

Innovation in liver function diagnostics: Possibilities and opportunities of the LiMAx-Test in clinical application

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1. Status of liver function diagnostics - current situation

Diagnosing liver function is a complex task and information about the liver function has so far only be derived from surrogate parameters. Currently, various "function tests" are available. Predominantly liver function is assessed based on certain blood values and clinical examinations. However, their specificity and sensitivity are low and dependent on experience. New procedures are urgently needed in everyday clinical practice, especially since liver function is also a relevant success factor in various non-liver-centred therapy procedures (e.g. oncology).

The Humedics LiMAx test offers the possibility of a completely new diagnostic approach that can significantly improve the treatment and care of affected patients. The LiMAx test is a non-invasive examination method to determine the actual liver function in patients with acute or chronic liver diseases, and it is the only test that can quantitatively measure liver function in real time. The LiMAx test allows for the diagnosis of the extent of liver impairment in order to accurately determine the prognosis of the liver disease and to initiate appropriate therapy. The success of a therapy and/or the progression of the liver disease can also be monitored by means of repeated LiMAx tests.

More than ever, new, innovative procedures in medicine require a comprehensible and resilient proof of benefit for patients and the underlying diagnostic-therapeutic process.

In the context of "evidence-based medicine" and institutionalised regulatory bodies (e.g. G-BA, IQWiG, InEK) certain minimum methodological standards for the proof of benefit are essential to their acceptance and the resulting consequences for reimbursement policy.

For the LiMAx test, a variety of experiences from different parties are available.

In hepatology as well as in visceral surgery, indication specific experiences are generated and individually published, clearly indicating the superiority of the LiMAx test over conventional liver diagnostic parameters. As a matter of fact, the non-invasive LiMAx procedure can even completely or partially replace the latter.

The LiMAx test is currently used in the diagnosis of

- chronic liver failure (CLF)
- acute liver failure (ALF)
- acute on chronic liver failure (AOCLF)
- alcohol-induced liver failure (ASH-LF)
- non-alcoholic liver inflammation (NASH)
- interventional radiology (TACE, SIRT, TIPS)
- intensive care medicine (monitoring liver function and optimizing drug therapy)
- oncology (monitoring and optimization of the influence of chemotherapy on liver function)
- visceral surgery (prior to major liver resections, in the context of liver transplantation, in abdominothoracic esophageal resection, gastric resection, pancreatic resection, sarcoma surgery, deep rectal resection with suspicious liver dysfunction)

2. Problem definition and work process

In the current financing model of DRGs, the LiMAx liver function test is not included. Due to its innovative character it does not appear in the calculation models, which are used for routine applications, nor has it undergone the NUB procedure indicated for such new modalities (currently in preparation).

In order to support this process and to establish a professional consensus amongst users about indications, benefits and risks as well as the perspectives of modern liver function diagnostics, Humedics has appointed a group of experts under coordination of the Institute for Health Economics and Health Care Research (IGV-research). The aim is to review the current state of knowledge and to provide a professional dialogue for decision-making in medicine, economics and regulatory processes.

In addition to representatives of Humedics, the following experts belong to this group:

- Prof. Dr. Guido Gerken (Emeritus Director, University Hospital Essen)
- Prof. Dr. Ali Canbay (University Hospital Magdeburg)
- Prof. Dr. Thomas Grünberger (Sozial Medizinisches Zentrum Süd, Vienna Clinics)
- Prof. Dr. Andreas Beivers (Fresenius University, Munich)
- Prof. Dr. Herbert Rebscher (IGV-research, Gylum-Hesedorf)

This expert group has in several sessions worked on the topic and decided to establish consensus on the status of liver function diagnostics using LiMAx in a user's conference.

Prior to the conference, all users were interrogated by a structured questionnaire on the individual use of the LiMAx test in their daily clinical routine. In particular, the focus was on the indications for the test, the frequency of its application, the aetiology of the relevant patients (viral hepatitis, HAV, HBV, HCV, HEV; as well as NAFLAD/NASH, ASH, mCRC, HCC, CCC, NET) and the advantages of LiMAx testing compared to conventional diagnostic procedures, as well as, its central diagnostic and predictive potential.

The evaluation of this survey was presented to the participants of the Consensus Conference on 28/29 June 2019 in Frankfurt and formed the basis for the further discussion.

A total of 33 participants from user hospitals in Germany, Austria and Switzerland took part in the consensus conference (see Appendix).

After a "state of the art" presentation on the state of liver function diagnostics (Professor Gerken), followed by an introduction to the "Methodology and economics of regulation" (Prof. Rebscher) and an overview of "The methodology of cost-benefit analysis" (Prof. Beivers), two separate working groups

- Internal Medicine/ Hepatology (chair: Prof. Canbay/ Prof. Beivers)
- Surgery (chair: Prof. Grünberger/ Prof. Rebscher)

discussed the topics in depth, collected experiences, reflected on the advantages and limitations of the method and sought the professional consensus of all participants.

In a subsequent concluding "plenum session", these results were agreed upon across the disciplines and options of further applications, as well as research questions in liver function diagnostics that had not previously been addressed were discussed.

3. The test and its alternatives

3.1 Description of the new method

The LiMAx test is based on the metabolism of the non-radioactive diagnostic agent ^{13}C -methacetine. ^{13}C -methacetine is a substrate of the hepatic cytochrome - P450 1A2- isoenzyme and is converted exclusively in the liver into paracetamol and $^{13}\text{CO}_2$. The latter is exhaled via the lungs, leading to an increase in the $^{13}\text{CO}_2$ concentration in the exhaled air compared to the $^{13}\text{CO}_2$ naturally present in the atmosphere.

In practical use, the base line concentration of the $^{13}\text{CO}_2/^{12}\text{CO}_2$ ratio in the patient's breath is first measured using a breathing hose and a face mask.

After intravenous injection of ^{13}C -methacetin, the LiMAx device then determines the thereby induced increase of $^{13}\text{CO}_2$ in the patient's exhaled air. The faster and higher the increase of $^{13}\text{CO}_2$ within 40 to 60 minutes, the better is the liver function of the patient. The difference between the maximum $^{13}\text{CO}_2$ value after the ^{13}C -methacetine administration and the value before the injection results in the so-called LiMAx value. Which is a quantitative measure of the functional capacity of the patient's liver.

The test is simple, complication-free and can be repeated at any time at the patient's bedside (also in mechanically ventilated patients in the intensive care unit).

3.2 Which existing method will be replaced or supplemented by the new method?

Based on certain blood values and clinical assessments, patients can be classified into different risk groups (e.g. CHILD-Pugh classification A-C, MELD Score) [1,2]. However, the results of such clinical investigations are often subjective.

Laboratory parameters are often unspecific, as they can be influenced by e.g. malnutrition, dietary errors or iatrogenic substitutions (vitamin K, albumin, etc.). Furthermore, biomarkers which are calculated into certain serum indices such as "AST/ALT-ratio (AAR)", "AST-to-platelet-ratio Index (APRI)" or "fibrosis-4 Index (FIB-4)" and are used for the evaluation of liver function are not liver-specific, i.e. they may show changes even without acute or chronic liver disease [3,4].

Elastography tests, as for example transient elastography (Fibroscan) [5] detect the disease-related remodelling of connective tissue in the liver but provide only indirect insights into liver function. In addition, these tests are dependent on the experience and skill of the user; in overweight patients (e.g. very frequent in NASH) no useful results can be determined in up to 30% of cases. It is also impossible to perform transient elastography in patients with ascites.

The gold standard for the assessment of acute or chronic liver disease is liver biopsy [6]. As an invasive procedure, however, it is associated with severe side effects (especially bleeding) and therefore biopsy is unsuitable as a repetitive procedure in the assessment of chronic liver diseases [7]. Furthermore, biopsy always represents only a small portion of the total liver ("sampling error") [8]. Like the non-invasive Fibroscan, biopsy allows the evaluation of the

tissue composition or its disease-related alteration, but it offers only indirect information on the actual function of the liver.

The LiMAx test is the only available method that enables an accurate, up-to-the-minute and at any time safely repeatable assessment of the actual liver function. The LiMAx test can thus partially replace the previously mentioned non-invasive "liver function tests", supplement the diagnosis of liver disease with a genuine assessment of liver function, and reduce the need for invasive, high-risk liver biopsy. Publications show that by using the LiMAx test, the degree of fibrosis of the liver can be determined, which was previously only possible with liver biopsy [9]. Similarly, with the LiMAx test the short-term prognosis of patients with liver cirrhosis [10] or with acute liver failure can be predicted as well [11]. More accurate monitoring of liver function after and during chemotherapy as well as during intensive care is also of great benefit to patients without additional physical stress [12, 13, 15].

3.3 Costs of the new method

In case of a direct purchase of the LiMAx system, clinics pay about € 70,000 acquisition costs plus a € 250 service fee per month and € 350 per measurement. In this case the material for 200 measurements is included in the acquisition price [14].

With the leasing model, the LiMAx system is made available free of charge without service fees. The costs for a LiMAx test then amount to € 500.90 per application. These costs are incurred by the mask and ¹³C Methacetin (€ 390.00), the indwelling cannula, the injection accessories and the bandage material (€ 15.00) as well as the costs for the physician performing the injection (working time approx. 15 minutes, at € 1.28 costs per physician-minute are € 19.12) [14].

At present, the LiMAx test is mainly used for inpatients who are billed with the basic DRGs (InEK Fallpauschalkatalog 2019) G46/47/66/67/71, H29/60/61/62/63/64, K63/64, R13/62, T60/63/64 and Z64/65. However, these DRGs do not include the costs of the LiMAx test; there is no additional charge or NUB fee.

4. Consensus of the LiMAx users

4.1 Suitable indication for the LiMAx test

- functional diagnostics, prior to large liver resection, no matter what indication (major hepatectomy)
- preoperatively for resection of hepatocellular carcinoma (size-independent), prior to liver metastasis resection after chemotherapy
- (in evaluation) in liver transplanted patients, before/after living donation, in ALPPS resection (intra surgery, before 2nd surgery)
- desirable in brain-dead organ donors, in patients before and immediately after completion of chemotherapy for intended liver resection
- before and 4 - 6 weeks after portal vein embolization +/- liver-vein embolization if necessary, with planned trisectomy
- chronic liver failure (CLF)

- acute-on-chronic liver failure (AOCLF)
- acute liver failure (ALF), potential for regeneration or HU-LTX candidate
- alcohol-induced liver failure (ASH-LF)
- interventional radiology (TACE, SIRT, TIPS)
- before cardiothoracic surgery
- intensive care (monitoring of liver function and drug therapy)
- oncology, especially before chemotherapy and post-chemotherapy before surgery (resection)
- optimization of drug dosage (in oncology and intensive care medicine)

4.2 Comparable non-invasive diagnostic methods

- HVP (Hepatic Venous Pressure Gradient)
- ICG Clearance (Indocyanine Green Clearance)
- Hepatobiliary Imino Diacetic Acid Scan (HIDA Scan)
- Child-Pugh-Score, MELD-Score, Albi-Score, conventional liver values, various non-invasive scores (NAS-Score, FIB-4, etc.)
- imaging techniques: sonography, ultrasound, MRT, CT

The LiMAx test is the only test that shows exactly what is of utmost importance for both medical decision-making and the patient: the actual function of the liver. All other methods mentioned so far, and all other clinically available methods, only give a picture of the *condition* of the liver, but in the end the *function* is always decisive. Even a liver in a bad condition (morphology, degree of cirrhosis, etc.) can warrant a good survival prognosis in a patient with sufficient functional capacity.

5. Benefit of the LiMAx - measurement

5.1 Clinical advantages of the LiMAx procedure

The clinical advantages of the application of the LiMAx test are directly relevant to patient care. They increase the certainty of the therapeutic decision making and the assessment of the therapy process by physicians and directly adds to patient safety through non-invasive diagnostics and an individually appropriate therapy.

The agreed advantages in detail:

- dynamic liver function parameters
- liver function comparison before/after chemotherapy or after a certain time after the end of chemotherapy
- "timely" surgery after neoadjuvant chemotherapy; early enough to prevent new tumour growth, late enough to prevent chemo-damaged liver from being additionally burdened by surgery
- the above not only in liver carcinoma and colon metastases surgery, but in principle in any neoadjuvant chemotherapy

- knowing the maximum "liver resilience", any drug therapy can be used to the maximum, but cannot be overused
- before and after TIPS
- before and after (repeated) TACE
- before and after SIRT
- before, after PVE
- measurement of liver function in icteric patients (not possible with other function tests)
- estimation of the liver functional reserve before pancreas head resection (with/after icterus)
- before major visceral surgery in the case of clinically impaired liver function
- determination of the degree of fibrosis without biopsy and thus no patient overnight stay (economic advantages)
- simplified monitoring of the degree of fibrosis (not possible with biopsy, or only with high burden for the patient)
- possibility of predictive therapy decision, especially for transplantation (ALF) yes/no
- increase in therapy adherence and compliance, accurate prognosis (chronic liver damage), no complications (compared to liver biopsy with bleeding and pain)
- avoidance of unnecessary medication (dosage, metabolism)
- avoidance of unnecessary transplantations (ALF dynamic bedside liver function testing) and thus also avoidance of morbidity and mortality
- evaluation of donor organs → despite possibly poor morphology more livers can be used for transplantation

5.2 Economic benefits (cost and benefit dimension)

The economic advantages of the method result primarily from improved diagnostics, which enable targeted therapy decisions:

- More accurate diagnosis and determination of indications can lead to a reduction of anticipated complications during inpatient admission (measurable through reduced nursing burden, shorter stay and better quality of results), having a direct impact on costs and benefits.
- Avoidance of alternative and expensive drug administrations (especially in intensive care units) through more targeted diagnostics, leading to fewer side effects for the patients (economically, this can be measured directly through lower drug costs). Fewer side effects can lead to shorter patient stays, a lower number of nursing and physician procedures, putting less burden on personnel resources; patient adapted dosage avoids secondary organ damage (kidney failure, liver failure, etc.).
- Support of transplantation decisions (which patient must be transplanted) can have effects on mortality, but also on the rejection rate of the organs (effects hardly economically assessable, but of invaluable benefit for the patients).
- In the case of acute liver failure, the LiMAX test can reduce the length of stay in the intensive care unit (thus again relieving the burden of caregivers).

- The number of biopsy patients is decreasing (via a control group it would be possible to evaluate how high this proportion is in order to subsequently calculate the savings).
- The LiMAx test can lead to an increase in patient adherence; patients know their own values and can see how they can control them through their lifestyle; this would be a great asset, especially for the ambulatory sector. In turn, this may have major implications for care (such effects would have to be investigated in a study of about one to two years).

The MINI HEALTH TECHNOLOGY ASSESSMENT of the LiMAx procedure [14], published in September 2019, focused on the economic cost-benefit dimension of the procedure. The investigations are based mainly on a systematic literature search and on an economic evaluation of the clinical advantages of the LiMAx system for interventional use in liver surgery. Based on the clinical effects and the costs per measurement, the use of the LiMAx system resulted in cost savings of at least € 2,159 per liver operation. The cost-benefit analysis showed that € 4.51 to € 23.54 could be saved for each Euro spent.

Due to the high evidence level of one of the clinical benefits and a cost-benefit ratio of less than 1/4, it can be strongly assumed, according to the authors Schwartz and Ring, that the use of the LiMAx system in liver surgery may lead to a cost reduction in everyday clinical practice despite the limitations of the models with regard to potential biases. However, the authors call for further prospectively planned studies in order to evaluate the clinical and economic advantages of the LiMAx system in non-interventional diagnostics more conclusively [14].

6. Conclusion

The consensus conference was future-oriented and interdisciplinary. For the first time, it assessed the benefits and advantages of a new, innovative, non-invasive diagnostic modality from a patient-oriented, as well as a from a medical and health-economic point of view.

LiMAx is an innovative, CE-certified and non-invasive dynamic semiquantitative liver function test with 100% reproducibility. The examination can be carried out at the bedside and may be used independent of a laboratory by Hospitals and clinical practices in daily "real-life" medicine as well as in scientific studies.

The LiMAx test represents a procedure with high potential benefits for diagnostic reliability, therapy decision making, course of therapy and patient safety and satisfaction.

Based on suitable medical indications (indication quality), the method has health economic advantages, especially for those directly bearing the costs.

The text is based on the results of the consensus conference of the LiMAx users on 28/06 and 29/06/2019 in Frankfurt am Main.

Literature by the authors

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Appendix: Attendees of the Consensus Conference Frankfurt

1. Dr. Katrin Hoffmann, University Hospital Heidelberg
2. Dr. Bianka Hummel, Klinikum Wiener Neustadt
3. Dr. Klaus Alexander, BHS
4. Dr. Marcus Fink, BHS
5. Dr. Nikolaus Pfister, Rudolfstiftung Vienna
6. Prof. Christian Madl, Rudolfstiftung Vienna
7. PD Dr. Robert Sucher, University Hospital Leipzig
8. Dr. Jan Bednarsch, University Hospital Aix-la-Chapelle
9. PD Dr. Johan Lock, University Hospital Würzburg
10. PD Dr. Florian Vondran, MHH
11. Dr. Tilo Wünsch, Charité
12. Dr. Maximilian Jara, Charité
13. Dr. Christian Oberkofler, University Hospital Zurich
14. Dr. Florian Berreth, Hospital Stuttgart
15. Prof. Dr. Peter Galle, University Hospital Mainz
16. PD Dr. S. Güldütuna, Frankfurt
17. Prof. Dr. Günther Winde, Herford
18. Dr. Elisabeth Menges, Herford
19. Dr. Christina Ficke, St. Pölten
20. Prof. Dr. Stefan Fichtner-Feigl, University Hospital Freiburg
21. Prof. Dr. Martin Stockmann, Ev. KH Wittenberg
22. Prof. Dr. Guido Gerken, University Hospital Essen
23. Prof. Dr. Ali Canbay, University Hospital Magdeburg
24. Prof. Dr. Thomas Grünberger, KFJ Hospital Vienna
25. Prof. Dr. Andreas Beivers, Fresenius University
26. Prof. Dr. Herbert Rebscher, IGVresearch Hesedorf

From the company Humedics

- Karsten Damgaard-Iversen, CEO
- Dr. Ralf Kohnen, CCO
- PD Dr. Oliver Gödje, CMO
- Dr. Catalin Cocuz, Director Regional Sales DACH
- Daniela Barth, Marketing & Sales