



User manual for the FIB-4 Index

Version 1.0, Feb 2026, in English

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1. The Evidencio platform

The Evidencio platform facilitates the creation, use, validation and implementation of medical prediction algorithms and clinical decision support tools. This user manual specifically relates to the FIB-4 Index. The User Manual can also be referred to as the Instructions For Use (IFU). The FIB-4 Index meets the requirements laid down in: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. Compliance with the applicable regulations is provided by means of declaration of conformity.

Throughout this manual CE-marked content and the term medical device are used interchangeably.

2. Disclaimer

Evidencio provides certain CE-marked information, calculators, equations, and algorithms (tools) on any of its websites, applications, apps, or services. These tools may only be used in accordance with the intended use / intended purpose that has been published with the respective CE-marked tool.

In general, and unless explicitly stated otherwise, CE-marked tools on Evidencio are only to be used by physicians in a clinical setting and are not for patient use.

The CE-marked content on the platform is to be regarded as a specific set of tools, apart from the general platform content. Any available content, on any of the websites, applications, apps, or services provided by Evidencio that is not clearly labelled as a CE-marked tool is explicitly not covered by this disclaimer for CE-marked content, the general Evidencio Disclaimer for non-CE-marked content applies.

CE-marked tools may provide limited professional advice to the intended user(s). However, the intended user must exercise their clinical judgment as to the information these tools provide.

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Your use of the websites, applications, apps, or services provided by Evidencio is subject to our Terms & Conditions, which can be found here: <https://www.evidencio.com/terms-conditions>.

3. Warnings



Calculations alone should never dictate patient care, and are no substitute for professional judgement. This tool is only to be used by physicians in a clinical setting, and is not for patient use.

Always read the intended use before using this tool.

Always make sure the patient complies with the clinical indications and clinical contra-indications as stated on the Evidencio website and in **section 6.3.2** of this user manual.

Before reading the result, double check the filled in values to prevent errors.

Results that concern risk percentages, do not guarantee certain outcomes. When there is a risk present, do not expect an event to not occur at all, even if the risk is very small. Conversely, a high risk does not guarantee that an event will occur.

This algorithm is only intended for use in settings where the usage and result of an algorithm are never immediately needed.

Calculations alone should never dictate patient care, and are no substitute for professional judgement. See our full disclaimer on: <https://www.evidencio.com/disclaimer>.

The data used to perform the calculations is stored by Evidencio to enhance algorithm function and allow issues to be traceable for further improvements. For details, see the privacy policy on our website at: <https://www.evidencio.com/privacy-policy>.

3.1. Notice to the user

Any serious incident that has occurred in relation to the device should be reported to the manufacturer and the competent authority of the country in which you, the reader, are established. A competent authority is the institute that governs all issues related to medical devices in a country.

Please contact Evidencio when you suspect any malfunction or changes in the performance of a medical device. Do not use the device, until Evidencio replies to your message that it is safe to start using it again.

4. Device Description FIB-4 Index

The FIB-4 Index is a scoring algorithm which can be used to estimate the risk of advanced fibrosis. The algorithm can be used to assist support clinical decision-making regarding prognosis and diagnosis.

The device is intended to be used for patients older than 18 years who have an increased risk of, or currently have, liver disease, and who are at risk of advanced fibrosis. It should not be used for patients who do not have an increased risk of advanced liver fibrosis.

The results of the FIB-4 Index should be reviewed with extra attention for patients with; diabetes and/or metabolic syndrome symptoms, haemochromatosis, and Sustained virologic response (SVR) in HCV patients.

The calculation of the algorithm is performed by communication with the Evidencio platform, hosted at www.evidencio.com. Local hosting of the algorithm on another platform is possible using Docker images. The algorithm is also accessible by 3rd party applications through the API and iFrame implementation. The Evidencio platform is managed under Evidencio's certified quality management system that ensures the correctness of calculations and availability of its services.

A summary of safety and performance (SSP) is made publicly available on the EUDAMED database. Information on publicly available CE-marked algorithms, including their corresponding SSP's, can be found on the manufacturer's page of Evidencio within the EUDAMED database.

4.1. Lifetime, residual risks and side effects

The FIB-4 Index is software, and does not expire. The lifetime is initially set at 5 years from certification, if the state of the art does not change in such a way as to negatively affect the benefit-risk of the device, the lifetime can be extended.

No steps are required to be undertaken by the user to decommission a product when it is taken off the market. If the lifetime is not extended, a notice will be placed on the algorithm page on the platform. When a device is taken off the market, users may be informed about this (e.g. through e-mail).

Evidencio has identified a series of risk associated with the use of this algorithm.

The FIB-4 Index is a low-risk device, there are no noticeable risks involved outside of possible mis-estimation of patient risk for liver fibrosis, and all residual risks are accepted.

Most risk can be defined into two main groups, depending on their outcome.

- a) The risk calculation was wrong or;
- b) The MDSW prediction algorithm is inaccessible.

A wrong risk calculation can be the result of erroneous input values or an error in the mathematical calculation. Technical risks, including the erroneous calculations or the inaccessibility due to a technical error, have been mitigated when possible. These measures focussed on reducing the risks' probability and severity. Concluding that the risks could not be mitigated further, the residual risks were classified as *low-level and acceptable*. It should be noted that the use of Evidencio's Medical Device Software is itself a risk mitigation measure, as Evidencio's certified Quality Management System ensures and monitors the reliability of the calculations performed with its certified medical devices.

The FIB-4 Index does not have any direct side effects.

5. Electronic Label

The electronic label of this device contains the following information:

	Name of the device	FIB-4 Index
	Manufacturer information	Evidencio B.V., Irenesingel 19, 7481 GJ Haaksbergen, The Netherlands
	LOT number	V-1.0-10277.25.06.17
	UDI number	(01)08720938015113(8012)v1.0(4326)240412(240)10277
	IVD indication	<i>In vitro</i> diagnostic medical device

The electronic label can be found on the Evidencio website. An example can be seen in **Chapter 9 Section I** and **Figure 5**.

The electronic label on the website further contains the option to download the **User Manual** and **Declaration of conformity** (DoC).

5.1. LOT number

The LOT number indicated the algorithm version, the algorithm identifier, and the algorithm publication date. Publication date is indicated as YY.MM.DD.

5.2. UDI number

Stands for Unique Device Identifier (UDI) number is an international tool that helps users identify and find information on products. Evidencio's UDI's have the following format:

(01)[UDI-DI number](8012)[versionnumber](4326)[releasedate](240)[identificationnumber]

The UDI-DI (Device Identifier) number is a unique numeric code. For each medical device of Evidencio, a unique UDI-DI is ascribed. This UDI-DI is used as an "access key" for information stored in a unique device identification database (UDID). Information on Evidencio's medical devices can be found by searching for the UDI-DI number in the following data base: <https://gepir.gs1.org/index.php/search-by-gtin>.

6. Intended Purpose

6.1. Intended Medical Use

The FIB-4 Index is a non-invasive risk stratification tool intended to be used by healthcare professionals as the first-line step in assessing the likelihood of advanced liver fibrosis (stage F3-F4). It is intended for use in adults suspected of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) or with chronic Hepatitis C Virus (HCV) infection to triage patients into low, Intermediate, or high likelihood and therefore at-risk categories.

The FIB-4 Index combines age, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and platelet count. AST and ALT (enzymes) and platelet count are all measured in a blood specimen. The FIB-4 Index is medical device software that automates the calculation of the formula. It requires quantitative inputs to provide a semi-quantitative output.

The FIB-4 Index is not intended to replace clinical decision-making; it can only provide information to the healthcare professional on the risk stratification of advanced liver fibrosis (stage F3-F4). FIB-4 Index must be interpreted in conjunction with other diagnostic findings and clinical information in accordance with standard clinical management guidelines.

6.2. Clinical Benefit

The FIB-4 Index is intended to assist patients with relevant and specified clinical outcome parameters. Concretely, this is achieved by estimating a risk in order to support clinical decision-making aimed at patients with (potential) liver disease who are suspected or at risk of having advanced liver fibrosis, in order to support clinical decision-making regarding patient prognosis and diagnosis. Correct functioning of the FIB-4 Index can result in these clinical benefits:

- The FIB-4 Index can assist in risk stratification for patients
- Digital implementation of the algorithm underlying the FIB-4 Index as a medical device can improve the speed and reliability of calculation.

6.3. Intended target population and exclusion

The FIB-4 Index is intended to be used only for a specific group of patients, corresponding to the below indications and contra-indications. The result of the FIB-4 Index is intended to be reviewed and interpreted by healthcare professionals only. The device is not intended for use by patients on their own.

6.3.1. Clinical Indications

The FIB-4 Index should be used for patients who meet the following inclusion criteria:

- Adults (≥ 18 years of age)
- Patients with suspected or established chronic liver disease due to one or more of the following etiologies:
 - Patients suspected of Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) including Metabolic dysfunction-Associated Steatohepatitis (MASH)
 - Chronic hepatitis C (HCV)

6.3.2. Clinical contra-indications

The FIB-4 Index should not be used for patients who meet the following exclusion criteria:

- Patients with Hepatocellular Carcinoma (HCC)

Although not considered exclusion criteria, the results of the FIB-4 Index should be reviewed with extra attention if the patient meets one or more of the following:

- Haemochromatosis, since there is little data on this in the context of risk prediction algorithms, including the FIB-4 Index
- Sustained virologic response (SVR) in HCV patients
- In chronic hepatitis B (HBV), standard FIB-4 cut-offs may misclassify fibrosis stage (reported in the EASL clinical practice guideline on the management of HBV infection, based on the SONIC-B study).

6.4. User profile

The FIB-4 Index is intended to be used by professional users capable of operating the device and interpreting its results. It is intended to be used in two ways; by healthcare professionals using the algorithm interface on the Evidencio website or an image of the algorithm hosted by a distributor, or by using an automatic calculation through Evidencio's API. Results shall always be reviewed and interpreted by healthcare professionals, in the context of the patient's clinical history and other diagnostic test results. Healthcare professionals do not require additional training prior to the use of the medical device. The device is not intended for use by patients on their own.

6.5. Intended use environment

The MDSW can be used as made available on the Evidencio platform in any actively supported web-browser on personal computers, mobile devices, or tablet PCs. The MDSW can also be used through Evidencio's iFrame representation as an embedded view, provided that the specific Evidencio guidelines for iFrame implementations of this MDSW are adhered to. Automated calculation of the device is enabled through Evidencio's API. The device is only intended for use in healthcare settings where the immediate application and outcomes of the device are not required.

6.6. Physical interaction

The MDSW is stand-alone software and does not come into contact with any bodily or other material of the patient, user or otherwise.

6.7. Versions of the MDSW

The version of the FIB-4 Index concerns the initial version of MDSW of which Evidencio is the manufacturer.

7. Result interpretation

Primary outcome

The primary output of this device is given as a score between 0 and 20,000, which can be used to estimate the probability of advanced fibrosis and/or estimate the severity of the fibrosis. The exact relation of the outcome with the risk of the patient depends on both patient population and what is being predicted.

Conditional information

Depending on the guideline selected, the model provides an output with an associated next step, as illustrated in the example below.

FIB-4 Index result: The patient has low likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for MASLD population

Next step: Re-assess FIB-4 every 1 - 3 years (EASL-EASD-EASO (2024)).

Reference: EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol. 2024 Sep;81(3):492-542. doi: 10.1016/j.jhep.2024.04.031.

Calculations alone should never dictate patient care, and are no substitute for professional judgement. See the Evidencio website for the full disclaimer; <https://www.evidencio.com/disclaimer>.

FIB-4 Index cut-offs

The FIB-4 Index outcome is a numeric score that can be interpreted as the likelihood of having advanced liver fibrosis. More precisely, based on cut-off values, outcomes of the FIB-4 Index can be interpreted as different likelihoods of having advanced liver fibrosis. Based on the condition of the patient, FIB-4 Index outcomes can be interpreted as presented in **Table 1**.

Table 1. Outcome and corresponding interpretation of the FIB-4 Index.

Condition	Guideline/ reference	Outcome	Interpretation
Susp. MASLD <i>No age specific cutoff</i>	UK local (NHS Oxford) AASLD AACE APASL	FIB-4 Index < 1.3	The patient has low likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for MASLD population.
		FIB-4 Index ≥ 1.3 & ≤ 2.67	The patient has intermediate likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for MASLD population.
		FIB-4 Index > 2.67	The patient has high likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for MASLD population.
Susp. MASLD ≤ 65 years	EASL-EASD-EASO (2024)	FIB-4 Index < 1.3	The patient has low likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for MASLD population.
		FIB-4 Index ≥ 1.3 & ≤ 2.67	The patient has intermediate likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for MASLD population.
		FIB-4 Index > 2.67	The patient has high likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for MASLD population.
Susp. MASLD > 65 years	BASL AGA	FIB-4 Index < 2.0	The patient has low likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for MASLD population.
		FIB-4 Index ≥ 2.0 & ≤ 2.67	The patient has intermediate likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for MASLD population.
		FIB-4 Index > 2.67	The patient has high likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for MASLD population.
Chronic HCV <i>no age specific cutoff</i>	Sterling et al. EASL GL HCV (2020)	FIB-4 Index < 1.45	The patient has low likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for Chronic HCV population.
		FIB-4 Index ≥ 1.45 & ≤ 3.25	The patient has intermediate likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for Chronic HCV population.
		FIB-4 Index > 3.25	The patient has high likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for Chronic HCV population.

8. Additional information

8.1. Details

Algorithm author:	Evidencio
Root model ID	10277
Version	1.0
Revision date	2025-06-11
Speciality	Hepatology
Model type	Custom calculation
MeSH terms	<ul style="list-style-type: none"> Fibrosis, Liver Hepatitis C HIV

8.2. Input variables

To perform the calculations successfully, the FIB-4 Index requires the input variables as listed in **Table 2**.

Table 2. Variables used as input for the FIB-4 Index.

Name	Description	Type	Range (step size)*	Units
Age	Age of patient in years	Continuous	18 – 100 (1)	<i>Years</i>
AST	Aspartate aminotransferase	Continuous	1 – 200 (1)	<i>U / L</i>
ALT	Alanine aminotransferase	Continuous	1 – 300 (1)	<i>U / L</i>
PLT	Platelet count in 10 ⁹ / L	Continuous	1 – 500 (1)	<i>10⁹ / L</i>
Applicable guideline	The guideline applicable to the patient	Categorical	N/A	<i>EASL-EASD-EASO (2024)</i>
			N/A	<i>AASLD</i>
			N/A	<i>AGA</i>
			N/A	<i>AACE</i>
			N/A	<i>APASL</i>
			N/A	<i>Sterling et al.</i>
			N/A	<i>EASL GL HCV (2020)</i>
			N/A	<i>BASL</i>
			N/A	<i>UK local (NHS Oxford)</i>

*The step size refers to the smallest possible difference in the value that can be entered. Any value submitted within range will automatically be rounded to the nearest possible value. For example, submitting 3.2 will be rounded to 3, and 3.7 will be rounded to 4. If a value is exactly halfway between two numbers, it will be rounded up to the higher number (e.g., 3.5 will be rounded to 4).

8.3. Formula

The formula of the FIB-4 Index is:

$$FIB - 4 \text{ Index Score} = \frac{Age * AST}{PLT * ALT^2}$$

8.4. Study characteristics

The FIB-4 Index was developed in a population of patients from the APRICOT trial, infected with both HIV and HCV, with elevated serum alanine amino-transferase at least twice or more within the 12 previous months, as well as compensated liver disease, and liver biopsy with histology consistent with chronic HCV. The algorithm was initially derived with 555 patients, and internally validated in 277 patients.

The FIB-4 index has been validated as a measure for liver fibrosis beyond the combination of HIV and HCV, such as in both Hepatitis B and C alone, as well as in NAFLD/MASLD. It is considered the state of the art as a first step in Fibrosis assessment for at-risk patients, even in populations where it only performs moderately well. Information on the characteristics of the patient data used to derive and validate the algorithm is provided in tables 3 and 4.

Table 3. This table contains information on the patient group data used to derive and validate the algorithm.

Name	Mean	SD	Unit
Age	40	7	Years
Weight	73	14	kg
BMI (body mass index)	25	4	kg/(m ²)
AST (aspartate aminotransferase)	56	39	U/L
ALT (alanine aminotransferase)	83	62	U/L
AST/ALT Ratio	0.75	0.31	–
AP (alkaline phosphatase)	80	34	U/L
Albumin	42	5	g/L
Glucose	5.3	1.6	mmol/L
HCV RNA	6.4	0.8	log IU / mL
PLT (platelet count)	194	66	(10 ⁹)/L
INR (international normalized ratio)	1.04	0.15	–
PTT (partial thromboplastin time)	33	7	sec
CD4	529	255	cells/μL
CD8	970	425	cells/μL
HIV RNA	9031	44590	copies/mL
HAI (hepatitis activity index)	8.1	3.8	–

Table 4. This table contains categorical characteristics on the patient group data used to derive and validate the algorithm.

Name	Subset / Group	Number of patients
Gender	Male	444
Gender	Female	111
Race	Caucasian	427
Race	Other	128
HCV genotype	HCV Genotype 1	339
HCV genotype	HCV Genotype other	216
NRTI use	NRTI Use	461
NRTI use	No NRTI Use	94
NNRTI use	NNRTI Use	189
NNRTI use	No NNRTI Use	366
PI use	PI Use	244
PI use	No PI Use	311
Fibrosis level	Mild Fibrosis (Ishak 0-1)	198
Fibrosis level	Moderate Fibrosis (Ishak 2-3)	242
Fibrosis level	Advanced Fibrosis (Ishak 4-6)	115

8.5. Supporting publication & Related files

Several relevant studies, such as the original derivation study by Sterling *et al.* (2006) are contained in **Table** . These publications have tags to identify their link with the algorithm. Examples of relevant tags are; “Peer review”, “Internal validation”, “External validation”, and “TRIPOD”. Publications that have the tags: “Internal validation” or “External validation”, contain data on the performance characteristics of the device.

Table 5. Overview of selection of supporting publications & Related files.

Derivation Internal validation	<p>Development of a Simple Non-invasive Index to Predict Significant fibrosis in Patients with HIV/HCV Coinfection <i>Richard K Sterling, Eduardo Lissen, Nathan Clumeck, Ricard Sola, Mendes Cassia Correa, Julio Montaner, Mark S Sulkowski, Francesca J Torriani, Doug T Dieterich, David L Thomas, Diethelm Messinger, Mark Nelson; APRICOT Clinical Investigators.</i></p> <p>DOI: 10.1002/hep.21178</p>
External Validation	<p>Age as a Confounding Factor for the Accurate Non-Invasive Diagnosis of Advanced NAFLD Fibrosis</p> <p>DOI: 10.1038/ajg.2016.453</p>
Guideline	<p>EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis – 2021</p> <p>DOI: 10.1016/j.jhep.2021.05.025</p>
Guideline	<p>Guidelines on the management of abnormal liver blood tests.</p> <p>DOI: 10.1136/gutjnl-2017-314924</p>
Guideline	<p>EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) (2024) <i>European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO).</i> https://pubmed.ncbi.nlm.nih.gov/38851997/ DOI: 10.1016/j.jhep.2024.04.031</p>

8.6. Analytical performance characteristics

To demonstrate the analytical performance of the FIB-4 Index, evidence was collected based on five requirements. This led to the following results:

- A code review and functional test showed that the calculation of the online tool provides the exact same results as described in the paper by Sterling et al. (2006).
- Monthly uptime reports show that the device is available online with an uptime of at least 99%.
- The calculation time is within 2 minutes, otherwise an error is given to the manufacturer, this is analysed each 6 months in the analysis of quality data.
- Absence of unacceptable cybersecurity vulnerabilities.
- On a scale from 1 to 5, where 5 means that users trust the implementation very much, the reliability score was 4.44, and the accuracy score was 4.56 on average.

8.7. Clinical performance characteristics

A total of 11 systematic reviews and guidelines were identified that assessed the performance and clinical utility of the FIB-4 Index in addition to original derivation and validation studies. Combined, these studies include data from more than 41500 patients with 72000 cases of advanced fibrosis. The algorithm had an AUROC of 0.737 in the derivation dataset, discriminating between Ishak scores 0-3 and 4-6. In the original validations sets, this was 0.765, 0.793 and 0.756, all in patients with coinfection of HIV and HCV. In patients with NAFLD, A C-statistic of 0.83 (95% CI 0.79-0.86) was reported. For patients with HBV, AUC's ranged from 0.76 for significant fibrosis to 0.80 for advanced fibrosis and 0.78 for cirrhosis. For patients with NAFLD and T2DM, AUROC's of 0.75 and 0.82 were reported.

Specific cutoffs used vary per study and use case, but the recommendation of the EASL is to use cutoff thresholds at either 1.30 or 2.67 to separate patients into low, intermediate and high risk, with a threshold at 2.0 instead of 1.3 for patients above 65 years of age.

8.8. Release notes

The release notes for each publicly available version of the device can be found on the Evidencio website page for the FIB-4 Index: <https://www.evidencio.com/models/show/10277>, selecting the correct device (version), and clicking on Release Notes. It is recommended to read these notes after a version update to see if these changes are relevant to you. Please make sure the correct algorithm version is selected.

9. Using the algorithm on the Evidencio website

Using the tool on the Evidencio website requires a stable internet connection. The tool was developed to work on the four most commonly used internet browsers; Google Chrome (version 137.0.7151.103 and higher), Mozilla Firefox (version 139.0.4 and higher), Microsoft Edge (version 137.0.3296.68 and higher), and Apple Safari (version 18.4 and higher). The medical device cannot be used in combination with Internet Explorer.

The tool can also be accessed on mobile devices running the most recent versions of the Android (version 15 and higher) and iOS (version 18.4 and higher) operating systems.

Correct functioning of the tool with earlier versions of these browsers cannot be guaranteed.

The personal computers, laptops, tablets or smartphones used should at least be able to have an internet connection and use the browsers mentioned above.

Furthermore, the algorithm may be used through the Evidencio iFrame representation of the calculator, as an embedded view, provided that the specific Evidencio guidelines for iFrame implementations of that algorithm are adhered to.

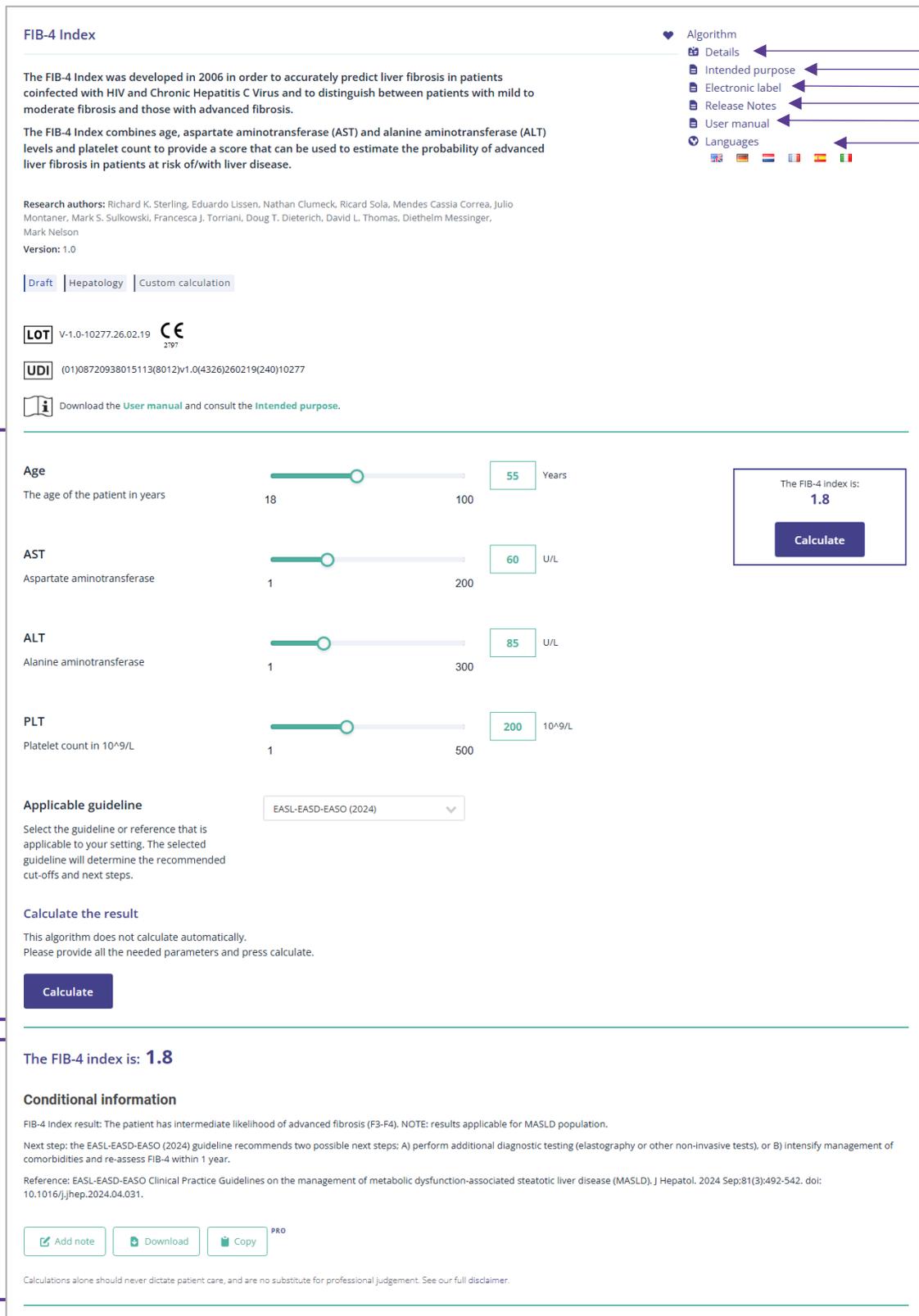
The Evidencio MDSW algorithms can be used with any browser settings that don't distort the regular display of websites, with a 50% to 500% zoom rate, and at a display minimal screen resolution starting from 800x600. However, factory recommended browser settings, 100% zoom rate and regular display resolution are recommended.

The MDSW is intended for authorised users only, and should not be used by unauthorised personnel.

This algorithm is only intended for use in settings where the usage and result of an algorithm are never immediately needed.

9.1. General algorithm landing page

The medical device algorithm interface on the Evidencio platform is shown in **Figure 1**. The different sections indicated are explained in this chapter.



A. FIB-4 Index

B. The FIB-4 Index was developed in 2006 in order to accurately predict liver fibrosis in patients coinfecting with HIV and Chronic Hepatitis C Virus and to distinguish between patients with mild to moderate fibrosis and those with advanced fibrosis.

The FIB-4 Index combines age, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and platelet count to provide a score that can be used to estimate the probability of advanced liver fibrosis in patients at risk of/with liver disease.

C. **Research authors:** Richard K. Sterling, Eduardo Lissen, Nathan Clumeck, Ricard Sola, Mendes Cassia Correa, Julio Montaner, Mark S. Sulkowski, Francesca J. Torriani, Doug T. Dieterich, David L. Thomas, Diethelm Messinger, Mark Nelson

Version: 1.0

D. Draft | Hepatology | Custom calculation

E. **LOT** V-1.0-10277.26.02.19 **CE** 2197

F. **UDI** (01)08720938015113(8012)v1.0(4326)260219(240)10277

K. Download the [User manual](#) and consult the [Intended purpose](#).

M.

Age
The age of the patient in years: 18 — 100 | 55 Years

AST
Aspartate aminotransferase: 1 — 200 | 60 U/L

ALT
Alanine aminotransferase: 1 — 300 | 85 U/L

PLT
Platelet count in 10⁹/L: 1 — 500 | 200 10⁹/L

Applicable guideline
EASL-EASD-EASO (2024)

Select the guideline or reference that is applicable to your setting. The selected guideline will determine the recommended cut-offs and next steps.

Calculate the result
This algorithm does not calculate automatically. Please provide all the needed parameters and press calculate.

Calculate

The FIB-4 index is: **1.8**

N.

Conditional information

FIB-4 Index result: The patient has intermediate likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for MASLD population.

Next step: the EASL-EASD-EASO (2024) guideline recommends two possible next steps: A) perform additional diagnostic testing (elastography or other non-invasive tests), or B) Intensify management of comorbidities and re-assess FIB-4 within 1 year.

Reference: EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol. 2024 Sep;81(3):492-542. doi: 10.1016/j.jhep.2024.04.031.

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G. Algorithm

H. Details

I. Intended purpose

J. Electronic label

K. Release Notes

L. User manual

Languages:

Figure 1. Graphical user interface of the FIB-4 Index.

A. Algorithm title

This is the title and name of the algorithm.

B. Algorithm description

This is a short description of the algorithm.

C. Research Authors

These are the research authors of the paper that originally published the algorithm.

D. Algorithm tags

These are the tags that are assigned to the algorithm. Evidencio has the following status tags: "Draft", "Public", "Private", "Under review". Evidencio has the following algorithm type tags: "Composite model", "Sequential model", "API model". Evidencio has the following calculation method tags: "Linear model", "Logistic regression", "Cox regression", "RScript" and "Custom model". Next to this, there are tags that indicate the specialty e.g. "Cardiology".

E. LOT number

The LOT number indicated the algorithm version, the algorithm identifier, and the algorithm publication date. Publication date is indicated as YY.MM.DD.

(Additionally, the CE mark is displayed next to the LOT number. This way, medical devices can be easily recognized.)

F. UDI-PI number

For a description of the UDI-PI number, see **section 5.2** of this manual.

G. Details button

On the top right of the algorithm page, several clickable buttons are displayed that show a pop-up when clicked. The first button opens a pop-up concerning additional information about the algorithm. This pop-up has three sections: Details, Study characteristics and Supporting publications & related files.

Details

The first part of the additional information concerns the details of the algorithm as shown in Figure 2. This section shows the mathematical formula used in the calculation of the device.

Details

Algorithm author	Evidencio	Status	Draft
Algorithm ID	10277	Share	  
Version	1.0		
Revision date	2025-12-29		
Specialty	Hepatology		
Algorithm type	Custom calculation <small>(Calculation)</small>		
MeSH terms	<ul style="list-style-type: none"> • Fibrosis, Liver • Hepatitis C • HIV 		

Formula

$$\frac{\text{Age} \cdot \text{AST}}{\text{PLT} \cdot \text{ALT}^{\frac{1}{2}}}$$

Study characteristics

Figure 2. The first part of the Details section.

Study Characteristics

Below the 'Details section' the section labelled 'Study characteristics' provides information on the characteristics of the patient data used to derive and validate the algorithm. Additional information is provided on the methods used to develop and/or validate the algorithm. The Study characteristics section can be seen in **Figure 3**.

Study characteristics			
Additional information		Study Population	
<p>The FIB-4 Index was developed in a population of patients from the APRICOT trial, infected with both HIV and HCV, with elevated serum alanine amino-transferase at least twice or more within the 12 previous month, as well as compensated liver disease, and liver biopsy with histology consistent with chronic HCV. the model was initially derived with 555 patients, and internally validated in 277 patients.</p> <p>The FIB-4 index has been validated as a measure for liver fibrosis beyond the combination of HIV and HCV, such as in both Hepatitis B and C alone, as well as in NAFLD.</p>		<p>Total population size: 555</p>	
Continuous characteristics			
NAME	MEAN	SD	UNIT
Age	40	7	Years
Weight	73	14	kg
BMI (body mass index)	25	4	kg/(m ²)
AST (aspartate aminotransferase)	56	39	U/L
ALT (alanine aminotransferase)	83	62	U/L
AST/ALT Ratio	0.75	0.31	-
AP (alkaline phosphatase)	80	34	U/L
Albumin	42	5	g/L
Glucose	5.3	1.6	mmol/L
HCV RNA	6.4	0.8	log IU/mL
PLT (platelet count)	194	66	(10 ⁹ /L)
INR (international normalized ratio)	1.04	0.15	-
PTT (partial thromboplastin time)	33	7	sec
CD4	529	255	cells/ μ L
CD8	970	425	cells/ μ L
HIV RNA	9031	44590	copies/mL
HAI (hepatitis activity index)	8.1	3.8	-
Categorical characteristics			
NAME	SUBSET / GROUP	NR. OF PATIENTS	
Gender	Male	444	
Gender	Female	111	
Race	Caucasian	427	
Race	Other	128	
HCV genotype	HCV Genotype 1	339	
HCV genotype	HCV Genotype other	216	
NRTI use	NRTI Use	461	
NRTI use	No NRTI Use	94	
NNRTI use	NNRTI Use	189	
NNRTI use	No NNRTI Use	366	
PI use	PI Use	244	
PI use	No PI Use	311	
Fibrosis level	Mild Fibrosis (Ishak 0-1)	198	
Fibrosis level	Moderate Fibrosis (Ishak 2-3)	242	
Fibrosis level	Advanced Fibrosis (Ishak 4-6)	115	

Figure 3. Study characteristics for the FIB-4 Index.

Supporting publications & Related files

An important part of the Study characteristics is the information on Supporting publications and related files. The list of related files and relevant tags can also be found in **Section 8.5**. These sections can be found at the bottom of the Details-pop-up as shown in **Figure 4**.

Supporting Publications

Title or description	Tags
Development of a Simple Noninvasive Index to Predict Significant Fibrosis in Patients With HIV/HCV Coinfection DOI: 10.1002/hep.21178	<ul style="list-style-type: none"> <li style="background-color: #f0f0f0; padding: 2px 5px; margin-bottom: 2px;">Internal validation <li style="background-color: #f0f0f0; padding: 2px 5px; margin-bottom: 2px;">Patient characteristics <li style="background-color: #f0f0f0; padding: 2px 5px; margin-bottom: 2px;">Paper <li style="background-color: #f0f0f0; padding: 2px 5px; margin-bottom: 2px;">ROC curve <li style="background-color: #f0f0f0; padding: 2px 5px; margin-bottom: 2px;">Model formula
EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update DOI: 10.1016/j.jhep.2021.05.025 Guidelines on the management of abnormal liver blood tests DOI: 10.1136/gutjnl-2017-314924 Age as a Confounding Factor for the Accurate Non-Invasive Diagnosis of Advanced NAFLD Fibrosis DOI: 10.1038/ajg.2016.453	<ul style="list-style-type: none"> <li style="background-color: #f0f0f0; padding: 2px 5px; margin-bottom: 2px;">Paper <li style="background-color: #f0f0f0; padding: 2px 5px; margin-bottom: 2px;">Paper <li style="background-color: #f0f0f0; padding: 2px 5px; margin-bottom: 2px;">External validation
EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) DOI: 10.1016/j.jhep.2024.04.031	<ul style="list-style-type: none"> <li style="background-color: #f0f0f0; padding: 2px 5px; margin-bottom: 2px;">Paper <li style="background-color: #f0f0f0; padding: 2px 5px; margin-bottom: 2px;">Information on topic

Related files

No related files available

Figure 4. Supporting publication & Related files section under the Details tab.

H. Intended purpose

Under this tab, the intended purpose can be found, containing a lot of information regarding the algorithm, its user, target population, clinical benefit, etc. This information is also provided in this manual and can be found in **Chapter 6**.

I. Electronic label

The electronic label button opens a pop-up with the location and address of Evidencio, the LOT number, the UDI number, the CE-mark, the medical device logo and a download link for the declaration of conformity of the medical device. The example of the electronic label is shown in **Figure 5**.

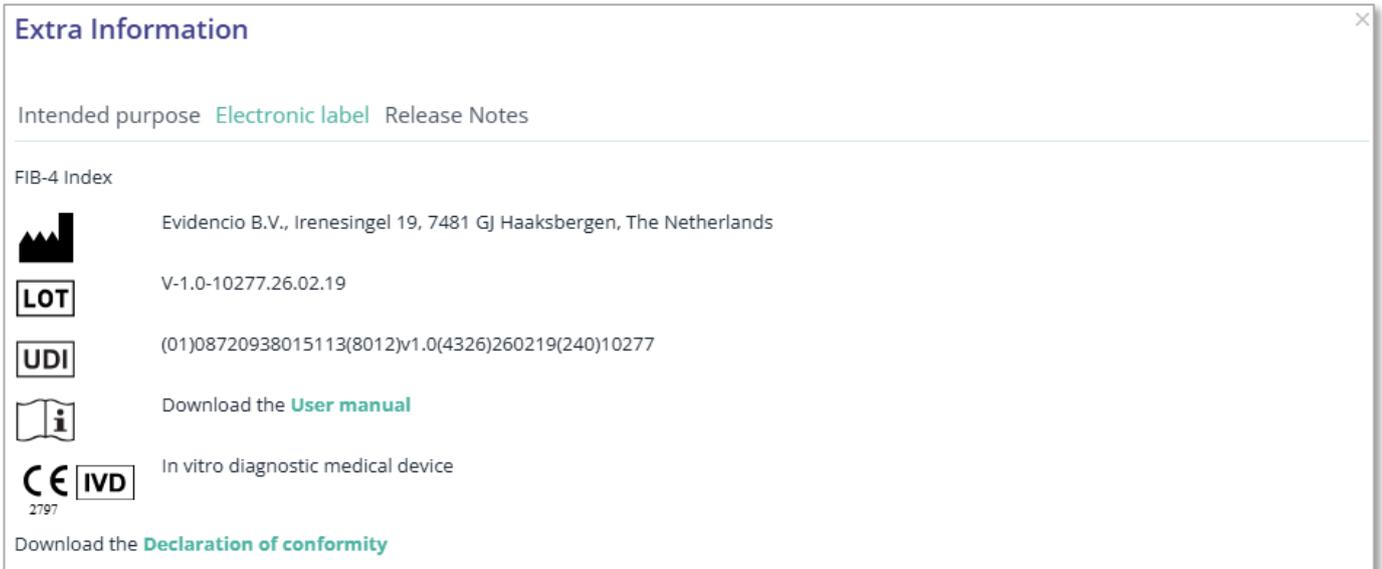


Figure 5. Electronic label under the Electronic Label tab.

J. Release notes

Under this tab the most recent release notes can be found, noting the most significant changes between the versions of the algorithm found on the Evidencio website.

The 'Release Notes' button opens a pop-up with the latest release notes of the algorithm. Here you can find a list of the most significant changes over the different versions of the algorithm. Additionally, if there are any known residual anomalies the user should be aware of, they are listed here. It is recommended to read these notes after a version update to see if these changes are relevant to you.

K. User manual

This user manual can be found in three places: 1) under the short description of the algorithm on the Evidencio algorithm page, 2) on the top right of the algorithm page, and 3) as a tab in the electronic label screen. Additionally, all versions of the user manual can be found in the general page for all user manuals for medical devices. The page can be found under the 'About' drop-down menu button as shown in **figure 6**.

This version of the manual can be printed if required. If necessary, a paper version of the manual can be requested to be sent to you by mail. Evidencio's contact details are listed in **Chapter 11** of this user manual.

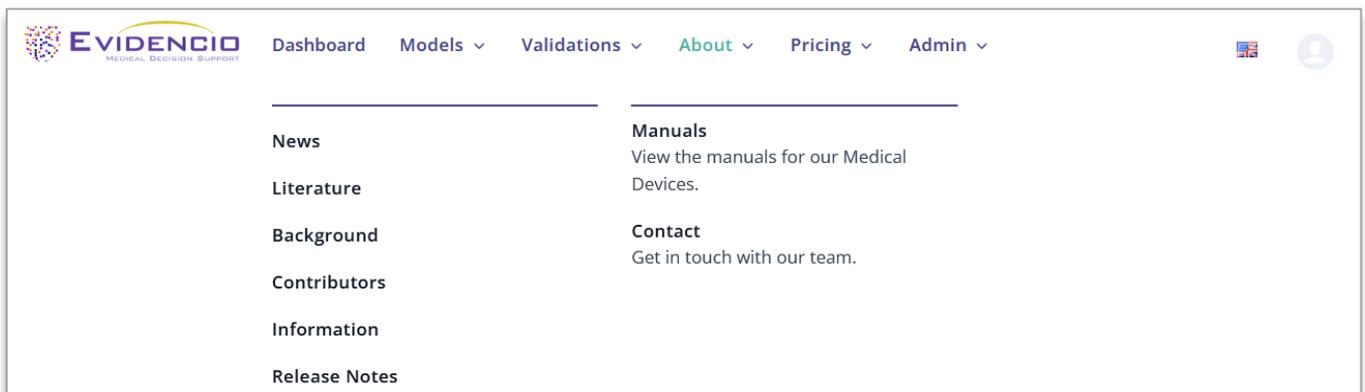


Figure 6. The drop-down menu where the user manual page can be found.

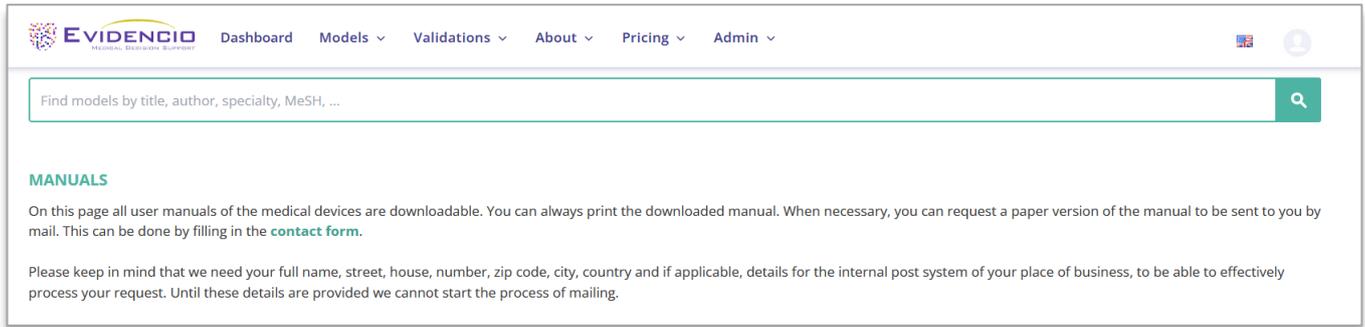


Figure 7. The user manual page for all user manuals.

L. Languages

The standard language on the Evidencio website is English. When other languages are available, these can be selected here. The list of languages may be different between algorithms and may change when in time more languages will become available. Currently the FIB-4 Index and its user manual are available in German, French, Spanish, Italian, Dutch, and English.

Please note that, if a language is selected, only the user interface of the specific algorithm will be translated, other general features and information on the site might still be set to one of our primary languages English, German, and Dutch.

When you find mistranslations, irregularities, confusing or ambiguous use of language in English or any other language on the Evidencio website or in one of our manuals, please do not hesitate to contact us using the contact information provided at the end of this manual.

M. Input section

The FIB-4 Index utilizes two types of input variables; categorical variables and continuous variables.

Categorical variables

In **Figure 8** and **Figure 9** the variable **Applicable guideline** is shown. The correct guideline can be selected by clicking on the button 'Select one option', which displays a list of guidelines to choose from, as seen in **Figure 9**.

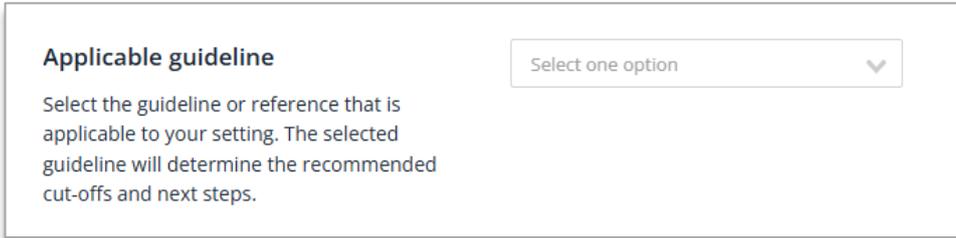


Figure 8. No button has been clicked and thus no input has been provided by the user.

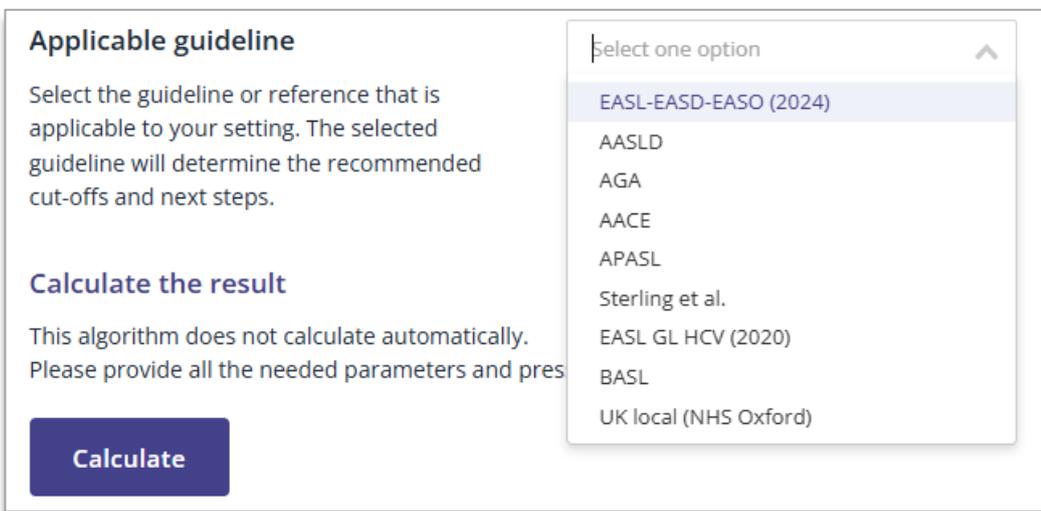


Figure 9. List with guidelines to choose from.

Continuous variables

In **Figure 10**, the Continuous Variable **Age** is displayed. The plausible ranges for which the algorithm is tested and deemed valid are displayed below the slider.

The details for a patient can be entered by sliding the button to the correct value, or by entering the correct value in the box on the right-hand side (i.e., where the 45 years is entered).

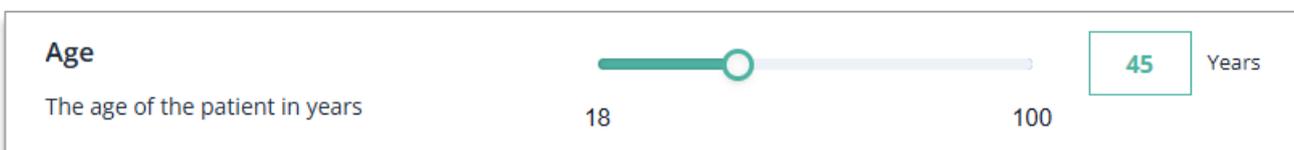


Figure 10. Example of a continuous variable, where "45 years" has been entered.

Details on variable measurements

Directly underneath the name for each variable, additional details can be provided on the methods required to enter the correct value for each variable. Details may include but are not limited to; more detailed explanation of the variable, the ranges of the variables (for healthy individuals), or a description when a continuous variable should be true or false.

N. Result section

At the bottom of the page, the results of the algorithm are shown.

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Result calculation

When all variables are filled in, and the user presses calculate, a result will be calculated. No result is displayed until all variables are filled in and the result section will indicate; *"Set all parameters to calculate prediction."*

Result interpretation

In the result interpretation, the details will be displayed based on the chosen guideline and calculated FIB-4 Index. This section includes the following details:

- **FIB-4 Index result**
- **Next step**
- **Reference**

Figure 11 below displays an example of an output, and the associated interpretation shown by the device.

The user can add a specific note in the context of the values that have been entered and the results that are displayed by clicking on **Add note**. Notes are only visible in the result download and will not be saved by Evidencio.

The user can download the results in a PDF by clicking on **Download** or copy the results directly to the users' clipboard by clicking on **Copy**. The downloaded PDF contains the information that is displayed in **figure 1** in sections A, B, C, M, and N. It also displays the electronic label of the device, and includes a timestamp. The copy button copies the following sections to the clipboard: Device title, URL to the device, device version, timestamp corresponding to when the copy button was used, Entered input parameters, result, conditional result information, disclaimer text.

The FIB-4 index is: 1.8

Conditional information

FIB-4 Index result: The patient has intermediate likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for MASLD population.

Next step: the EASL-EASD-EASO (2024) guideline recommends two possible next steps; A) perform additional diagnostic testing (elastography or other non-invasive tests), or B) intensify management of comorbidities and re-assess FIB-4 within 1 year.

Reference: EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol. 2024 Sep;81(3):492-542. doi: 10.1016/j.jhep.2024.04.031.

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Figure 11. Example of the result interpretation of the FIB-4 Index.

10. Implementation of the algorithm through an API

The FIB-4 Index can be used through Evidencio's API to allow for (automated) calculation of the FIB-4 Index score, which can be used to stratify patients' risk to belong to severity classes of hepatic fibrosis. In the case of use of the MDSW through the API, the user should take into account the different inputs for the algorithm, in order to properly interpret the results.

The information provided over the API is the same as the information that is displayed in the graphical user interface on the web application provided by Evidencio. In **Box 1** below, an example of a result from the FIB-4 Index over the API is shown. The result concerns a JSON formatted text. The API for the FIB-4 Index leverages the generic API that is provided for the Evidencio platform and therefore contains information that may be applicable for different software algorithms and devices. This means that not all of the details provided over the API may be relevant for the FIB-4 Index.

```

{
  "CIPercentage": 0,
  "id": 10277,
  "author": "Evidencio",
  "title": "FIB-4 Index",
  "variables": {
    "4112035423": 50,
    "1440172457": 30,
    "4458760794": 40,
    "3746946291": 120,
    "4524756109": 1
  },
  "min": 2,
  "max": 2,
  "additionalResultSet": [],
  "mintxt": "2",
  "maxtxt": "2",
  "result": "2",
  "resultText": "The FIB-4 index is:",
  "postresultText": "",
  "formulaSegments": [],
  "conditionalResultArray": [
    "<p><p>FIB-4 Index result: The patient has intermediate likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for MASLD population.</p></p>",
    "<p><p>Next step: the EASL-EASD-EASO (2024) guideline recommends two possible next steps; A) perform additional diagnostic testing (elastography or other non-invasive tests), or B) intensify management of comorbidities and re-assess FIB-4 ≤1 year.</p></p>",
    "<p><p>Reference: EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol. 2024 Sep;81(3):492-542. doi: 10.1016/j.jhep.2024.04.031.</p></p>"
  ],
  "conditionalResultText": "<p><p>FIB-4 Index result: The patient has intermediate likelihood of advanced fibrosis (F3-F4). NOTE: results applicable for MASLD population.</p></p><p><p>Next step: the EASL-EASD-EASO (2024) guideline recommends two possible next steps; A) perform additional diagnostic testing (elastography or other non-invasive tests), or B) intensify management of comorbidities and re-assess FIB-4 ≤1 year.</p></p><p><p>Reference: EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol. 2024 Sep;81(3):492-542. doi: 10.1016/j.jhep.2024.04.031.</p></p>",
  "UDI": "(01)08720938015113(8012)v1.0(4326)260126(240)10277",
  "medicalDevice": "This is an in vitro diagnostic medical device. The electronic label is available at: https://www.evidencio.com/models/show/10277?v=1.0",
  "userManual": "Always refer to the user manual for correct use of the in vitro diagnostic medical device. The user manual can be found at: https://www.evidencio.com/manuals"
}

```

Box 1: Example of an API output for the FIB-4 Index.

Table 6 shows a match between the separately listed items in the API output with the items listed on the graphical user interface on the Evidencio website (elaborated in **Chapter 9**).

API Item	GUI item	Comment
CIPercentage	N/A	Not applicable for the FIB-4 Index as this feature is not used for the FIB-4 index.
id	Algorithm ID under 'details' Id used in the URL (www.evidencio.com/models/show/10277)	The ID is the Evidencio specific identification number of the algorithm.
author	Algorithm author under 'details'	Name of the Evidencio user who created the algorithm on the Evidencio platform.
title	Title of the algorithm (part A of figure 1).	-
variables	Input variables and their entered value. (part N. of figure 1)	The API displays the variables as unique IDs.
min	N/A	Depicts the lowest value when the result of the algorithm is a range. Since the FIB-4 Index always displays a single value as a result, this value is the same as the 'result'.
max	N/A	Depicts the highest value when the result of the algorithm is a range. Since the FIB-4 Index always displays a single value as a result, this value is the same as the 'result'.
additionalResultSet	N/A	N/A
mintxt	N/A	Same as 'min', but as a string.
maxtxt	N/A	Same as 'max', but as a string.
result	The main result of the algorithm, the FIB-4 Index.	-
resultText	The text displayed in front of the main result	e.g. "The FIB-4 Index is:".
postresultText	The text displayed behind the main result	Not used for the FIB-4 Index.
formulaSegments	N/A	N/A
conditionalResultArray	Result interpretation displayed beneath "Conditional Information" (section O. in figure 1).	The API result shows the raw HTML text that is rendered by the software used for the graphical user interface.
conditionalResultText	Result interpretation displayed beneath "Conditional Information" (section O. in figure 1).	This section is the same as 'conditionalResultArray', but displayed as a single string.
UDI	Same as the UDI displayed in the GUI (section F. in figure 1).	-
medicalDevice	The electronic label (section I. in figure 1).	The API refers to the electronic label on the graphical user interface.
userManual	The user manual (section K. in figure 1).	The API refers to the location of the user manual at the user interface & Evidencio website).

Instructions on how to implement the API within a system are included in a separate document that is made available to the party performing the technical implementation. The party performing the integration of the FIB-4 Index using the API should adhere to the requirements outlined in **10277-DOC-45 Instructions for API integration FIB-4 Index**.

NOTE: Specific input variables, such as the input which guideline/reference applies, can be fixed for integrated use of FIB-4. In such cases, the user is unable to change the selected guideline/reference.

11. User manual revision history

Version	Revision notes
V1.0	Original version

12. Manufacturer details

Contact details of Evidencio:



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