Serum glycomics as prognostic and diagnostic biomarkers of graft loss and hepatocellular carcinoma recurrence in liver transplant recipients

Published:
Last updated: 13-06-2025

Primary Objective: * To validate the prognostic value of a serum glycomics biomarker for graft survival at 3 months after liver transplantation. * To validate the prognostic value of a serum glycomics biomarker for overall survival at 3 months after...

Ethical review	Approved WMO
Status	Pending
Health condition type	Hepatic and hepatobiliary disorders
Study type	Observational invasive

Summary

ID

NL-OMON57576

Source
ToetsingOnline

Brief title
GLYLT

Condition

- Hepatic and hepatobiliary disorders

Synonym
Liver transplantation

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Ziekenhuis Gent

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Biomarkers, Glycomics, Graft loss, Liver Transplantation

Outcome measures

Primary outcome

The primary end points of the study are graft loss and death at 3 months after liver transplantation. **

Secondary outcome

The secondary endpoints are graft and overall survival at 12 months and 3 year after liver transplantation. The prognostic value of a serum glycomics biomarker for graft and overall survival at 12 months and 3 years after liver transplantation, to study the value of repeated glycomic measurements after liver transplantation and the optimal time-point of biomarker measurement.

n the subset of patients receiving a liver transplantation for HCC: HCC recurrence. The predictive value of a serum glycomics biomarker determined before liver transplantation for HCC recurrence, liver-related death, and overall death. The predictive value of a serum glycomics biomarker as marker of early recurrence in patients receiving liver transplantation for HCC when determined during follow up after liver transplantation*

Study description

Background summary

***Liver transplantation (LT) is the only currently available lifesaving treatment for patients with end-stage liver disease, for a distinct subset of patients with hepatocellular carcinoma (HCC), and in acute liver failure (ALF). Due to improvements in surgical techniques and immunosuppressive regimens, outcome has improved throughout the years, with current 1-year overall survival in adults ranging between 86% and 92.1% (2, 3). The first 12 months after LT are decisive in post-LT outcome, as almost half of deaths and two thirds of graft loss requiring retransplantation occur in the first year after LT (2).
Due to the widespread success of liver transplantation, demand for transplantable organs has increased and with it, morbidity and mortality of patients on the waiting list(1). In order to compensate for the shortage of donor organs, the most important evolution in adults is expansion of the donor pool by use of ECD livers. These organs are, however, harvested from a heterogeneous group of donors with either risk of disease transmission, or poor graft function. The latter category is harvested from donors with advanced age, steatotic livers, prolonged critical illness, or from donation after circulatory death which in itself carries an augmented risk of ischemia-reperfusion injury. *
Regardless of early (primary graft nonfunction, graft dysfunction or hepatic artery thrombosis) or late (ischemic cholangiopathy, chronic rejection, tumor or non-tumor disease recurrence) causes of graft loss, up to 10% of patients experience graft loss requiring retransplantation.(2, 4)
Timely decision to retransplantation in primary non-function and severe graft dysfunction are major determinants of graft and patient survival, making early management of these complications of paramount importance in improving patient outcome(5). Moreover, balancing the need and right timing for retransplantation in individual patients with a complicated posttransplantation course is currently a difficult challenge that relies on imperfect clinical variables and biomarkers, as well as the experienced judgment of the transplant team.*

A large part (30%) of patients is transplanted because of hepatocellular carcinoma, mostly in an cirrothic liver, next to the above mentioned risk of graft failure an additional risk of recurrence of HCC influencing prognosis plays a role in these patients. despite selection models (Milan criteria, AFP model, UCSF criteria) we see recurrence in 12-15% of patients, posing an additional risk for mortality. A improved selection tool to select the patients benefiting most from transplantation with lowest risk of recurrence would greatly improve the outcomes

Protein glycosylation, the addition of glycan structures to glycosylation sites, is the most common and complex post-translational modification of proteins. It occurs in the Golgi complex and endoplasmic reticulum and is indispensable for a plethora of protein functions (20) Glycomics, the systematic study of glycosylation, allows detection of alterations in the abundance of particular glycans reflecting an altered physiological state (21). The majority of N-glycans found in whole serum are attached to serum proteins produced by hepatocytes and, to a lesser extent, to IgG that is secreted by

plasma cells. This makes serum glycomic profiling an attractive technique to study alterations in liver homeostasis (22-24). In close collaboration with the laboratory of Glycobiology from Prof. Dr. Nico Callewaert from the Vlaams Instituut voor Biotechnologie (VIB, Zwijnaarde, Belgium), a high-throughput platform to profile sialidase-treated N-glycans from whole serum was developed based on DNA sequencer-assisted fluorophore-assisted capillary electrophoresis (DSA-FACE) (25, 26). Exploitation of this platform has led to the development of diagnostic and prognostic biomarkers based on the serum glycomic profile of patients with chronic liver diseases, such as liver cirrhosis (25), fibrosis (27) hepatocellular carcinoma (28, 29), and non-alcoholic steatohepatitis(30). *

Study objective

Primary Objective: * To validate the prognostic value of a serum glycomics biomarker for graft survival at 3 months after liver transplantation. * To validate the prognostic value of a serum glycomics biomarker for overall survival at 3 months after liver transplantation. Secondary Objectives: To validate the prognostic value of a serum glycomics biomarker for graft survival at 12 months and 3 years after liver transplantation.* To validate the prognostic value of a serum glycomics biomarker for overall survival at 12 months and 3 years after liver transplantation.* To study the value of repeated glycomic measurements after liver transplantation.* To study the optimal time-point of biomarker measurement.* To identify other serum glycomics biomarkers for LT outcomes (graft survival, HCC recurrence) And in a subset of patients receiving a liver transplantation for HCC: To validate a serum glycomics biomarker as predictor of prognosis (HCC recurrence, liver-related death, and overall death) when analysed before liver transplantation* To explore the potential of serum glycomics as marker of early recurrence in patients receiving liver transplantation for HCC when analysed after liver transplantation

Study design

This research study will be composed of a prospective, multicentric, interventional study design. The study will be performed together with the liver transplantation centrers in Belgium and the Erasmus MC in the Netherlands At specific time points an additional serum tube will be collected next to the blood sample drawn via venipuncture for standard of care.
First collection will be at the moment of waitlist placement, the second on the day of transplantation. After liver transplantation the samples will be collected on specific time points as well. Day 1-14 daily; Week 3-6: weekly; month 3-6: monthly; month 9- end of FU: 3 monthly. Always during standard of care venipuncture.

Study burden and risks

This project starts from the medical unmet need for the prognostication of risk of graft and patient survival in patients after liver transplantation. Current models fall short in stratifying patients on an individual level. The implementation of serum glycomics as a reliable and readily available marker of graft function that is independently associated with graft survival could imply a paradigm shift in transplantation management. More specifically, improving prognosis of patients who benefit from retransplantation through timely decision making and conversely, avoiding futile retransplantation could really impact outcome of liver transplant recipients on a large scale in light of the expansion of the donor pool by grafts with lesser quality.**

Furthermore, in the growing population of patients transplanted for HCC, there is an unmet need for the correct estimation of the risk of recurrence in HCC patients after liver transplantation. All current models fall short here and recurrence of HCC after transplantation is still common. As such, the implementation of personalised medicine in this field, based on powerful biomarkers accounting for the tumour*s biological activity, could really change clinical practice. More specifically, patients who are eligible for liver transplantation based on the current criteria but who score *poorly* on the glycomics biomarker should not undergo a liver transplantation. This will prevent a futile liver transplant in this patient which will improve his survival, and provide an extra organ in the donor pool for a patient who will benefit. Moreover, patients who currently fall out of scope for liver transplantion but score *good* on the glycomics biomarker could still be selected. As such, the liver transplants could be used in a more efficient manner.*

The included subjects will not directly benefit from inclusion in this study, however it is impossible to perform this study in another population and the risks in participating in this study are negligible, we do not ask for additional interventions and all samples are collected during scheduled visits and standard-of-care venipunctures.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Age >= 18 years*
Consulted the department of Gastroenterology and Hepatology*
Diagnosis of end-stage liver disease, primary hepatic malignancy meeting the AFP model criteria for liver transplantation, or acute liver failure
Eligible for liver transplantation and/or active on the waiting list for liver transplantation*
Ability to comply with protocol-specified evaluations and scheduled visits*
Be able to read and write
Understand the patient information

Exclusion criteria

Transplantation of multiple organs that do not include the liver, eg. Combined heart and lung transplantation - subjects who do not fulfill the inclusion criteria

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2025
Enrollment:	100
Type:	Anticipated

Ethics review

Approved WMO

Date:	02-06-2025
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL87937.078.24