User manual for the ALBI Score

Version 5, September 2024, in English

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1. The Evidencio platform

The Evidencio platform facilitates the creation, use, validation and implementation of medical prediction models and clinical decision support tools. This User Manual specifically relates to the ALBI Score. The User Manual can also be referred to as the Instructions For Use (IFU).

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

2. Disclaimer

Evidencio provides information, models, calculators, equations, and algorithms (tools) intended for use by healthcare professionals. Some of these tools have been certified as CE-medical devices. For such CE-marked content the 'Official Legal Disclaimer for CE-marked content' applies. All other content and tools provided by Evidencio are explicitly only covered by the 'Official Legal Disclaimer for non-CE-marked content. Both are available on the Evidencio website: https://www.evidencio.com/disclaimer.

3. Warnings

3.1. Warnings for CE-marked content

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 **paragraphs 6.3.1** and **6.3.2** of this user manual respectively.

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 model is only intended for use in settings where the usage and result of a model 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 model 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.

4. Device Description ALBI Score

The **AL**bumin and **BI**lirubin (ALBI) Score combines bilirubin and albumin to estimate the grade of liver (dys)function in patients with liver disease.

The ALBI Score can be used to stratify hepatocellular carcinoma (HCC) patients into prognostic **ALBI grades**. Patients diagnosed with liver diseases are recommended to have extensive laboratory assessment as part of the diagnostic work-up to provide a measure of liver function, part of which can be performed using the ALBI Score.

The model outperforms the state of the art in liver function assessment for liver disease patients. It is able to improve risk stratification of patients compared to the current SoTA, or is regarded as the SoTA tool.

4.1. Lifetime, residual risks and side effects

The ALBI Score 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 model 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 risks associated with the use of this model.

The ALBI Score is a low-risk device, there are no noticeable risks involved outside of possible mis-estimation of patient degree of liver (dys)function, and all residual risks are accepted.

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

a) The risk calculation was wrong or;
b) The MDSW prediction model 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 ALBI Score does not have any direct side effects relevant for the patient.

5. Electronic Label

The electronic label of this device contains the following information:

Name of the device	ALBI Score
Manufacture information	Evidencio B.V., Irenesingel 19, 7481 GJ Haaksbergen, The Netherlands
LOT number	V-1.16-9982.24.07.02
UDI-PI number	872029952649982U5

The electronic label can be found on the Evidencio website, see also **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 model version, the model identifier, and the model publication date. Publication date is indicated as YY.MM.DD.

5.2. UDI-PI number

Stands for Unique Device Identifier Production Identifier (UDI-PI) number is an international tool that helps users identify and find information on products. Evidencio's UDI-PIs 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 ALBI Score is intended to be used by professional users who are capable of operating the device and interpreting its results.

The ALBI Score combines serum albumin and serum bilirubin to provide an ALBI Score, which can then be used to estimate the degree of liver (dys)function in patients with liver disease. In the case of patients with hepatocellular carcinoma (HCC), the calculated ALBI Score has an associated ALBI grade

The device is intended to be used for liver disease patients. The result of the ALBI Score is intended to be reviewed and interpreted by qualified medical specialists only. The device is not intended for use by patients on their own.

The ALBI Score is not intended to replace clinical decision-making, it can only provide information to the user on the estimation of liver (dys)function. The user can use this information to support decision-making regarding clinical management of the patient.

6.2. Clinical benefit

Correct functioning of the ALBI Score can result in these clinical benefits:

- The ALBI Score can assist in risk stratification for patients with liver diseases.
- The ALBI grade can assist in risk further risk stratification for HCC patients.
- Risk stratification can reduce the burden of (invasive and intensive) medical procedures for diagnostic and treatment purposes.
- Risk stratification can reduce the unnecessary consumption of (scarce) medical resources, decreasing costs, and optimise allocation of resources.
- Digital implementation of the algorithm underlying the ALBI Score as a medical device can improve the speed and reliability of calculation.

6.3. Indented target population and exclusion

While the ALBI Score was originally developed for patients diagnosed with hepatocellular carcinoma (HCC), there are a number of other diseases for which its validity has been confirmed. The ALBI Score is intended to be used only for a specific group of patients, corresponding to the below clinical indications and clinical contra-indications.

6.3.1. Clinical indications

The ALBI score should be used for patients who meet the following inclusion criteria:

- Being at least 18 years old

Non-HCC use:

- Chronic viral hepatitis C
- Chronic viral hepatitis B
- Autoimmune hepatitis
- Primary biliary cholangitis
- Liver cirrhosis
- Acute-on-Chronic liver failure
-

The associated ALBI grade should only be used for the following patients:

- Patients with hepatocellular carcinoma

6.3.2. Clinical contra-indications

The ALBI Score should not be used for patients who meet one or more of the following exclusion criteria:

- Patients without the diagnosis of a liver disease.
- Patients with non-liver malignancies.

6.4. User profile

The ALBI Score is intended to be used by Healthcare Professionals or automatically calculated through Evidencio's API. Results shall always be reviewed and interpreted by qualified medical specialists only, 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, and on the mobile app provided by Evidencio. 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 current version of the ALBI Score concerns the initial version of MDSW of which Evidencio is the manufacturer.

6.8. Functioning, physical principle

The MDSW's underlying mathematical formula is based on a Cox regression model. The ALBI Score is the prognostic index of the fitted Cox regression model. The ALBI grade is subsequently derived from specific cut-off values applied to the ALBI Score. The acquisition and processing of the data, the analyses to assemble the relevant criteria for the MDSW as well as the setup and refinement of the ALBI Score are provided in the instructions for use. Entering the details for an individual in the MDSW initiates the estimation of liver (dys)function.

7. Result interpretation

The primary output of is the device is a number, as obtained from the calculation. This number is the ALBI score, which can be linked to the degree of liver (dys)function.

Conditional information

A higher grade represents worse liver function.
In hepatocellular carcinoma (HCC) patients specifically, of then the ALBI grade is calculated to stratify liver function, where;

- An ALBI Score ≤ -2.60 corresponds with ALBI grade 1
- An ALBI Score > -2.60 to ≤ -1.39 corresponds with ALBI grade 2
- An ALBI Score > -1.39 corresponds with ALBI grade 3

A higher grade represents worse liver function; thus, an ALBI Grade 1 represents the best liver function and ALBI grade 3 the worst.

The ALBI Score outperforms the state of the art in liver function assessment for liver disease patients. The ALBI Score is able to improve risk stratification of patients compared to the current state of the art, or is regarded as the state-of-the-art tool.

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.

8. Additional information

8.1. Details

Model author:	Vanity Steneker
Root model ID	9982
Version	1.16
Revision date	02-07-2024
Speciality	Hepatology, Oncology
Model type	Custom Model
MeSH terms	-

8.2. Input variables

To perform the calculations successfully, the ALBI Score requires the input variables as listed in **Table 1.**

Table 1. Variables used as input for the ALBI Score.

Name	Description	Type	Range (step size)	Units
Bilirubin	Patient's blood bilirubin concentration	Continuous	1.5 – 850 (0.1)	$\mu mol/L$
			0.1 – 45 (0.1)	mg/dL
Albumin	Patient's blood albumin concentration	Continuous	0 – 50 (0.1)	g/L
			0 – 5 (0.1)	g/dL

8.3. Formula

The formula for the ALBI Score is: $\log(10([Bilirubin]) \times 0.66) + ([Albumin] \times (-0.085)) = [ALBI\ score]$

8.4. Study characteristics

The derivation of the ALBI Score was published in a paper by Johnson et al. (2014).

To develop the ALBI Score algorithm, data from multiple large HCC centres and different international clinical trials about HCC were used. This data set represents patients with all disease stages of many different etiologies from different geographical regions (Japan, China, Europe (United Kingdom and Spain) and the United States). The Japanese cohort (n = 2599) was used to generate a linear prediction model by splitting the dataset randomly into two groups: The training and test/validation set (n = 1313 and n = 1286, respectively). To create the model, a cox regression analysis was performed on the training set. Its linear predictor (xb) was divided into three groups based on survival by splitting it at the 25th and 90th percentiles. According to this categorization, patients with HCC were categorized as low, medium or high risk, corresponding to the lowest 25% of risk, medium risk between the 25th and 90th percentile, and the greatest 10% of risk, respectively. Depending on which geographical region patients are from, median survival in months ranged between 18.5–85.6, 5.3–46.5, and 2.3–15.5, respectively, for these three risk groups.

In the tables **Table 2** and **Table 3** more information on the characteristics of the patient data from the Japanese cohort, used to derive and validate the model, is provided.

Table 2. This table contains information on the patient group data used to derive the model.

	Mean	SD	Unit
Age	66.4	8.9	*Years*

	Q1	Median	Q3	Unit
Bilirubin	10.3	15.4	22.2	$\mu mol/L$
Albumin	31	35	39	g/L
Survival	-	47.2	-	*Months*

Table 3. This table contains categorical characteristics on the patient group data used to derive the model.

Name	Subset / Group	Number of patients
Sex	Male	1863
Sex	Female	736
Child-Pugh grade	A	1743
Child-Pugh grade	B	684
Child-Pugh	C	172
Prescence of macroscopic vascular invasion	Presence of macroscopic vascular invasion	366

8.5. Supporting publication & Related files

The performance of the ALBI Score has been assessed in a total of over 69250 patients. In terms of discrimination, the ALBI Score performed equal to or better than the Child-Pugh Score for various outcomes in patients with liver disease.

In **Table 4** the most important publications on the development and possible validation of the ALBI Score are presented. These publications have tags to identify their link with the model. 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 4. Overview of selection of supporting publications & Related files.

Derivation study ALBI Score *Internal validation*	**Assessment of Liver Function in Patients With Hepatocellular Carcinoma: A New Evidence-Based Approach—The ALBI Grade** *Philip J. Johnson, Sarah Berhane, Chiaki Kagebayashi, Shinji Satomura, Mabel Teng, Helen L. Reeves, James O'Beirne, Richard Fox, Anna Skowronska, Daniel Palmer, Winnie Yeo, Frankie Mo, Paul Lai, Mercedes Iñarrairaegui, Stephen L. Chan, Bruno Sangro, Rebecca Miksad, Toshifumi Tada, Takashi Kumada, and Hidenori Toyoda* https://ascopubs.org/doi/full/10.1200/JCO.2014.57.9151

8.6. Release notes

The release notes for each publicly available version of the device can be found on the Evidencio website page for the ALBI Score: https://www.evidencio.com/models/show/9982. Selecting the correct device, 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 model version is selected.

9. Implementation of the model through an API

The ALBI Score can be used through Evidencio's API to allow for (automated) calculation of the estimate the degree of liver (dys)function through a point-based scale. In the case of use of the MDSW through the API, the user should take into account the different inputs for the model, in order to properly interpret the results. Furthermore, the information contained within this user manual, specifically chapters 3-8, should be read and understood by the user.

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.

When using the MDSW through the API, the warnings and descriptions given in this document all apply, as does the additional information. The information for use included in this document regards both use through the website as well as use through the API, as long as the API is properly implemented. The API is only intended for authorized users.

10. Using the model on the Evidencio website

Using the tool on the Evidencio website requires a stable internet connection. The tool was tested on the following browsers and will run on these versions and higher;

- Personal computers or laptops using the following browsers:
  - Safari (version 17.5 and higher)
  - Chrome (version 126.0.6478.127 and higher)
  - Firefox (version 128.0 and higher)
  - Edge (version 126.0.2592.102 and higher)
- Tablets or smartphones running on the next operating systems:
  - IOS (version 17.5.1 and higher)
  - Android (version 13 and higher)

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

The medical device cannot be used in combination with Internet Explorer. The personal computers, laptops, tablets or smartphones used should at least be able to have an internet connection and use the browsers mentioned above. The minimal screen resolution should be 800x600.

Furthermore, the model 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 model are adhered to.

The Evidencio MDSW models 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 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 model is only intended for use in settings where the usage and result of a model are never immediately needed.

10.1. General modelling landing page

The medical device model on the Evidencio platform is shown in **Figure 1**. The model landing page contains the following sections, that are indicated in **Figure 1**.

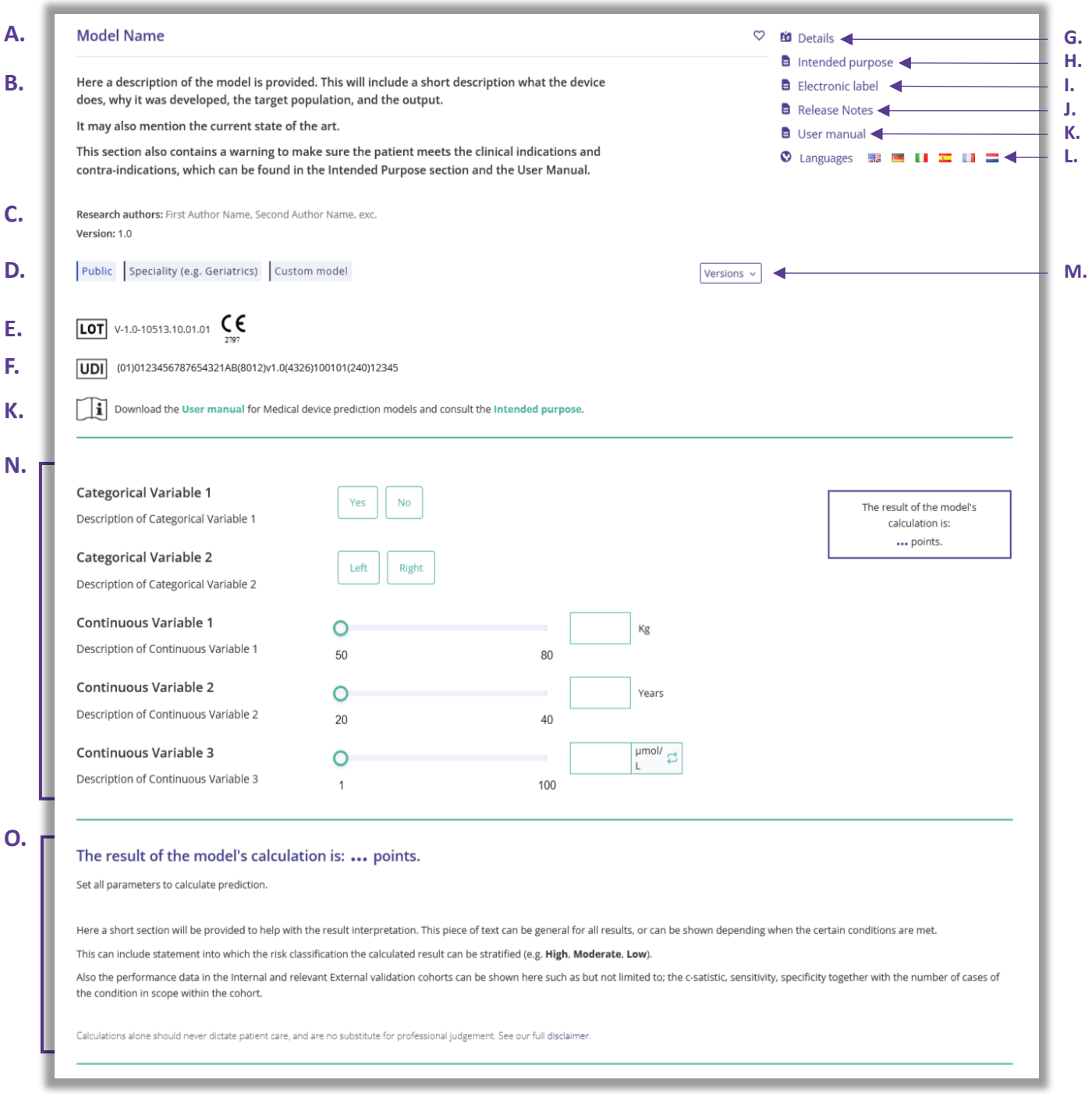

Figure 1. Example of a model landing page on the Evidencio website.

A. Model title

This is the title and name of the model

B. Model description

This is a short description of the model.

C. Research Authors

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

D. Model tags

These are the tags that are assigned to the model. Evidencio has the following status tags: “Draft”, “Public”, “Private”, “Under review”. Evidencio has the following model 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 model version, the model identifier, and the model 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 information on the UDI-PI Number see **Section 5.2** on **page 4** of this manual.

G. Details button

On the top right of the model 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 model. 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 model as shown in **Figure 2**. This section may show the calculation if it is built as a mathematical formula and, if applicable, shows the conditions at which certain formulas are used.

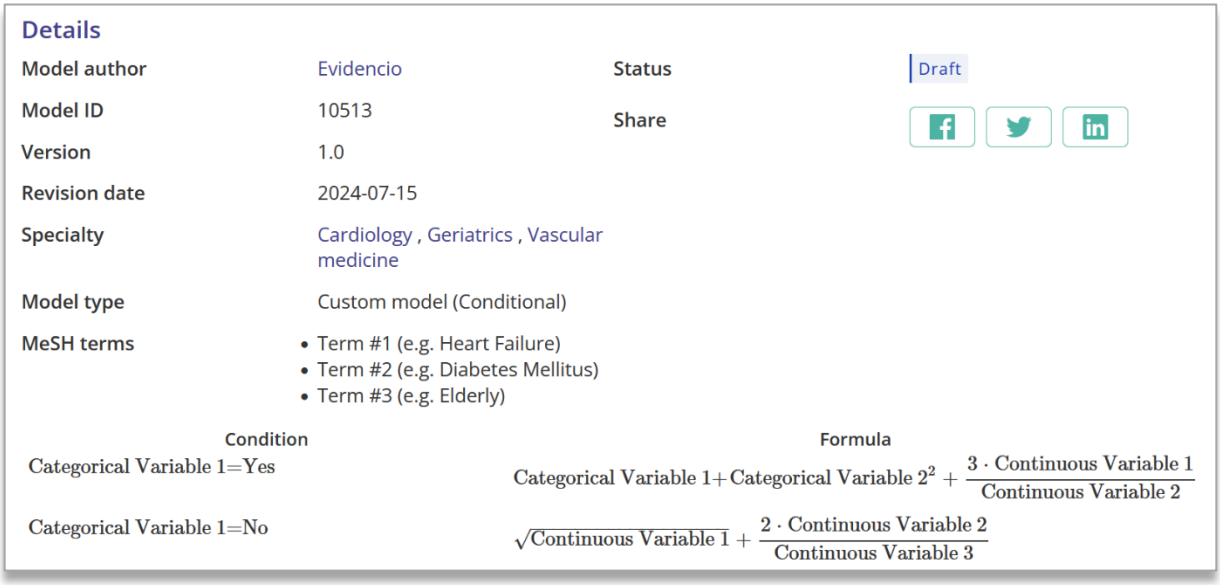

Figure 2. Example of first part of detail section.

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 model. Additional information is provided on the methods used to develop and/or validate the model. An example of the Study characteristics section can be seen in **Figure 3**.

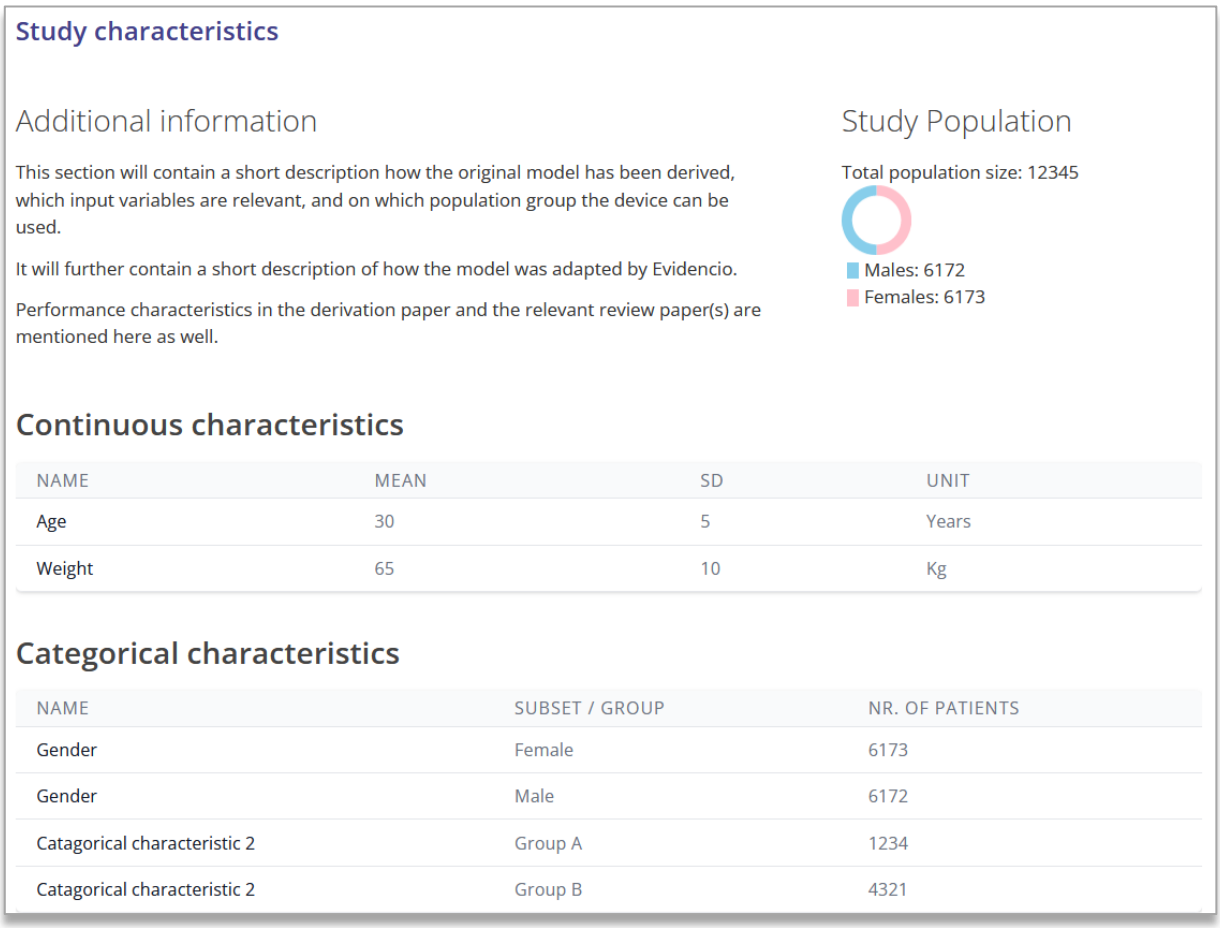

Figure 3. Example of the study characteristics section under the Details tab.

Supporting publications & Related files

An important part of the Study characteristics is the information on Supporting publications and related files. These sections can be found at the bottom of the Details-pop-up as shown in **Figure 4**. Tags are attached to the different files to identify their link with the model. Examples of relevant tags are a.o.; "Peer review", "Internal validation", "External validation", and "TRIPOD". Publications that have the tags: "Internal validation" or "External validation", contain the performance characteristics of the device. Figures and tables which help to interpreted the results may also be provided here.

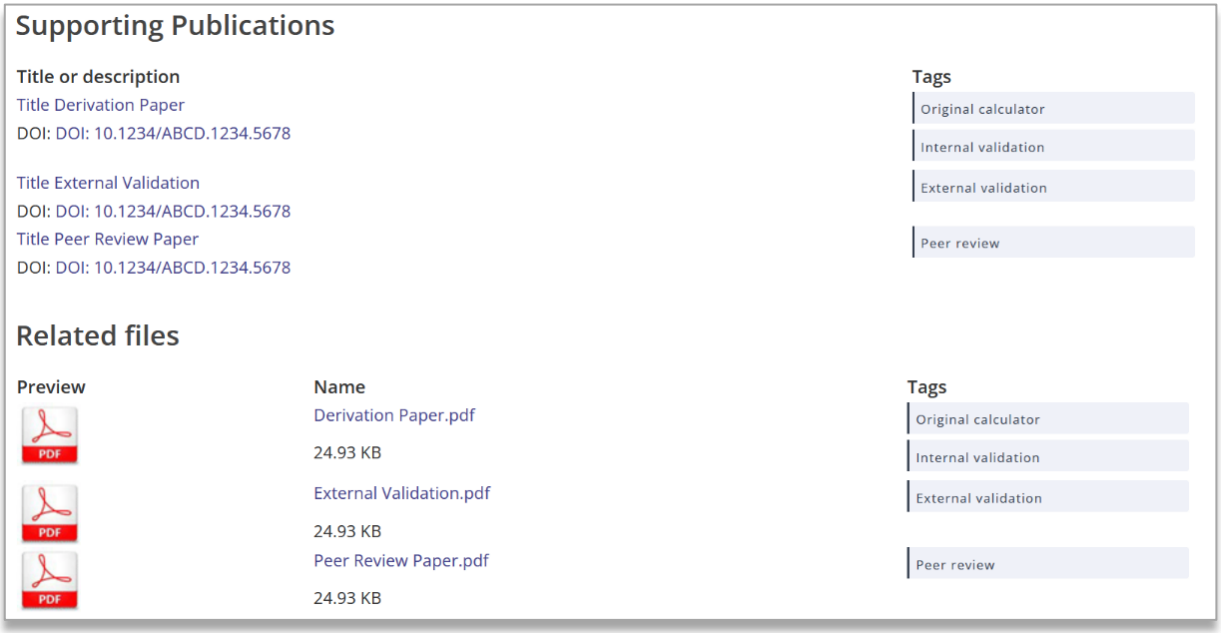

Figure 4. Example of the Supporting publication & Related files section under the Details tab.

H. Intended purpose

Under this tab, the intended purpose can be found, containing a lot of information regarding the model, its user, target population, clinical benefit, etc. This information is also provided in this manual and can be found in **Chapter 6** on **page 5**.

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**.

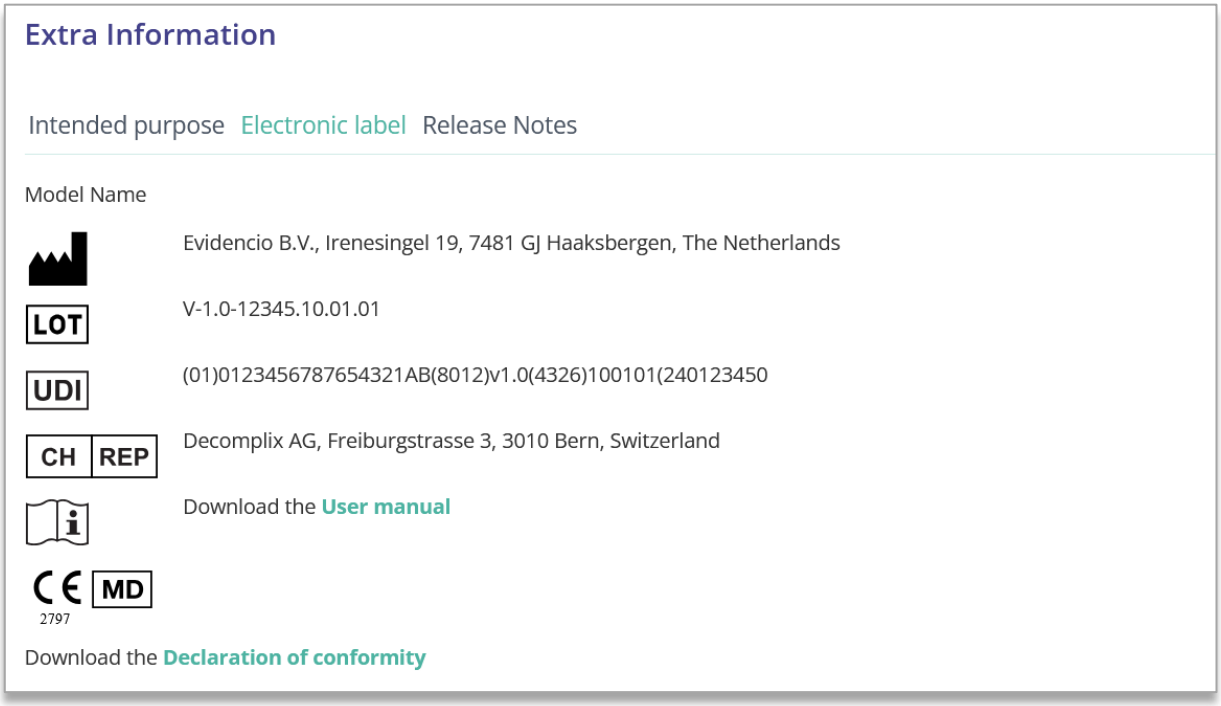

Figure 5. Example of an electronic label under the Electronic Label tab.

J. Release notes

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

The 'Release Notes' button opens a pop-up with the latest release notes of the model. Here you can find a list of the most significant changes over the different versions of the model. 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 model on the Evidencio model page, 2) on the right of the model 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**. The user manual page is shown in **Figure 7**.

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.

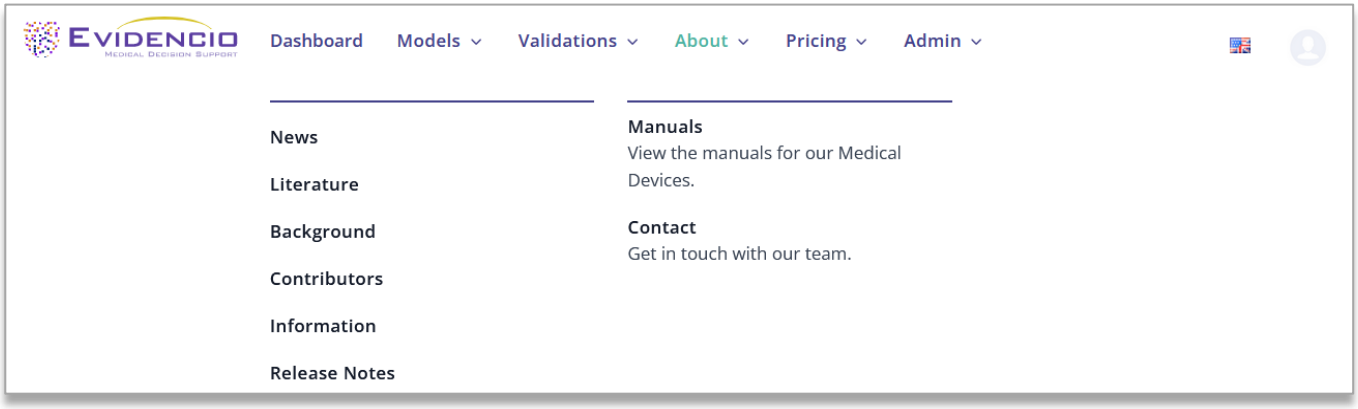

Figure 6. The drop-down menu where the user manual page can be found.

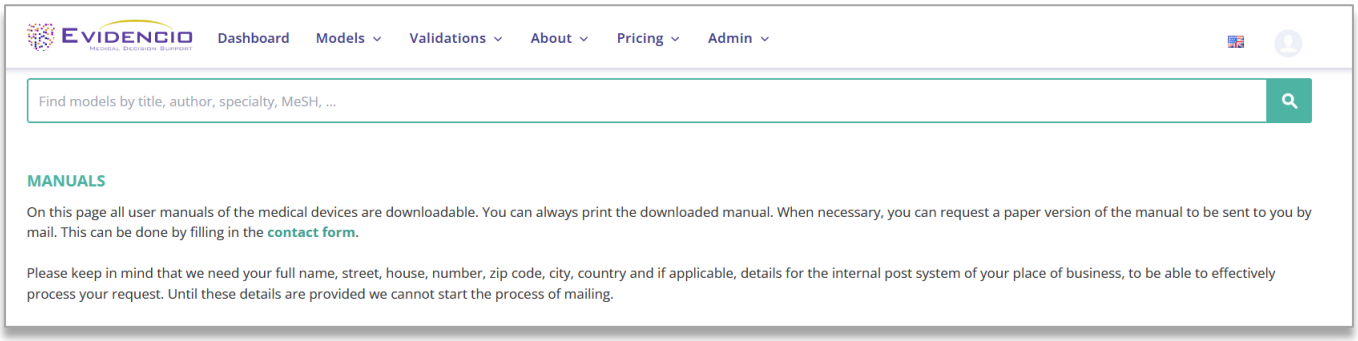

Figure 7. The user manual page for all user manuals.

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 models and may change when in time more languages will become available. Currently the ALBI Score 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 model 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. Version selection

Clicking on the Version tab allows the user to select a different version of the ALBI Score for a list as displayed in **Figure 8**. Please note that the model currently selected is not presented in the dropdown menu.

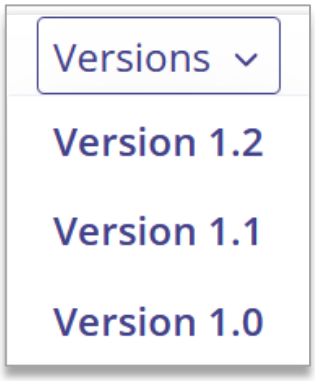

Figure 8. Example of version selection tab.

N. Input section

The Evidencio platform allows two separate input variables; categorical variables and continuous variables.

Categorical variables

In the example shown in shown in **Figure 9** and **Figure 10**, the example **Categorical Variable 1** concerns a categorical variable. The input that is wished to be used can be entered by clicking on either button. The selected button changes to green, as seen in **Figure 10**.

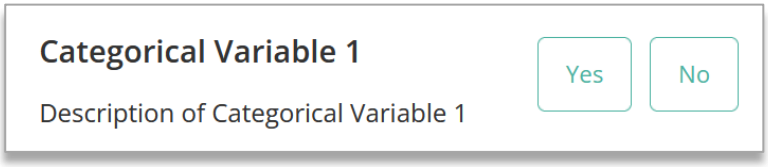

Figure 9. Example of a categorical variable, no button has been clicked and thus no input has been provided by the user.

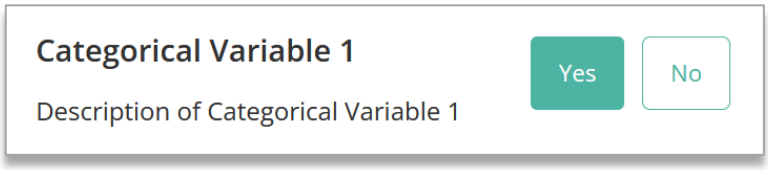

Figure 10. Example of a categorical variable, where the "Yes" button has been clicked.

Continuous variables

In the example shown in **Figure 11**, the **Continuous Variable 3**, exemplifies a continuous variable. The plausible ranges for which the model is tested and deemed valid are used.

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 10.2 mg/dL is entered for the **Continuous Variable 3**).

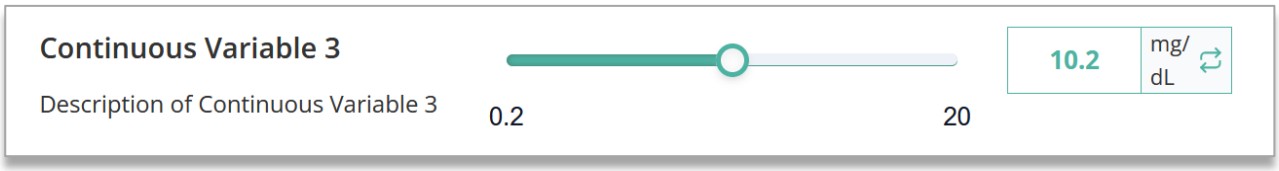

Figure 11. Example of a continuous variable, where "10.2 mg/dL" has been entered.

Unit conversion

Sometimes it is possible to use a unit conversion, by clicking on the unit when the green arrows are present. See **Figure 12** below where the unit has been clicked and switched.

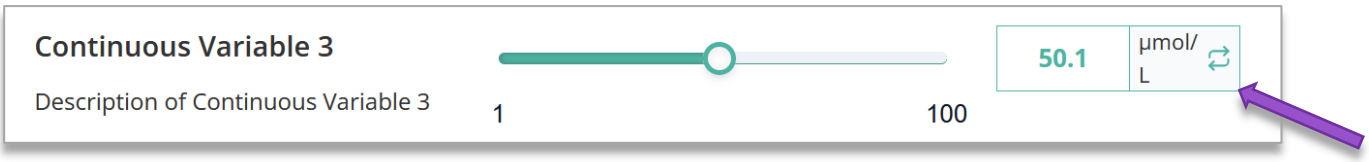

Figure 12. Example of a continuous variable where "50.1 $\mu mol/L$" has been entered.

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.

O. Result section

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

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

Result calculation

When all variables are filled in, 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 section, a risk stratification is provided based on the point score and ALBI grade. Additional information about this stratification and the classification as found in the derivation and important validation cohorts may also be provided. An example of the information is shown in **Figure 13**.

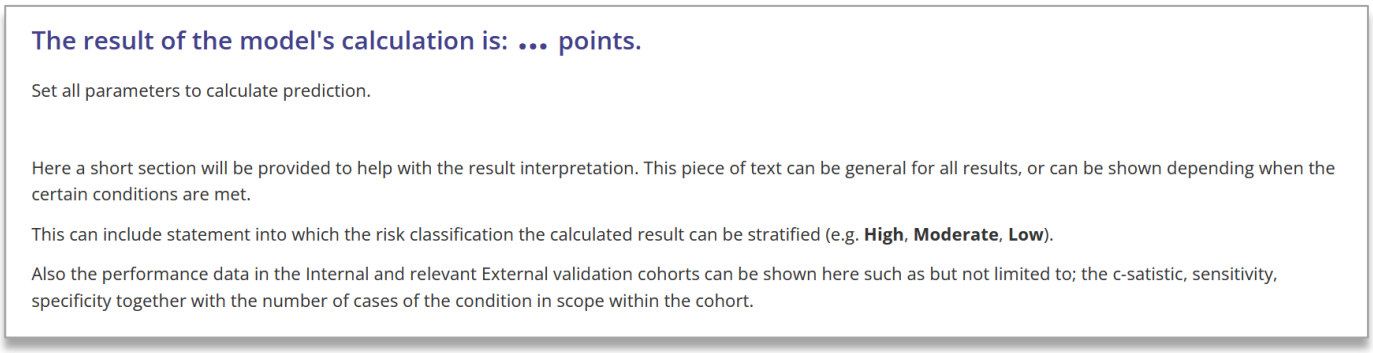

Figure 13. Example of the result display and information section.

11. Manufacturer details

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.

Contact details of Evidencio:

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