type-2 Diabetes and NAFLD	Advanced fibrosis (F ≥ 3)	Sensitivity %	44.1	39	49.3	2.67	NR	
				Specificity %	93	91.3	94.8			
				Sensitivity %	72.6	68	77.2	1.45		
				Specificity %	64.4	61.1	67.8			
Younossi et al. (2023) (18)	463	NAFLD	Significant fibrosis (F ≥ 2)	AUC	0.79	0.75	0.83	-	NR	
				Sensitivity %	47.4	39.9	54.9	1.45		
				Specificity %	92.1	88.8	95.4			
				Sensitivity %	12.9	7.9	17.9	3.25		
				Specificity %	99.6	98.8	100			
Anstee et al. (2019) (19)	3,123	NASH	Advanced fibrosis (F ≥ 3)	Sensitivity %	82	81	84	1.3	NR	
				Specificity %	57	54	60			
				Sensitivity %	36	34	38	2.67		
				Specificity %	93	91	94			
Ismaiel et al. (2021) (16)	NR	NAFLD	NASH	AUC	0.729	0.678	0.78			0.358
			Fibrosis stages 0 vs. 1-4		0.723	0.696	0.751		0%	0.607
			Fibrosis stages 0-1 vs. 2-4		0.789	0.714	0.864			0.443
			Fibrosis stages 0-2 vs. 3-4		0.821	0.773	0.87		92.06%	<0.001
Sanyal et al. (2023) (22)	1,073	NAFLD	NASH	Sensitivity %	76.4			Varied		
				Specificity %	58.4					
			Significant fibrosis (F ≥ 2)	Sensitivity %	65.6					
				Specificity %	80.6					
			Advanced fibrosis (F ≥ 3)	Sensitivity %	70.3					
				Specificity %	72.4					
			Cirrhosis (F=4)	Sensitivity %	84.7					
				Specificity %	62.9					

4.3. NALFD Fibrosis Score (NFS)

Study characteristics

Four systematic reviews with meta-analyses,(13–16) and two cross-sectional studies (17,19) reported on the sensitivity, specificity or AUC of the NFS.

Relevant outcomes

Reported sensitivity and specificity of the NFS in detecting NASH in NAFLD patients was estimated at 30% (SE) and 96% (SP) at a cut-off value ≥0.676.(13) The sensitivity and specificity of the NFS in detecting advanced fibrosis (F≥3), also with a 0.676 cut-off, was estimated to be 38% (SE) and 89% (SP) in the NASH population,(19) 34% (SE) and 94% (SP) (14) and 27% (SE) and 98% (SP) (15) in NAFLD patients only, and 64% (SE) and 70% (SP) in a NAFLD population with Type-2 Diabetes.(17) Sensitivity and specificity measurements at a range of other cut-off values, and for the detection of specific fibrosis stages are listed in Table 3, below.

Table 3 - NFS results

Author (year)	# Participants	Initial disease stage	Outcome	Measure	Est.	LCI	UCI	Cut-off	I2	P-value
Contreras et al. (2023) (13)	2749	NAFLD	NASH	AUC	0.82	0.78	0.85	-	NR	
				Sensitivity %	30	27	33	0.676		
				Specificity %	96	95	96			
Castellana et al. (2021) (14)	9,221	NAFLD	Advanced fibrosis (F ≥ 3)	Sensitivity %	81	73	86	-1.455	NR	
				Specificity %	64	56	72			
	11,411			Sensitivity %	34	25	45	0.676		
				Specificity %	94	91	96			
Sun et al. (2016) (15)	1,038	NAFLD	Advanced fibrosis (F ≥ 3)	Sensitivity %	77	69	84	-1.455	NR	
				Specificity %	70	67	73			
				Sensitivity %	27	19	35	0.676		
				Specificity %	98	96	98			
Singh et al. (2020) (17)	1,157	Type-2 Diabetes and NAFLD	Advanced fibrosis (F ≥ 3)	Sensitivity %	63.7	58.5	68.8	0.676	NR	
				Specificity %	70	66.7	73.4			
				Sensitivity %	94.6	92.2	97.1	−1.455		
				Specificity %	16.9	14.2	19.7			
Anstee et al. (2019) (19)	2,417	NASH	Advanced fibrosis (F ≥ 3)	Sensitivity %	89	88	91	-1.455	NR	
				Specificity %	37	33	42			
				Sensitivity %	38	36	40	0.676		
				Specificity %	89	86	92			
Ismaiel et al. (2021) (16)	NR	Varied (metareview)	NASH	AUC	0.687	0.612	0.762	-	0%	0.348
			Fibrosis stages 0 vs. 1-4		0.718	0.651	0.785		69.19%	0.072
			Fibrosis stages 0-2 vs. 3-4		0.787	0.733	0.84		92.86%	<0.001

4.4. Enhanced Liver Fibrosis (ELF) Test

Study characteristics

One systematic review with meta-analysis,(2) and five cross-sectional studies,(18–22) reported on the sensitivity, specificity, or AUC of the ELF test.

Relevant outcomes

The sensitivity and specificity of the ELF test in detecting significant fibrosis (F≥2) in the NAFLD population was estimated to be 71.8% (SE) and 81.5% (SP) by Sanyal et al. (no specified cut-off value),(22) 17% (SE) and 99% (SP) by Vali et al. (cut-off value = 11.3) (2)

and 12.8% (SE) and 99.3% (SP) by Younossi et al. (cut-off value = 11.3).(18) The sensitivity and specificity of the test in detecting advanced fibrosis (F≥3) in the NAFLD population was estimated to be 80.8% (SE) and 70.2% (SP) by Sanyal et al. (no specified cut-off value),(22) 47.3% (SE) and 89.6% (SP) by Guillaume et al. (cut-off value = ≥10; p-value = 0.497 and 1, respectively) (20) and 36% (SE) and 96% (SP) by Vali et al. (cut-off value = 11.3).(2) The sensitivity and specificity of the test in detecting advanced fibrosis in the NASH population was reported by Anstee et al. at 20% (SE) and 98% (SP),(19) respectively, with a cut-off value of 11.3. Sensitivity and specificity measurements at a range of other cut-off values are listed in Table 4, below.

Table 4 - ELF results

Author (year)	# Participants	Initial disease stage	Outcome	Measure	Est.	LCI	UCI	Cut-offs	P-value
Vali et al. (2020) (2)	2655	NAFLD	Advanced fibrosis (F ≥ 3)	Sensitivity %	93	82	98	7.7	NR
				Specificity %	34	13	65		
				Sensitivity %	65	49	77	9.8	
				Specificity %	86	77	92		
				Sensitivity %	51	31	70	10.51	
				Specificity %	93	85	96		
				Sensitivity %	36	15	63	11.3	
				Specificity %	96	90	99		
	550		Significant fibrosis (F ≥ 2)	Sensitivity %	97	88	99	7.7	
				Specificity %	10	3	26		
				Sensitivity %	57	40	73	9.8	
				Specificity %	89	73	96		
				Sensitivity %	35	22	50	10.51	
				Specificity %	97	89	99		
				Sensitivity %	17	9	29	11.3	
				Specificity %	99	96	1		
Younossi et al. (2023) (18)	463	NAFLD	Significant fibrosis (F ≥ 2)	AUC	0.78	0.74	0.82	NR	NR
				Sensitivity %	44.4	37.2	51.7	9.8	
				Specificity %	91.5	88.3	94.8		
				Sensitivity %	12.8	7.9	17.7	11.3	
				Specificity %	99.3	98.3	100		
Anstee et al. (2019) (19)	3,173	NASH	Advanced fibrosis (F ≥ 3)	Sensitivity %	74	72	75	9.8	NR
				Specificity %	73	70	76		
				Sensitivity %	20	19	22	11.3	
				Specificity %	98	96	99		
Guillaume et al. (2019) (20)	417	NAFLD	Advanced fibrosis (F ≥ 3)	Sensitivity %	73.1	NR		9.30	0.312
				Specificity %	72				0.306
				Sensitivity %	89.8			8.64	1
				Specificity %	42.4				0.042
				Sensitivity %	47.3			10	0.497
				Specificity %	89.6				1

Sanyal et al. (2023) (22)	1,073	NAFLD	Significant fibrosis (F ≥ 2)	Sensitivity %	71.8	NR		
				Specificity %	81.5			
			Advanced fibrosis (F ≥ 3)	Sensitivity %	80.8			
				Specificity %	70.2			
			Cirrhosis (F=4)	Sensitivity %	82.1			
				Specificity %	73.3			
Seko et al. (2023) (21)	371	NAFLD	F0 vs. F1-4	AUC	0.825	NR	9.1	NR
			F0-1 vs. F2-4		0.817		10.11	
			F0-2 vs. F3-4		0.802		11.1	
			F0-3 vs. F4		0.812		11.54	

4.5. PRO-C3-based fibrosis algorithm that included age, presence of diabetes, PRO-C3, and platelet count (ADAPT)

Study characteristics

Data was extracted from one cross-sectional study on the ADAPT tool.(1)

Relevant outcomes

The sensitivity and specificity of the ADAPT tool in detecting NASH in the NAFLD population was estimated by Nielsen et al. at 77% and 69%, respectively, at a cut-off greater than 5.5.(1)

Table 5 - ADAPT results

Author (year)	# Participants	Population	Outcome	Measure	Est.	Cut-off	P-value
Nielsen et al. (2021) (1)	517	NAFLD	NASH	Sensitivity %	77	5.5	NR
				Specificity %	69		

5. Discussion

Brief overview of findings

Eight studies reported on the FIB-4 index,(13–19,22) six studies reported on the NFS,(13–17,19) six studies reported on the ELF test,(2,18–22) and one study reported on the ADAPT tool.(1) Whilst no evidence on the diagnostic accuracy of the tools was specific to the Australian context, there was a substantial amount of meta-analysis evidence conducted on a large scale,(2,13–16) involving participants from a wide range of geographical locations and ethnicities, including evidence from developed countries such as the USA,(17,18,22) Japan,(21) and France.(20)

In all the diagnostic tests reviewed, there was a significant range of sensitivity and specificity observed across various cutoffs. This indicates the need for further research to determine the most appropriate cutoffs for specific settings and situations. No single diagnostic test was found to be conclusively superior to others.

Of the studies which measured the diagnostic accuracy of both the FIB-4 test and the NFS, three indicated slight preference of the FIB-4 test over the NFS (15–17), whilst two did not indicate a preference, concluding the two tests had similar accuracy.(13,14) Similarly, of the two studies which compared diagnostic accuracies of the FIB-4 and/or NFS with those of the ELF test, neither indicated a strong preference for either test.(18,19) Overall, FIB-4 is the most likely candidate for HCC surveillance in current practice due to its familiarity among general practitioners, while emerging algorithms like ADAPT may offer improvements to diagnostic performance.

Strengths and limitations of the review

A strength of this scoping review is the extensive nature of the search across all types of research studies published in both the international and national literature. Another strength of this review is that it was developed in accordance with expert opinion from a gastroenterologist/hepatologist based in Australia who assisted in the development of the search strategy, to ensure identification of the most prevalent diagnostic tools within the Australian context. A strength of all included studies was that liver biopsy was used as the standard reference tool to diagnose NASH or NAFLD, except for Contreras et al.(13) which also included studies that used abdominal ultrasound.

As this report was a scoping and not systematic review, no formal critical appraisal or risk of bias assessment was performed. Another limitation is that studies were restricted to those published in the last decade and in English. However, as the relevant patient population has changed dramatically and new technologies have emerged, it is unlikely that older evidence is relevant to the current study. Data was extracted from relevant studies only up until the point where there was a sufficient level of evidence to answer the research question, meaning that this scoping review is not exhaustive of all literature published on these diagnostic tests within the last decade.

Implications and future directions

There is accumulating evidence showing that combinations of multiple diagnostic tests may provide superior accuracy in diagnosing these conditions.(18,19) There is currently limited evidence demonstrating the correlations between these tests in individuals with and without MAFLD or MASH, limiting the inferences that can be made about test combinations. A further scoping review on the diagnostic accuracy of combinations of diagnostic tests would be an important area of future research.

Notably, there was a clear gap in the literature in that no studies were identified relating to the diagnostic accuracy of the tests in the MAFLD or MASH population. The MAFLD classification was proposed by expert consensus in 2020,(23,24) and has been endorsed in letter of more than 1,000 signatories from professional bodies as well as specialist and primary care physicians.(11) The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver are yet to endorse the change in terminology.(11) When this new definition is accepted into standard practice and adopted by practitioners, research on the transference of these tools to diagnose patients within this new diagnostic criterion will be vital.

Numerous biomarkers and algorithms for assessing liver disease are currently in development, with some undergoing validation. For example, Cheng (25) examined the predictive value of biomarkers such as extracellular vesicles for HCC development, and Carter et al. (26) assessed the cost-effectiveness of a serum-based biomarker. Tools like the GALAD score incorporate these biomarkers along with other risk factors to calculate an overall HCC risk score.(27) As these algorithms continue to mature, it is necessary to ensure that the healthcare system prioritizes the most promising technologies based on their health benefits and the cost burden on patients.

6. Conclusion

This scoping report identified and reviewed evidence from recently published national and international studies on the diagnostic tests that aim to identify MASH/NASH.

Whilst there seems to be a moderate body of evidence relating to the diagnostic accuracy of the tools in the NASH/NAFLD population, no studies have been conducted in the Australian context, nor in the MASH/MAFLD population.

Overall, the body of literature reviewed in this summary report substantiated that, at certain cut-offs, the FIB-4 Index, NFS, ELF Test and ADAPT Tool have reasonable sensitivity and specificity. However, there was limited evidence on the use of ELF to diagnose MASH/NASH in MAFLD/NAFLD patients; further evidence is required to determine whether ELF is appropriate for accurately diagnosing patients with NASH.

As rates of obesity and the metabolic syndrome rise in Australia, so too will the prevalence of MAFLD, MASH and related primary liver cancer. It is important that efforts continue to understand the tools which exist to diagnose MASH/NASH so that patients at elevated risk of HCC can be identified and referred to appropriate HCC surveillance. This will lessen the burden of screening for those at lower risk while providing protection for those at high risk.

References

1. Nielsen MJ, Leeming DJ, Goodman Z, Friedman S, Frederiksen P, Rasmussen DGK, et al. Comparison of ADAPT, FIB-4 and APRI as non-invasive predictors of liver fibrosis and NASH within the CENTAUR screening population. J Hepatol. 2021 Dec;75(6):1292–300.

2. Vali Y, Lee J, Boursier J, Spijker R, Loffler J, Verheij J, et al. Enhanced liver fibrosis test for the non-invasive diagnosis of fibrosis in patients with NAFLD: A systematic review and meta-analysis. J Hepatol. 2020;73(2):252–62.

3. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006 Jun;43(6):1317–25.

4. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021 Jan 21;7(1):6.

5. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: A noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007;45(4):846–54.

6. The Daffodil Centre. Preventing Liver Cancer: Assessing the benefits of risk assessment for patients with metabolic-associated fatty liver disease. Sydney: The Daffodil Centre; 2023 Jun.

7. The Daffodil Centre. Preventing liver cancer: obesity and alcohol consumption. [Internet]. The Daffodil Centre and The Australian Prevention Partnership Centre; 2023 Apr. Available from: https://preventioncentre.org.au/resources/preventing-liver-cancer-obesity-and-alcohol-consumption/

8. Cocker F, Chien Yee K, Palmer AJ, de Graaff B. Increasing incidence and mortality related to liver cancer in Australia: time to turn the tide. Australian and New Zealand Journal of Public Health. 2019 Jun 1;43(3):267–73.

9. Wallace MC, Preen DB, Short MW, Adams LA, Jeffrey GP. Hepatocellular carcinoma in Australia 1982-2014: Increasing incidence and improving survival. Liver Int. 2019 Mar;39(3):522–30.

10. Adams LA, Roberts SK, Strasser SI, Mahady SE, Powell E, Estes C, et al. Nonalcoholic fatty liver disease burden: Australia, 2019–2030. Journal of Gastroenterology and Hepatology. 2020;35(9):1628–35.

11. Méndez-Sánchez N, Bugianesi E, Gish RG, Lammert F, Tilg H, Nguyen MH, et al. Global multi-stakeholder endorsement of the MAFLD definition. Lancet Gastroenterol Hepatol. 2022 May 1;7(5):388–90.

12. Peters M, Godfrey C, McInerney P, Munn Z, Tricco A, Khalil H. JBI Manual for Evidence Synthesis. In: Chapter 11: Scoping Reviews (2020 version) [Internet]. JBI; 2020. Available from: https://synthesismanual.jbi.global

13. Contreras D, Gonzalez-Rocha A, Clark P, Barquera S, Denova-Gutierrez E. Diagnostic accuracy of blood biomarkers and non-invasive scores for the diagnosis of NAFLD and NASH: Systematic review and meta-analysis. Ann Hepatol. 2023;28(1):100873.

14. Castellana M, Donghia R, Guerra V, Procino F, Castellana F, Zupo R, et al. Fibrosis-4 Index vs Nonalcoholic Fatty Liver Disease Fibrosis Score in Identifying Advanced Fibrosis in Subjects With Nonalcoholic Fatty Liver Disease: A Meta-Analysis. Am J Gastroenterol. 2021;116(9):1833–41.

15. Sun W, Cui H, Li N, Wei Y, Lai S, Yang Y, et al. Comparison of FIB-4 index, NAFLD fibrosis score and BARD score for prediction of advanced fibrosis in adult patients with non-alcoholic fatty liver disease: A meta-analysis study. Hepatol res. 2016;46(9):862–70.

16. Ismaiel A, Leucuta DC, Popa SL, Fagoonee S, Pellicano R, Abenavoli L, et al. Noninvasive biomarkers in predicting nonalcoholic steatohepatitis and assessing liver fibrosis: systematic review and meta-analysis. Panminerva Med. 2021;63(4):508–18.

17. Singh A, Gosai F, Siddiqui MT, Gupta M, Lopez R, Lawitz E, et al. Accuracy of Noninvasive Fibrosis Scores to Detect Advanced Fibrosis in Patients With Type-2 Diabetes With Biopsy-proven Nonalcoholic Fatty Liver Disease. J Clin Gastroenterol. 2020;54(10):891–7.

18. Younossi ZM, Stepanova M, Felix S, Jeffers T, Younossi E, Goodman Z, et al. The combination of the enhanced liver fibrosis and FIB-4 scores to determine significant fibrosis in patients with nonalcoholic fatty liver disease. Aliment Pharmacol Ther. 2023;(a5d, 8707234).

19. Anstee QM, Lawitz EJ, Alkhouri N, Wong VWS, Romero-Gomez M, Okanoue T, et al. Noninvasive Tests Accurately Identify Advanced Fibrosis due to NASH: Baseline Data From the STELLAR Trials. Hepatology. 2019;70(5):1521–30.

20. Guillaume M, Moal V, Delabaudiere C, Zuberbuhler F, Robic MA, Lannes A, et al. Direct comparison of the specialised blood fibrosis tests FibroMeterV2G and Enhanced Liver Fibrosis score in patients with non-alcoholic fatty liver disease from tertiary care centres. Aliment Pharmacol Ther. 2019;50(11–12):1214–22.

21. Seko Y, Takahashi H, Toyoda H, Hayashi H, Yamaguchi K, Iwaki M, et al. Diagnostic accuracy of enhanced liver fibrosis test for nonalcoholic steatohepatitis-related fibrosis: Multicenter study. Japan Study Group of Nonalcoholic Fatty Liver Disease (JSG-NAFLD), editor. Hepatol res. 2023;53(4):312–21.

22. Sanyal A, Shankar S, Yates K, Bolognese J, Daly E, Dehn C, et al. The Nimble Stage 1 Study Validates Diagnostic Circulating Biomarkers for Nonalcoholic Steatohepatitis. Res Sq. 2023;(101768035).

23. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol. 2020 Jul 1;73(1):202–9.

24. Eslam M, Sanyal AJ, George J, Sanyal A, Neuschwander-Tetri B, Tiribelli C, et al. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterol. 2020 May 1;158(7):1999-2014.e1.

25. Cheng RM. Novel Biomarkers of Hepatocellular Carcinoma [Internet]. The University of Sydney; 2018. Available from: http://hdl.handle.net/2123/20294

26. Carter HE, Jeffrey GP, Ramm GA, Gordon LG. Cost-Effectiveness of a serum biomarker test for risk-stratified liver ultrasound screening for Hepatocellular Carcinoma. Value in Health. 2021 Oct;24(10):1454–62.

27. Yang JD, Addissie BD, Mara KC, Harmsen WS, Dai J, Zhang N, et al. GALAD Score for Hepatocellular Carcinoma Detection in Comparison with Liver Ultrasound and Proposal of GALADUS Score. Cancer Epidemiol Biomarkers Prev. 2019 Mar 1;28(3):531–8.

Appendix

Appendix 1 List of currently used and/or on the horizon diagnostic tests for steatohepatitis

Test Type	Name of Test
Biopsy	Invasive Liver Biopsy
Blood and Serum Test	NAFLD Fibrosis Score (NFS)
	Fibrosis-4-Score (FIB-4)
	AST to Platelet Ratio Index (APRI)
	FibroTest
	FibroMeter
	Hepascore
	NAFLD Activity Score
	CHeK score
	Enhanced Liver Fibrosis (ELF) test
	NASH score
	NASH ClinLipMet Score
	ADAPT Score
	NASHnext
	NASH-FibroTest
	oxNASH score
	Fatty Liver Index (FLI)
	CK18-M30 Tests
	Fatty Liver Inhibition of Progression (FLIP)
	Steatosis, Activity, Fibrosis (SAF) scoring system
	NASH Test (NT)
	HAIR test
	Palekar score
	Gholam score
	NAFIC score
	Aspartate transaminase (AST)/alanine transaminase (ALT) ratio
	METAVIR
	Ishak score
	Hepatic Steatosis Index (HIS)
	NAFLD Liver Fat Score
	NASH Diagnostics
	NASH Model of NAFLD Diagnostic Panel
Imaging Techniques	Vibration-controlled transient elastography (VCTE)
	Controlled Attenuation Parameter (CAP)

	Point Shear Wave Elastography (pSWE)
	Two-Dimensional (2D) Shear Wave Elastography
	Magnetic Resonance Elastography (MRE) – 2D and 3D
	Magnetic Resonance Imaging Derived Proton Density Fat Fraction (MRI-PDFF)
	Real-time elastography (RT-E)

Appendix 2 Database Search

Fibrosis-4 (FIB-4) Index for Liver Fibrosis

#	Searches	# Results
1	(Fibrosis-4-Score or FIB-4 or Fibrosis-4 or FIB4 or Fibrosis 4).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	2858
2	(Nonalcoholic steatohepatitis or NASH or metabolic associated steatohepatitis or MASH or steatohepatitis).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	21877
3	1 and 2	336

Database(s): Ovid MEDLINE® ALL 1946 to April 2023

NALFD Fibrosis Score (NFS)

#	Searches	# Results
1	(NAFLD fibrosis score or NFS).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	3612
2	(Nonalcoholic steatohepatitis or NASH or metabolic associated steatohepatitis or MASH or steatohepatitis).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	21877
3	1 and 2	215

Database(s): Ovid MEDLINE® ALL 1946 to April 2023

Enhanced Liver Fibrosis (ELF) Test

#	Searches	# Results
1	(Enhanced Liver Fibrosis or ELF).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	4006
2	(Nonalcoholic steatohepatitis or NASH or metabolic associated steatohepatitis or MASH or steatohepatitis).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	21877
3	1 and 2	70

Database(s): Ovid MEDLINE® ALL 1946 to April 2023

Appendix 3 Study selection criteria

Selection criteria	Inclusion	Exclusion
Publication type	Original research articles	Conference abstracts, letters, editorials, narrative reviews, posters, academic theses

Study design	Meta-analyses (MA), systematic reviews (SR), pooled analyses, randomised controlled trials (RCTs), cohort studies, cost-control studies, post-hoc analyses (e.g., cross-sectional, and longitudinal observational studies), models or modelling studies.	Case report or case series
Population	NA	NA
Intervention	NA	NA
Comparator	NA	NA
Outcome	Fibrosis (any stage), cirrhosis, NAFLD/MAFLD or NASH/MASH	NA
Outcome measures	Sensitivity, Specificity or area under the curve (AUC)	NA
Language	English	Not in English
Publication period	Studies published in the last decade (2013-2023)	Studies published in 2012 or earlier.