User manual

for

Combined MELD score

Version 3, February 2024, in English

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 combined MELD 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 here: https://www.evidencio.com/disclaimer

3. Warnings

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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.

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.

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

4. Model 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.

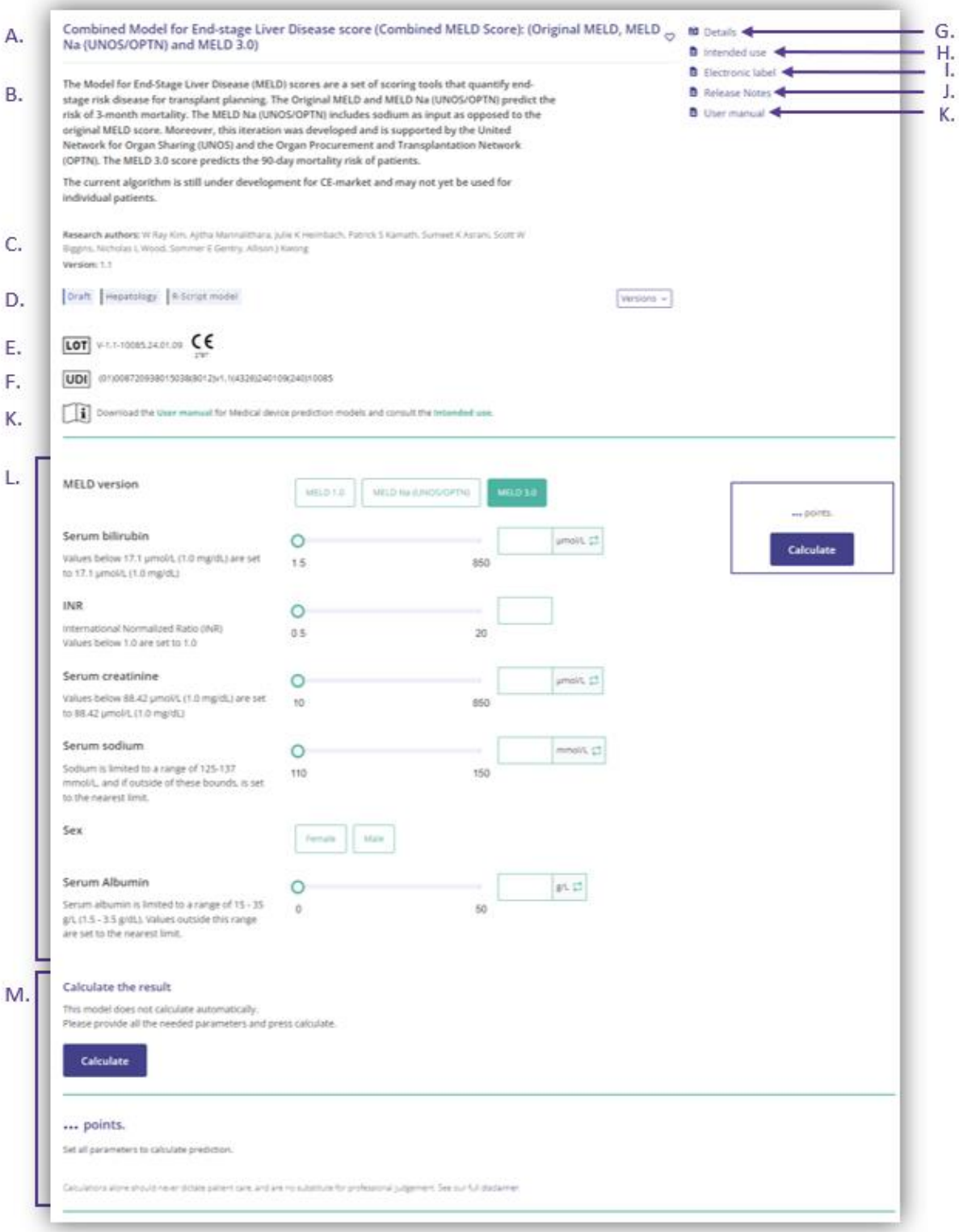

Figure 1. An example of a model landing page.

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 number

The UDI number is an international tool that helps users identify and find information on products. UDI stands for Unique Device Identifier. Evidencio’s UDIs have the following format:

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

The UDI-DI 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

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.

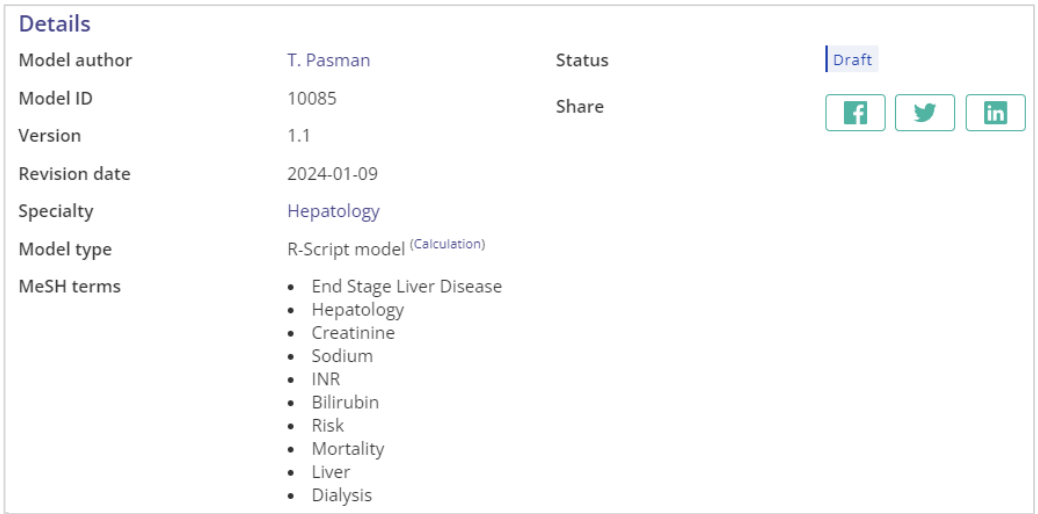

Figure 2. The model details.

Study characteristics

Below the 'Details section' the section labeled '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 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 3.

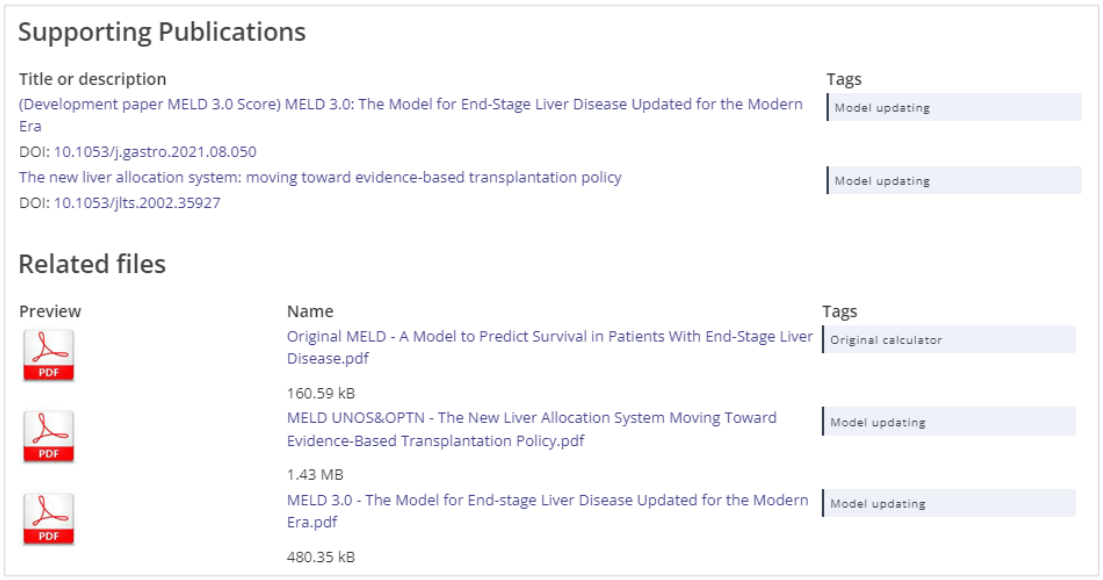

Figure 3. An example of Supporting publications & related files.

H. Intended use button

Intended medical use

The Combined MELD score is intended to be used by professional users who are capable of operating the device and interpreting its results. It can be used to estimate the 3-month mortality risk or 90-day survival probability.

The Combined MELD score consists of three different algorithms that largely overlap in their required input variables and presented outcomes. The MELD 1.0 score combines the values of bilirubin, creatinine, and international normalized ratio (INR) to predict the 3-month mortality risk. The MELD Na (UNOS/OPTN) requires the same input variables as the MELD 1.0 score, but added sodium as an additional risk factor to predict the 3-month mortality risk. The MELD 3.0 score further added sex and albumin values as risk factors to predict the 90-day survival probability.

The device is intended to be used for patients with end-stage liver disease. The result of the Combined MELD 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 Combined MELD score is not intended to replace clinical decision-making, it can only provide information to the user on the 3-month mortality risk or 90-day survival probability. The user can use this information to support clinical decision-making regarding the prognosis and treatment of the patient. In practice, this typically entails the decisions involving palliative care or liver transplantation.

Clinical Benefit

Correct functioning of the Combined MELD score can result in these clinical benefits:

- The Combined MELD Score can aid a professional in providing a patient with an accurate prognosis. More accurate prognosis can support necessary decision-making of patients with end-stage liver disease and organization of their life, such as the need for palliative care.
- Use of the Combined Meld Score can positively impact patient management by supporting the decision-making concerning application for a liver transplantation.
- Digital implementation of the algorithm underlying the Combined MELD Score as a medical device can improve the speed and reliability of calculation. This would further increase the accuracy of the prognosis and by extent increase the chance for the above-mentioned benefits.

Intended target population and exclusion

The Combined MELD score is intended to be used only for a specific group of patients, corresponding to the below indications and contra-indications.

Clinical indication

The Combined MELD Score should be used for patients who meet the following inclusion criteria:

- Patients should be at least 18 years or older *
- Having end-stage liver disease

**The authors of the MELD score suggest that it can be used for patients of 12 years or older. However, this is not universally accepted, e.g. the OPTN policy acknowledges three groups: less than 12 years, 12 or older and 18 or older. In contrast, Eurotransplant uses an age limit of 18 years or older, below which the PELD is recommended. Because of this lack of consensus, the age for the use of the Combined MELD Score is set to 18 years or older.*

Contra-indications

The MELD score is contra-indicated for patients with certain medical conditions, known as 'MELD Exceptions'. Several liver allocation and transplantation programs provide additional points to patients with these conditions to compensate for them for the purpose of equity among patients regarding liver allocation. This measure is due to the fact that the MELD score results are considered to not accurately represent the mortality risk of patients with these conditions. However, there is no consensus on the exact list of conditions that should be regarded as exceptions as well as how to deal with them (e.g. the amount of points to be distributed) to reach equity for all patients.
The following conditions are acknowledged as MELD Exceptions in different liver allocation and transplantation programs, and thus the use of the Combined MELD Score for patients with these conditions should be performed with caution and the MELD Score results should be interpreted within the context of the condition:
Generally acknowledged MELD Exceptions:

- Hepatopulmonary syndrome (HPS)
- Portopulmonary hypertension (PPH)
- Primary hyperoxaluria
- Cystic fibrosis (CF)
- Cholangiocarcinoma (CCA)
- Hepatocellular carcinoma (HCC) (often together with Milan criteria to determine if HCC patients are eligible/suitable for transplantation)

Additionally, the ELITA acknowledges the following exceptions:

- Cholangitis (Primary sclerosing cholangitis and biliary sepsis/secondary sclerosing cholangitis)
- Neuroendocrine tumors
- Polycystic liver disease (PLD)
- Hepatic artery thrombosis (HAT)
- Persistent hepatic dysfunction (incl. small-for-size syndrome)
- Hereditary hemorrhagic teleangiectasia (Rendu-Osler-Weber-Syndrome)
- Biliary atresia
- Non-metastatic hepatoblastoma
- Urea-cycle disorder/organic acidemia
- Hepatic hemangioendothelioma

Moreover, the following exceptions are mentioned in other literature:

- Familial amyloid polyneuropathy (FAP)
- (Unusual) metabolic disease
- Hepatorenal syndrome (HRS) (Eurotransplant region)
- Amyloidosis

Acknowledged by the 2006 MELD Exception Study Group and Conference (MESSAGE):

- Unusual tumor
- Unusual metabolic disease
- Ascites
- Hepatic encephalopathy
- Gastrointestinal bleeding
- Budd-Chiari Syndrome (BCS)
- Pruritis

Moreover, in an OPTN proposal for addition of serum sodium, it is stated that the serum sodium values for patients with hyperglycemia should be corrected via an additional formula. Thus, caution is also necessary if the Combined MELD Score is used for these patients.

User profile
The Combined MELD 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.

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.

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.

Versions of the MDSW
The version of the Combined MELD score concerns the initial version of MDSW of which Evidencio is the manufacturer.

Functioning, physical principle
The MDSW's underlying mathematical formula concerns a combination of a risk score model and a Cox regression model. The risk score model results in a specific number of points that correspond to a mortality risk. 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 Combined MELD score are provided in the instructions for use. Entering the details for an individual in the MDSW initiates the estimation of short term mortality risk.

I. Electronic label button

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 4.

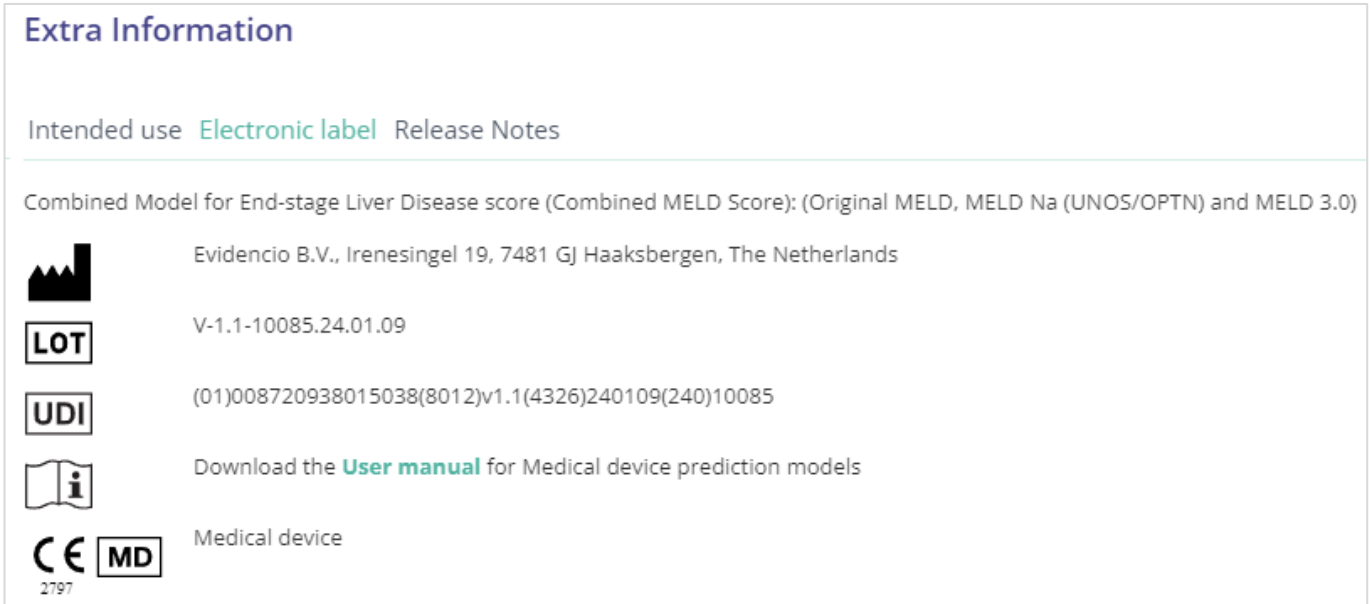

Figure 4. Example of the electronic label

J. Release notes

The 'Release Notes' button opens a pop-up with the latest release notes of the model. Here you can find what has changed over the last versions of the model. Additionally, if there are any known residual anomalies the user should be aware of, they are listed here.

K. User Manual

This user manual can be found in three places: 1) under the short description, 2) on the right of the model page, and 3) in the electronic label. 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 5. The user manual page is shown in Figure 6.

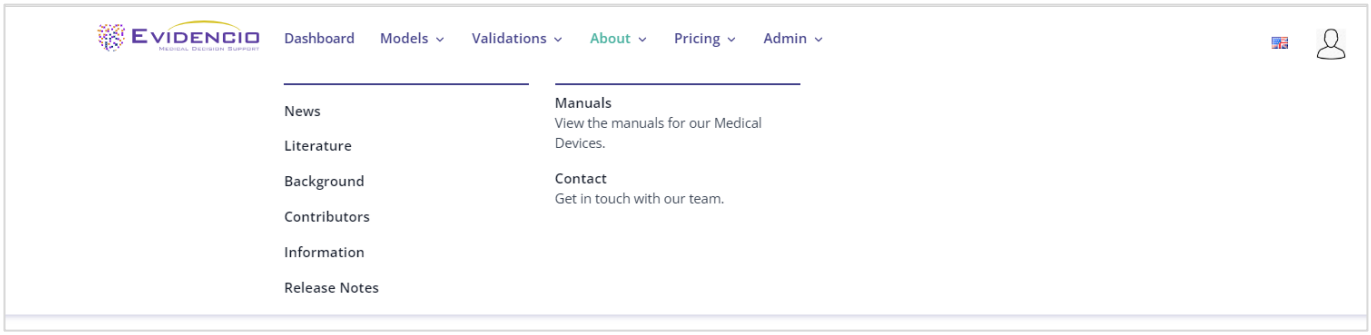

Figure 5. The drop-down menu where the user manual page can be found.

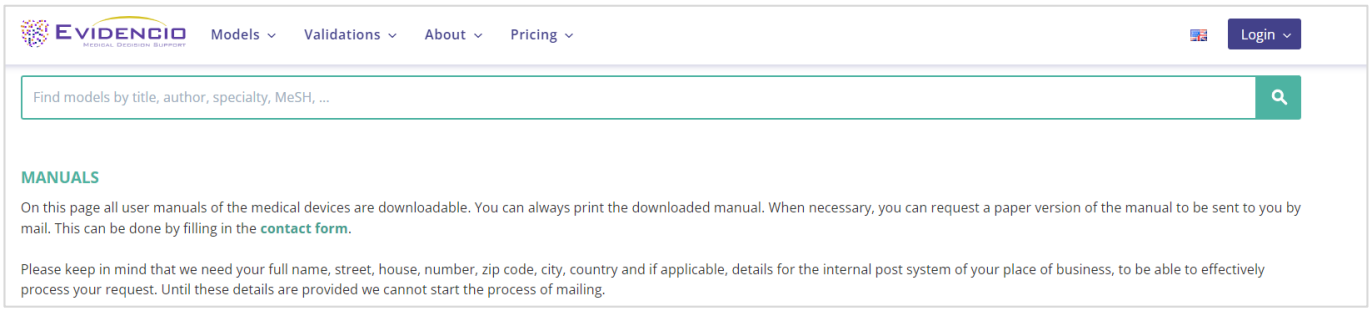

Figure 6. The user manual page for all user manuals.

You (The user) can always print this downloaded manual. When necessary, you can request a paper version of the manual to be sent to you by mail. Evidencio's contact details are listed in Chapter 6 of this user manual.

L. Input section

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

Categorical variables

In the example shown in Figures 7 and 8, the **MELD version** variable concerns a categorical variable. The version that is wished to be used can be entered by clicking on either button. The selected button changes to green, as seen in Figure 8.

Figure 7. The variable for MELD version, where no button has been clicked, and thus no input has been provided by the user.

Figure 8. The variable for MELD version, where the "MELD 3.0" button has been clicked.

Continuous variables

In the example shown in Figure 9, the **Serum bilirubin** variable, exemplifies a continuous variable. The plausible ranges for the variables are used for the model.

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 20 mg/dL is entered for **Serum bilirubin**).

Figure 9. The variable for Serum bilirubin, where "20 mg/dL" has been entered

It is possible to use unit conversion, by clicking on the unit. See the figure below where the unit is clicked.

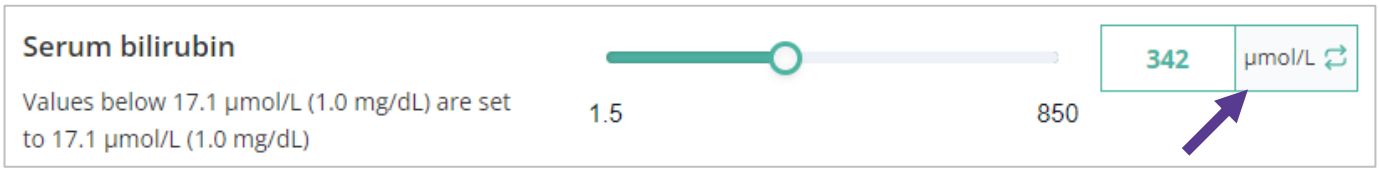

Figure 8. The variable for Bilirubin, where "342 µmol/L" has been entered

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. In Figure 10, the details below **Serum sodium** explain what the ranges of the variable is.

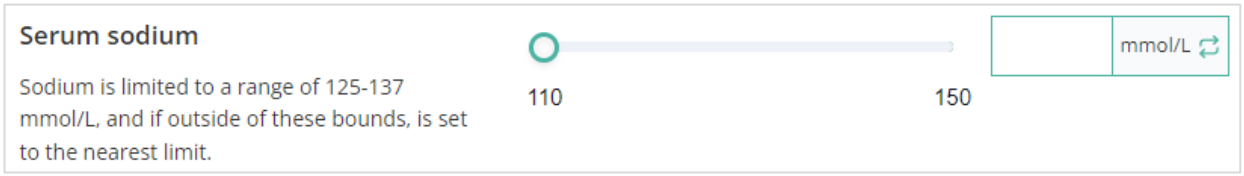

Figure 10. An example on how additional information can be provided for a variable.

M. Result section

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

Result calculation

The model does not calculate automatically, when all variables are filled in, a result can be calculated. No risk is displayed until all variables are filled in, and the *"Calculate"* is clicked. The result section indicates *"Set all parameters to calculate prediction."* Until all parameters are entered and the calculate button is clicked.

Result interpretation

In the result interpretation, a risk stratification is given based on the risk score. An example of the information is shown In Figure 11.

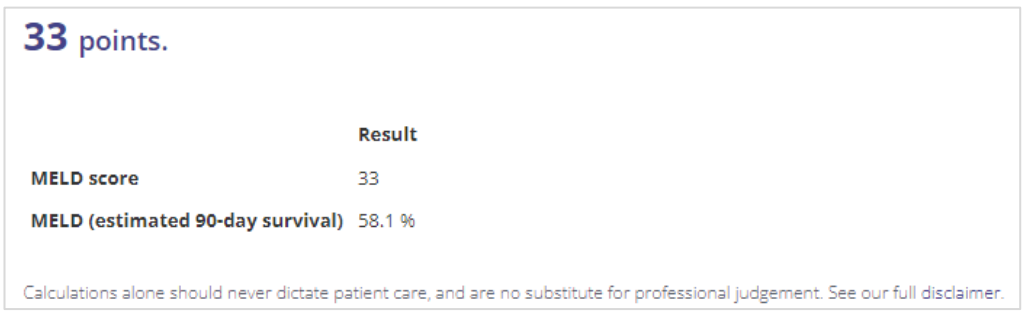

Figure 11. The result information

Relevant information for correct use of the model

At the bottom of the page, there is a link to Evidencio's terms and conditions of use, the privacy policy, and the disclaimer.

5. Use of Medical devices

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.

To use the tool, Evidencio requires a stable internet connection and runs on the following devices:

- Personal computers or laptops using the following browsers:
  - Safari (the latest three versions)
  - Chrome (the latest three versions)
  - Firefox (the latest three versions)
  - Edge (the latest three versions)
- Tablets or smartphones running on the next operating systems:
  - IOS (the latest three versions)
  - Android (the latest three versions)

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 algo's 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.

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

The combined MELD score can also be integrated in third party applications over the API. To use the API tools provided by Evidencio, authorization is required with an API key and access to the device must be granted. API keys and algorithm access requests must be submitted to info@evidencio.com. Specific requirements apply for the use of the device over the API. Use specifications are available upon request, and will be shared upon receiving the API key.

6. 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.
Contact details of your competent authority can be found here: https://www.ema.europa.eu/en/partners-networks/eu-partners/eu-member-states/national-competent-authorities-human

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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