Year : 2022

Increasing prevalence of obesity and diabetes among patients evaluated for liver transplantation in a Swiss tertiary referral center: a 10-year retrospective analysis

Kasmi Sophie

Kasmi Sophie, 2022, Increasing prevalence of obesity and diabetes among patients evaluated for liver transplantation in a Swiss tertiary referral center: a 10-year retrospective analysis

Originally published at : Thesis, University of Lausanne

Posted at the University of Lausanne Open Archive http://serval.unil.ch
Document URN : urn:nbn:ch:serval-BIB_3947CBAC799D4

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE
Département de Médecine interne
Service de gastro-entérologie et d'hépatologie

Increasing prevalence of obesity and diabetes among patients evaluated for liver transplantation in a Swiss tertiary referral center: a 10-year retrospective analysis

THESE

préparée sous la direction du Docteur Montserrat Fraga Christinet

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Sophie KASMI

Médecin diplômée de la Confédération Suisse
Originaire de Lausanne (Vaud/Suisse)

Lausanne
2022

UNIL | Université de Lausanne

Faculté de biologie et de médecine

Ecole Doctorale
Doctorat en médecine

Imprimatur

Vu le rapport présenté par le jury d'examen, composé de

Directeur.trice de thèse	Dre **Montserrat Fraga Christinet**
Co-Directeur.trice de thèse	
Expert.e	Prof. **Manuel A. Pascual**
Vice-Directeur de l'Ecole doctorale	Prof. **John Prior**

la Commission MD de l'Ecole doctorale autorise l'impression de la thèse de

Madame Sophie Kasmi

intitulée

Increasing prevalence of obesity and diabetes among patients evaluated for liver transplantation in a Swiss tertiary referral center: a 10-year retrospective analysis

Lausanne, le 3 février 2022

pour Le Doyen
de la Faculté de Biologie et de Médecine

Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale

Résumé

Contexte et objectifs : La stéatose hépatique non alcoolique (NAFLD, *Non alcoholic fatty liver disease*) est désormais la première cause de maladie chronique du foie dans les pays développés. Notre objectif a été d'évaluer les tendances de la prévalence de l'obésité, du diabète de type 2 et de la NAFLD chez les patients en cours d'évaluation pour une transplantation hépatique. Ensuite, nous avons déterminer si les patients obèses étaient moins susceptibles d'être inscrits sur liste d'attente de transplantation hépatique ou s'ils avaient un taux de rejet de liste de transplantation hépatique plus élevé après mise en liste que les non-obèses.

Méthodes : Nous avons mené une étude rétrospective incluant tous les patients qui ont subi une évaluation de transplantation hépatique dans un centre de référence tertiaire suisse entre janvier 2009 et mars 2020.

Résultats : 242 patients ont été inclus dans l'étude, 83% sont des hommes. L'âge médian est de 59 ans (IQR, 51-64 ans). Les causes les plus fréquentes de maladie hépatique au stade terminal sont l'hépatite virale (28%), la maladie alcoolique du foie (21%) et la NAFLD (12%). L'obésité est présente chez 28% des patients de notre cohorte, avec une augmentation significative au cours de la période d'étude. La prévalence du diabète de type II suit la même tendance (p = 0,02). La proportion de patients obèses inscrits et non-inscrits sur liste de transplantation n'est pas différente (21 % vs 30 %, respectivement ; p = 0,3).

Conclusions : La prévalence de l'obésité et du diabète de type II a augmenté de manière significative au cours de notre période d'étude. Les patients obèses avaient des chances similaires d'être inscrits sur liste d'attente de transplantation hépatique que les non-obèses. Le paysage de la transplantation hépatique évolue vers la NAFLD, soulignant le besoin urgent de prévenir la progression de la NAFLD.

Increasing prevalence of obesity and diabetes among patients evaluated for liver transplantation in a Swiss tertiary referral center: a 10-year retrospective analysis

Sophie Kasmi[1], Florent Artru[1], Joana Vieira Barbosa[1], Ansgar Rudolf Deibel[2], Lucie Favre[3], Claire Peuble[4], Anne-Catherine Saouli[4], Nicolas Goossens[5,6], Beat Müllhaupt[2], Manuel Pascual[4], Darius Moradpour[1], Julien Vionnet[1,4†], Montserrat Fraga[1]

Author affiliations

[1]Division of Gastroenterology and Hepatology, Lausanne University Hospital and University of Lausanne, Switzerland

[2]Division of Gastroenterology and Hepatology, University Hospital Zürich, Switzerland

[3]Division of Endocrinology, Diabetology and Metabolism, Lausanne University Hospital and University of Lausanne, Switzerland

[4]Transplantation Center, Lausanne University Hospital and University of Lausanne, Switzerland

[5]Division of Gastroenterology and Hepatology, University Hospital Geneva, Switzerland

[6]Division of Transplantation, University Hospital Geneva, Switzerland

Corresponding author:

Montserrat Fraga, MD, Division of Gastroenterology and Hepatology, Lausanne University Hospital (CHUV), Rue du Bugnon 44, CH-1011 Lausanne, Switzerland. Montserrat.Fraga@chuv.ch

Author contributions:

SK, DM and MFdesigned the study; SK , FA, CP, ACS and MFacquired data; FA and JV performed statistical analyses; SK, FA, DM, JV and MF wrote the manuscript; all authors revised the manuscript.

Key words: Diabetes | Hepatocellular carcinoma | LT | Metabolic syndrome | NASH

Electronic word count: 2260 words

Number of figures and tables: Six figures, two tables and two supplementary tables

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALD, alcoholic liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; BMI, body mass index; CHB, chronic hepatitis B; Diabetes mellitus, T2DM; EASL, European Association for the Study of the Liver; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; LT, liver transplantation; MELD, Model for end-stage liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PT, prothrombin time; T2DM, type 2 diabetes mellitus; WHO, World Health Organization

Conflict of interest statement: The authors have no conflict of interest to declare.

Financial support statement: This work was supported by a starting grant from the Fondation Lausannoise pour la Transplantation d'Organes (to MF). JVB was supported by stipends from Lausanne University Hospital, the Novartis Foundation for Medical-Biological Research and the Gottfried und Julia Bangerter-Rhyner Foundation.

Ethics approval: This study was approved by the "Commission cantonale d'éthique de la recherche sur l'être humain" (CER-VD) on November 28, 2019 (protocol number 2019-01728).

Abstract

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is now the first cause of chronic liver disease in developed countries. We aimed to assess trends in the prevalence of obesity, type 2 diabetes mellitus (T2DM) and NAFLD in patients undergoing liver transplant (LT) evaluation and to assess whether obese patients were less likely to be listed or had an increased drop-out rate after listing.

Methods: We conducted a retrospective study of all consecutive patients who underwent LT evaluation at a Swiss tertiary referral center between January 2009 and March 2020.

Results: A total of 242 patients were included, 83% were male. The median age was 59 years (IQR, 51-64 years). The most common causes of end-stage liver disease were viral hepatitis (28%), alcoholic liver disease (21%) and NAFLD (12%). Obesity was present in 28% of our cohort, with a significant increase over time. Prevalence of T2DM followed the same trend ($p = 0.02$). The proportion of non-listed and listed obese patients was not different (21% *vs*. 30%, respectively; $p = 0.3$).

Conclusions: The prevalence of obesity and T2DM significantly increased over our study period. Obese patients had similar chances of being listed. The landscape of LT indications is shifting towards NAFLD, highlighting the urgent need to prevent NAFLD progression.

Introduction

The prevalence of obesity has increased at an alarming pace over the last four decades. Once a relatively minor public health issue, overnutrition and obesity have become a major threat, and it is estimated that at least one third of the world's adult population is now overweight or obese (1). It is predicted that the prevalence of severe obesity will continue to increase and that by 2030 nearly one in two adults will be obese in the United States (2).

The global epidemic of obesity is also reflected among solid organ transplant recipients. In the renal transplant population, the proportion of recipients with a body mass index (BMI) ≥ 30 kg/m^2 has doubled every 15 years (3)(4). Similar observations were made in the liver transplant (LT) population in North America and in Europe (5)(6)(7).

Obesity, as defined by a BMI ≥ 30 kg/m^2 by the World Health Organization (WHO), is the most common risk factor for the development of nonalcoholic fatty liver disease (NAFLD), followed by type 2 diabetes mellitus (T2DM) (8)(9). The clinical spectrum of NAFLD ranges from simple steatosis to the more aggressive nonalcoholic steatohepatitis (NASH), that can eventually progress to advanced fibrosis and cirrhosis (10). Whereas chronic hepatitis C classically dominated the indications for LT in Europe and North America, the advent of direct-acting antivirals has dramatically changed the landscape of LT. In the meantime, NAFLD has become the most common chronic liver disease in many developed countries (11)(12)(13)(14).

In parallel to the development of cirrhosis in patients with NASH, obesity also contributes significantly to the burden of hepatocellular carcinoma (HCC), as recently highlighted by several large-scale epidemiological studies (15). A worrisome feature

is that HCC can even develop in individuals with NAFLD who do not have advanced liver fibrosis or cirrhosis (16)(17).

Obesity and NAFLD are also known to be associated with increased cardiovascular morbidity that, in turn, may preclude listing for LT (18). Of note, the American Association for the Study of Liver Diseases (AASLD) and the American Society of Transplantation have proposed that a BMI > 40 kg/m^2 should represent a relative contraindication to LT (19). Indeed, morbid obesity, defined by a BMI ≥ 40kg/m^2, was reported as independent predictor of drop-out and death in LT candidates (20)(21).

Here, we first aimed to assess the trend in prevalence of obesity, T2DM and NAFLD in patients undergoing LT evaluation at Lausanne University Hospital between January 2009 and March 2020. Second, we hypothesized that access to LT was impaired in obese patients, for instance because of the presence of other major comorbidities or because of the challenge of the surgical procedure in obese patients. Therefore, we assessed whether grade II (BMI ≥ 35kg/m^2) and grade III (BMI ≥ 40 kg/m^2) obese patients were less likely to be listed or had an increased drop-out rate from the waiting list.

Methods

Study population and design

This is a retrospective study analyzing medical data from the Division of Gastroenterology and Hepatology of Lausanne University Hospital, a tertiary referral center in Switzerland with more than 10,000 outpatient consultations per year.

All patients included in this study underwent a formal workup for LT at the Lausanne University Hospital between January 2009 and March 2020, whether they had been grafted or not at the end of the evaluation. After identifying all patients fulfilling our

inclusion criteria, we reviewed electronic medical records and medical archives. Data extraction and coding was manually performed from September 2020 to January 2021.

In our center, patients are referred for LT evaluation by primary care providers as well as gastroenterologists and other specialists in private practice or regional hospitals. They are, then, first evaluated at the outpatient hepatology unit. In case of advanced cirrhosis, patients are evaluated in the inpatient service.

Formal eligibility for LT is afterwards discussed on the occasion of a multidisciplinary meeting, including hepatologists, transplant surgeons, anesthesiologists radiologists, and psychiatrists in every patient with end-stage liver disease, HCC or other rare indications, in accordance with standard and commonly applied criteria (22)(23).

In case of a favorable evaluation by this multidisciplinary team, patients are then hospitalized to conduct an extensive assessment to rule out any medical or psychiatric contraindication to LT. This workup is performed within a few weeks prior to listing and systematically carries an extensive cardiopulmonary assessment including evaluation of cardiovascular risk factors and a nutritional evaluation including BMI calculation.

Inclusion criteria were: 1) age $\geq$ 18 years, 2) patients with a complete LT evaluation. Exclusion criteria were: 1) patients assessed for LT in the setting of acute liver failure, 2) patients assessed for retransplantation in the setting of graft dysfunction, 3) candidates for multi-organ transplantation and 4) patients who were lost to follow-up.

Baseline evaluation

Demographic, clinical and laboratory data were obtained from electronic medical records and medical archives. Demographic data were assessed at baseline and

included sex, age and origin. Clinical data such as BMI, and comorbidities, such as T2DM, hypertension and dyslipidemia were retrieved at the first inpatient evaluation for LT. Grade I, II and III obesity was defined by BMI ≥ 30, ≥ 35 and ≥ 40 kg/m^2, respectively, according to WHO definitions (9).

Subjects were considered as having metabolic syndrome when fulfilling the diagnostic criteria as defined by the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) (24).

Laboratory parameters were retrieved at the first visit for LT evaluation. These included sodium, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, total bilirubin, albumin, creatinine, prothrombin time and international normalized ratio (INR). Liver function was also assessed and included Child-Pugh score, model for end-stage liver disease (MELD) score and MELD-Na score.

Assignment of chronic liver disease etiology

Etiology of chronic liver disease was assessed for each patient based on medical records and liver histology to insure correct assignment to group. Six groups were defined: 1) chronic viral hepatitis (chronic hepatitis B, D and C), 2) alcoholic liver disease (ALD) defined as alcohol intake >30 g/day for men and >20 g/day for women, 3) NAFLD, 4) mixed etiologies including a NAFLD component (e.g. patient with chronic HCV and NAFLD), 5) mixed etiologies without a NAFLD component (e.g. ALD combined with chronic HCV), 6) other causes including auto-immune liver diseases (auto-immune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, overlap syndromes) and rare causes (e.g. Wilson disease, vascular liver disease, transthyretin amyloidosis). Every patient assessed for LT in our center underwent a transjugular liver biopsy. NAFLD was diagnosed based on the criteria defined by European Association for the Study of the Liver (EASL) Clinical Practice Guidelines

for the management of NAFLD (25). Patients with cirrhosis in the presence of two or more metabolic risk factors (diabetes, obesity, dyslipidemia and hypertension) and in the absence of other causes of chronic liver disease were assigned to the NAFLD group. Importantly, all patient underwent a formal histological assessment in our study. NAFLD diagnosis was systematically supported by histology after exclusion of other chronic liver diseases.

Follow-up evaluation

All patients included in the present study benefited from a regular medical follow-up at our outpatient hepatology clinic. Follow-up data were retrieved from consultation files and included: i) laboratory data, MELD and Child-Pugh scores; ii) liver-related complications, such as episodes of decompensation or HCC and iii) non liver related complications, such as extrahepatic neoplasia, cardiovascular events or death. Figure 1 illustrates the patient's medical course from initial assessment to LT.

The date of evaluation at our center, the transplant listing date, the date and reasons for delisting (HCC progression, extrahepatic neoplasia, comorbidities and other causes, death) and the date of LT were recorded.

Statistical analyses

Continuous variables were expressed as median and interquartile range (IQR). Categorical variables were described as frequency and percentage. The distribution of patients' characteristics was compared between 5 periods of time (January 2009-2011 vs. 2012-2013 vs. 2014-2015 vs. 2016-2017 vs. 2018-March 2020) using the Chi-square test. The drop-out curves at two years were estimated using the Kaplan-Meier method, calculated with a 95% confidence interval (CI), and compared across

the different groups using the log-rank test. Liver transplanted patients were excluded alive at time of LT. Univariate and multivariate analyses of variables associated with non listing or drop-out after placement on waiting list were performed using logistic regression and results were reported as Odds ratio (OR) and 95% CI. Covariates with $p \leq 0.1$ in the univariate regression model and obesity were retained for multivariable analysis. The significance level was set at 0.05 with a two-sided test. All statistical analyses were performed using NCSS 2011 software.

Results

Table 1 summarizes the demographic, clinical and laboratory characteristics of the patients included in the analysis. From January 2009 to March 2020, 266 adult patients were formally assessed for LT at Lausanne University Hospital. Twenty-four patients were excluded from the analysis for the following reasons: acute liver failure (n=6), multiorgan transplant (n=9), retransplantation for allograft dysfunction (n=5) and lost to follow-up (n=4).

Overall, 201 patients (83%) were male and the median age was 59 years (IQR, 51-64 years; range, 18-75 years). The vast majority (89%) were of Caucasian (89%), 6% were of African, 3% were of Asian and 2% were of Hispanic origin.

The number of patients evaluated for LT during each defined period of time markedly increased from 29 in 2009-2011 to 91 in 2018-2020 (+310%). The most common cause of end-stage liver disease in our cohort was viral hepatitis (28%), followed by NAFLD alone or combined (22%) and ALD (21%) and (Table 1). Distribution of causes of end-stage liver disease significantly changed over the 5 periods of time (p=0.0006). Indeed, the proportion of viral hepatitis as an indication for LT declined

231 over time from 32% to 14%, while ALD and NAFLD increased from 8% to 25% and
232 from 8% to 38% respectively (Figure 2).
233 Sixty-eight patients (28% of the study population) were obese as defined by a BMI >
234 30 kg/m^2, with grade II and III obesity in 28% of them. The highest BMI among
235 patients evaluated for LT was 43 kg/m^2.BMIs of two patients were not available. Of
236 note, only 12% of the patients were obese in the 2009-2011 period, whereas this
237 proportion increased to 34% in the last observation period, i.e. 2018-2020 (Figure 3).
238 Eighty-two patients had a diagnosis of T2DM (34%), 41 of them (17%) being insulin-
239 dependent. The prevalence of diabetes significantly increased over time (p=0.02)
240 (Figure 4). Overall, metabolic syndrome was present in 40 patients (17% of our study
241 population).
242 Of the 242 patients assessed for LT, 203 patients [60 (30%) obese patients] were
243 listed and 112 patients [35 (31%) obese patients] underwent LT (Table 2). In the
244 univariate analysis, none of the variables - including BMI and obesity - were
245 associated with no enlisting (Suppl. Table 1).
246 Along the same line, none of the variables included in the univariate and multivariate
247 analyses were independently associated with drop-out after listing (Suppl. Table 2).
248 When analyzing drop-out-free survival, there was no significant difference between
249 obese and non-obese patients (64% *vs*. 68%, respectively; p = 0.9) (Figure 5).
250 Reasons for drop-out are indicated in Table 2. The proportion of non-listed and listed
251 obese patients was not different (21% vs. 30%. P = 0.3) (Figure 5).
252 HCC represented the primary indication for LT in approximately half of our cohort
253 (46%). This proportion remained stable throughout the study period. Importantly,
254 underlying chronic liver disease among patients with HCC evolved significantly over

time, with increasing prevalence of NAFLD among patients with HCC (p=0.03) (Figure 6).

Discussion

We retrospectively assessed indications to LT in a tertiary referral center in Switzerland over the last decade. More specifically, we focused our analysis on the evolution of the prevalence of obesity, T2DM and NAFLD among patients referred for LT evaluation from January 2009 to March 2020.

First, our study demonstrates that the landscape of LT indications is shifting towards NAFLD in Switzerland, as predicted in a recent modelling study and described in other countries (11)(26)(24)(28). At the end of the study period, the prevalence of NAFLD in patients evaluated for LT had surpassed the prevalence of chronic hepatitis B and C as well as ALD. Indeed, during the last study period, i.e. between January 2018 and March 2020, NAFLD and chronic liver diseases with a component of NAFLD represented nearly ~~up to~~ 40% of the patients assessed for LT. This may be explained by the fact that viral hepatitis-related indications for LT declined over time notably following the introduction of potent DAA therapies to treat chronic hepatitis C and, also by the obesity and metabolic syndrome epidemics during the last decades. Importantly, all patients evaluated for LT were included in our cohort and not only patients who underwent LT. One main reason for this approach was to assess whether NAFLD may be even more frequent among patients evaluated for LT as compared to those who were transplanted. Thus, we hypothesized that these patients could have an increased risk an increased risk of not being listed or of drop-out from the LT waiting list, for instance because of increased cardiovascular or oncological risk (15)(29)(30). Indeed, the cardiovascular and oncological risks associated with obesity are known to be further increased post-LT (31). Moreover, morbid obesity

was reported as an independent predictor of death and drop-out of LT candidates (21). Based on these considerations, AASLD advises against LT in grade III obesity whereas EASL recommends multidisciplinary evaluation in patients in grade II (19)(22). In our cohort, no patient was denied access to LT evaluation and listing solely based on the BMI. Drop-out rates in grade II to III obese patients were equivalent to those in non-obese patients in our center, thus, in relative contradiction with recently published data, reporting increased drop-outrates in patients with BMI > 40kg/m^2 (21).

We acknowledge that our study has some limitations, in particular regarding the comparison of drop-out rates in obese *vs*. non-obese patients evaluated for LT. Indeed, our cohort is relatively small. Further investigations will require a multicentric and prospective extension of our study. It is also possible that some obese patients with criteria for LT assessment were not referred to our center, as it is known that stigma associated with obesity negatively impacts on quality of care and outcomes (32). Secondly, weight loss, malnutrition and sarcopenia affects up to 60% of cirrhotic patients (33). Thus, it is possible that the obesity burden among our patients may have been underestimated.

Increased morbidity after surgery is well documented in obese patients (34). The outcome of obese patients after LT is an important question that goes beyond the scope of our analysis and will have to be addressed in future studies. Recent data from the European Liver Transplant Registry (ELTR) suggests that survival of patients and grafts in patients with NASH is comparable to that of patients transplanted for other indications (35).

We report that the worldwide epidemic of obesity has a direct impact on the characteristics of the LT waiting list population also in Switzerland. Epidemiological

data in Switzerland show increasing numbers of patients requiring LT over the last decade (36). Considering the increasing prevalence of NAFLD and obesity, this trend is likely to continue in the coming years and to further impact on organ shortage. Based on our observations, we advocate for the improvement and implementation of multidisciplinary strategies to screen for and treat NAFLD in order to prevent liver fibrosis progression.

There are currently few therapeutic alternatives for obesity, with bariatric surgery remaining one of the main options. This procedure was linked to the resolution of NASH in up to 85% of patients, with improved histological features at one year (37)(38). It is indeed a recognized therapeutic option for obese patients with NASH who do not respond to lifestyle modifications. Bariatric surgery at the time of LT or in the postoperative course has the potential not only to improve obesity-related conditions such as diabetes, but also to reduce the incidence of *de novo* NASH of the allograft (39). Facing the increasing prevalence of obesity among patients evaluated for LT, bariatric surgery should be considered and discussed at earlier stages, in order to prevent further progression of liver disease and, in consequence, a need for LT.

In conclusion, our study confirms the changing landscape of indications to LT and highlights the many challenges that lie ahead, including the implementation of early multidisciplinary strategies to treat obese patients in order to prevent NAFLD progression and its consequences. Finally, because of a similar pre-LT drop-out rate in obese and non-obese patients, we encourage to refer obese patients needing LT for a proper assessment and not to preclude them from access to LT solely based on BMI.

References

1. Seidell JC, Halberstadt J. The global burden of obesity and the challenges of prevention. Ann Nutr Metab. 2015;66 Suppl 2:7–12.

2. Ward ZJ, Bleich SN, Cradock AL, Barrett JL, Giles CM, Flax C, et al. Projected U.S. State-Level Prevalence of Adult Obesity and Severe Obesity. N Engl J Med. 2019;381(25):2440–50.

3. Yach D, Stuckler D, Brownell KD. Epidemiologic and economic consequences of the global epidemics of obesity and diabetes. Nat Med. 2006;12(1):62–6.

4. Friedman AN, Miskulin DC, Rosenberg IH, Levey AS. Demographics and trends in overweight and obesity in patients at time of kidney transplantation. Am J Kidney Dis. 2003;41(2):480–7.

5. Parikh ND, Marrero WJ, Wang J, Steuer J, Tapper EB, Konerman M, et al. Projected increase in obesity and non-alcoholic-steatohepatitis-related liver transplantation waitlist additions in the United States. Hepatology. 2019;70(2):487–95.

6. Belli LS, Perricone G, Adam R, Cortesi PA, Strazzabosco M, Facchetti R, et al. Impact of DAAs on liver transplantation: Major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. J Hepatol. 2018;69(4):810–7

7. Cholankeril G, Ahmed A. Alcoholic Liver Disease Replaces Hepatitis C Virus Infection as the Leading Indication for Liver Transplantation in the United States. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2018;16(8):1356–8.

8. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology.

2018;67(1):328–57.

9. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med J Br Diabet Assoc. 1998 ;15(7):539–53.

10. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002;346(16):1221–31.

11. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73–84.

12. Terrault NA, Pageaux G-P. A changing landscape of liver transplantation: King HCV is dethroned, ALD and NAFLD take over! J Hepatol. 2018;69(4):767–8.

13. Axley P, Ahmed Z, Arora S, Haas A, Kuo Y-F, Kamath PS, et al. NASH Is the most rapidly growing etiology for acute-on-chronic liver failure-related hospitalization and disease burden in the United States: A population-based study. Liver Transplant. 2019;25(5):695–705.

14. Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, et al. Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin Gastroenterol Hepatol. 2019;17(4):748–755.e3.

15. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348(17):1625–38.

16. Baffy G, Brunt EM, Caldwell SH. Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. J Hepatol. 2012;56(6):1384–91.

17. Paradis V, Zalinski S, Chelbi E, Guedj N, Degos F, Vilgrain V, et al. Hepatocellular carcinomas in patients with metabolic syndrome often develop without significant liver fibrosis: A pathological analysis. Hepatology. 2009;49(3):851–9.

18. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med. 2010;363(14):1341–50.

19. Martin P, DiMartini A, Feng S, Brown R, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Hepatology 2014;59(3):1144–65.

20. Kardashian AA, Dodge JL, Roberts J, Brandman D. Weighing the risks: Morbid obesity and diabetes are associated with increased risk of death on the liver transplant waiting list. Liver Int. 2018;38(3):553–63.

21. Kaur N, Emamaullee J, Lian T, Lo M, Ender P, Kahn J, et al. Impact of Morbid Obesity on liver transplant candidacy and outcomes: National and regional trends. Transplantation. 2021;105(5):1052–60.

22. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol. 2016;64(2):433–85.

23. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182–236.

24. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112(17):2735–52.

25. European Association for the Study of the Liver (EASL), European Association

406 for the Study of Diabetes (EASD), European Association for the Study of Obesity
407 (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-
408 alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402.
409 26. Angulo P, Lindor KD. Non-alcoholic fatty liver disease. J Gastroenterol
410 Hepatol. 2002;17 Suppl:S186-190.
411 27. Goossens N, Bellentani S, Cerny A, Dufour J-F, Jornayvaz FR, Mertens J, et
412 al. Nonalcoholic fatty liver disease burden - Switzerland 2018-2030. Swiss Med Wkly.
413 2019;149:w20152.
414 28. Younossi ZM, Stepanova M, Ong J, Trimble G, AlQahtani S, Younossi I, et al.
415 Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver
416 transplantation in the United States. Clin Gastroenterol Hepatol.2021;19:580-89.
417 29. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez
418 M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An
419 international expert consensus statement. J Hepatol. 2020;73(1):202–9.
420 30. Csige I, Ujvárosy D, Szabó Z, Lőrincz I, Paragh G, Harangi M, et al. The impact
421 of obesity on the cardiovascular system. J Diabetes Res. 2018;2018:3407306.
422 31. Lucey MR, Terrault N, Ojo L, Hay JE, Neuberger J, Blumberg E, et al. Long-
423 term management of the successful adult liver transplant: 2012 practice guideline by
424 the American Association for the Study of Liver Diseases and the American Society
425 of Transplantation. Liver Transplant. 2013;19(1):3–26.
426 32. Phelan SM, Burgess DJ, Yeazel MW, Hellerstedt WL, Griffin JM, van Ryn M.
427 Impact of weight bias and stigma on quality of care and outcomes for patients with
428 obesity. Obes Rev. 2015;16(4):319–26.
429 33. Bunchorntavakul C, Reddy KR. Review article: malnutrition/sarcopenia and
430 frailty in patients with cirrhosis. Aliment Pharmacol Ther. 2020;51(1):64–77.

34. Ri M, Aikou S, Seto Y. Obesity as a surgical risk factor. Ann Gastroenterol Surg. 2018;2(1):13–21.

35. Haldar D, Kern B, Hodson J, Armstrong MJ, Adam R, Berlakovich G, et al. Outcomes of liver transplantation for non-alcoholic steatohepatitis: A European Liver Transplant Registry study. J Hepatol. 2019;71(2):313–22.

36. Swisstransplant - Annual figures [Internet]. Available from: https://www.swisstransplant.org/en

37. Lassailly G, Caiazzo R, Buob D, Pigeyre M, Verkindt H, Labreuche J, et al. Bariatric surgery reduces features of nonalcoholic steatohepatitis in morbidly obese patients. Gastroenterology. 2015;149(2):379-388-16.

38. Lassailly G, Caiazzo R, Ntandja-Wandji L-C, Gnemmi V, Baud G, Verkindt H, et al. Bariatric surgery provides long-term resolution of nonalcoholic steatohepatitis and Regression of Fibrosis. Gastroenterology. 2020;159(4):1290–1301.e5.

39. Diwan TS, Rice TC, Heimbach JK, Schauer DP. Liver transplantation and bariatric surgery: Timing and outcomes. Liver Transplant. 2018;24(9):1280–7.

FIGURE LEGENDS

Figure 1. Patient flow chart

Illustration of the patient's medical course from initial assessment to LT. Reasons for exclusion as well as drop-out preceding listing and LT, are detailed. LT, Liver transplantation; ALF, acute liver failure; FU, follow-up.

Figure 2. Aetiology of liver disease among patients evaluated for liver transplantation between January 2009 and March 2020.

Frequency of liver disease causes (y axis, %) among patients evaluated for LT is represented by continuous lines over time. Number of patients (x axis, n) evaluated for LT for each period of time is represented by columns. Frequencies of liver disease etiology were compared within 5 periods of time using the Chi-square test (p= 0.0006). ALD, alcoholic liver disease; NAFLD, nonalcoholic fatty liver disease.

Figure 3. Evolution of BMI distribution over time in patients evaluated for liver transplantation.

Distribution of body mass index (BMI) classes among patients evaluated for LT (y axis) is represented by histograms over the 5 periods of time (x axis). Grade I obesity (BMI ≥ 30 kg/m^2), grade II (BMI ≥ 35 kg/m^2) and grade III (BMI ≥ 40 kg/m^2). Frequencies of BMI classes were compared within 5 periods of time using the chi-square test (p=0.4). (*,**),two BMI values were missing. BMI, body mass index.

Figure 4. Evolution of T2DM prevalence over time

Frequency of T2DM among patients evaluated for LT (y axis) over time (x axis) is represented by columns and was compared using the Chi-square tests (p=0.02).

Figure 5. Drop-out curves for obese and non-obese patients over time

Drop-out free rate (y axis) was compared over time (x axis) between obese and non-obese patients using the log-rank test and did not statistically differ when comparing the two groups (p=0.9). Results are represented by a Kaplan-Meier curve. Drop-out includes delisted patients or death while on waiting list.

Figure 6. Causes of chronic liver disease among patients with hepatocellular carcinoma (HCC)

Proportion of chronic liver disease aetiologies among patients with HCC evaluated for LT (y axis, %) is represented by columns over 5 periods of time (x axis, year). Distribution of different aetiologies significantly varied over time (p=0.03).

TABLES

Table 1. Demographic and clinical characteristics of patients at liver transplantation assessment

	n=242
Male, n (%)	201 (83)
Female, n (%)	41 (17)
Age (years), median (IQR)	59 (51- 64)
Caucasian, n (%)	215 (89)
African, n (%)	15 (6)
Asian, n (%)	8 (3)
Hispanic, n (%)	4 (2)
Etiology of chronic liver disease	
Viral hepatitis, n (%)	67 (28)
ALD, n (%)	52 (21)
NAFLD	30 (12)
Mixed etiologies with NAFLD component, n (%)	23 (10)
Mixed etiologies without a NAFLD component, n (%)	29 (12)
Others, n (%)	41 (17)
BMI (kg/m^2), median (IQR)	26 (24-31)
Obesity	
Obesity grade I, n (%)	49 (20)
Obesity grade II, n (%)	15 (6)
Obesity grade III, n (%)	4 (2)
Total, n (%)	68 (28)
Cardiovascular risk factors	
T2DM, n (%)	82 (34)
Arterial hypertension, n (%)	91 (38)
Dyslipidemia, n (%)	42 (18)
Metabolic syndrome, n (%)	40 (17)
Child-Pugh score in cirrhotic patients (n=236)	
A, n (%)	197 (84)
B, n (%)	29 (12)
C, n (%)	10 (4)
Hepatocellular carcinoma, n (%)	115 (48)
HCC as indication to LT, n (%)	111 (46)

Laboratory parameters, median (IQR)	
Total bilirubin (µmol/l)	27 (2-703)
Albumin (g/l)	36 (21-51)
Creatinine (µmol/l)	78 (40-464)
Prothrombin time (%)	65 (11-120)
INR	1 (1-3)
MELD score, median (IQR)	12 (6-40)
MELD-Na score, median (IQR)	14 (6-62)

Obesity grades and the metabolic syndrome are defined according to WHO definitions (40)(9).

ALD, alcoholic liver disease; BMI, body mass index; HCC, hepatocellular carcinoma; INR, international normalized ratio; IQR, interquartile range; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus

Table 2. Follow-up of patients after first assessment for LT.

	n=242
Follow-up (days), median (IQR)	689 (238-1656)
Time from assessment to listing (days), median (IQR)	59 (31-93)
Time from listing to LT (days), median (IQR)	362 (194-454)
Patients still on the waiting list, n (%)	48 (20)
Patients transplanted, n (%)	112 (46)
Patients dropped out from the transplant program, n (%)	82 (34)
Drop-out before listing, n (%)	39 (16)
Drop-out while on waiting list, n (%)	43 (18)
Reason for drop-out while on waiting list	
Death, n (%)	23(53)
HCC progression, n (%)	9 (21)
Other malignancy[#], n (%)	3 (7)
Comorbidities[§], n (%)	4 (9)
Other, n (%)	4 (9)

HCC, hepatocellular carcinoma; IQR, interquartile range

[#]Colorectal cancer, urothelial carcinoma and pulmonary adenocarcinoma.

[§]Advanced pulmonary sarcoidosis, severe emphysema and severe pulmonary arterial hypertension.

Supplementary Table 1. Univariate analysis of variables associated with non listing

	Univariate analysis		
Covariant	OR	95% CI	p value
Male Gender	0.92	0.66 - 1.76	0.52
Age	0.99	0.96 - 1.03	0.81
BMI	1.01	0.95-1.09	0.63
Obesity	1.58	0.66-3.65	0.26
T2DM	0.75	0.49-2.12	0.95
Arterial hypertension	1.90	0.89-4.21	0.12
Metabolic syndrome	1.38	0.50-3.99	0.52
Etiology of chronic liver disease			
Viral hepatitis	1.15	0.92-1.43	0.21
ALD	0.84	0.60-1.18	0.32
NAFLD and mixed etiologies with NAFLD	1.21	0.88-1.53	0.44
Mixed etiologies without a NAFLD component	1.15	0.84-1.32	0.30
Other	1.45	0.43-2.99	0.59
HCC as indication to LT	1.36	0.67 – 3.74	0.38
Child-Pugh score	1.14	0.95-1.36	0.15
MELD score	1.04	0.98 – 1.10	0.12
Periods of times			
2009-2011	1.01	0.36-2.77	0.98
2012-2013	1.90	0.38-9.44	0.42
2014-2015	1.17	0.31-4.42	0.81
2016-2017	2.66	0.54-13.0	0.22
2018-2020	0.56	0.18-1.87	0.36

ALD, alcoholic liver disease; BMI, body mass index; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; T2DM, diabetes mellitus

Supplementary Table 2. Univariate and multivariate analysis of variables associated with drop-out after placement on waiting list

Covariant	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	OR	95% CI	p value
Male Gender	1.31	0.58- 2.94	0.51			
Age	1.02	0.98 -1.05	0.19			
BMI	1.01	0.79-1.02	0.56			
Obesity	0.77	0.36-1.64	0.50	0.82	0.36-1.67	0.58
T2DM	1.32	0.67-2.57	0.41			
Hypertension	0.84	0.43-1.66	0.62			
Metabolic syndrome	1.26	0.55-2.88	0.58			
Etiology of chronic liver disease						
Viral hepatitis	0.67	0.32-1.40	0.29			
ALD	2.01	0.76-5.34	0.15			
NAFLD and mixed etiologies with	1.49	0.52-4.28	0.45			
NAFLD	2.07	0.73-5.92	0.17			
Mixed etiologies without NAFLD	0.27	0.03-2.41	0.25			
Other						
HCC as indication	1.06	0.55 2.04	0.88			
Child-Pugh score	1.07	0.97-1.24	0.30			
MELD score	**1.03**	**0.99-1.09**	**0.09**	1.04	0.99-1.09	0.10
Periods of time						
2009-2011	0.37	0.09-1.54	0.17	0.34	0.12-1.69	0.12
2012-2013	3.09	0.58-16.42	0.18	1.7	0.31-9.9	0.53
2014-2015	**4.92**	**0.98-23.60**	**0.06**	3.80	0.754-19.18	0.12
2016-2017	3.72	0.75-18.37	0.11	2.77	0.54-14.27	0.22
2018-2020	1.47	0.30-7.21	0.63	1.18	0.22-6.14	0.84

ALD, alcoholic liver disease; BMI, body mass index; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; T2DM, diabetes mellitus

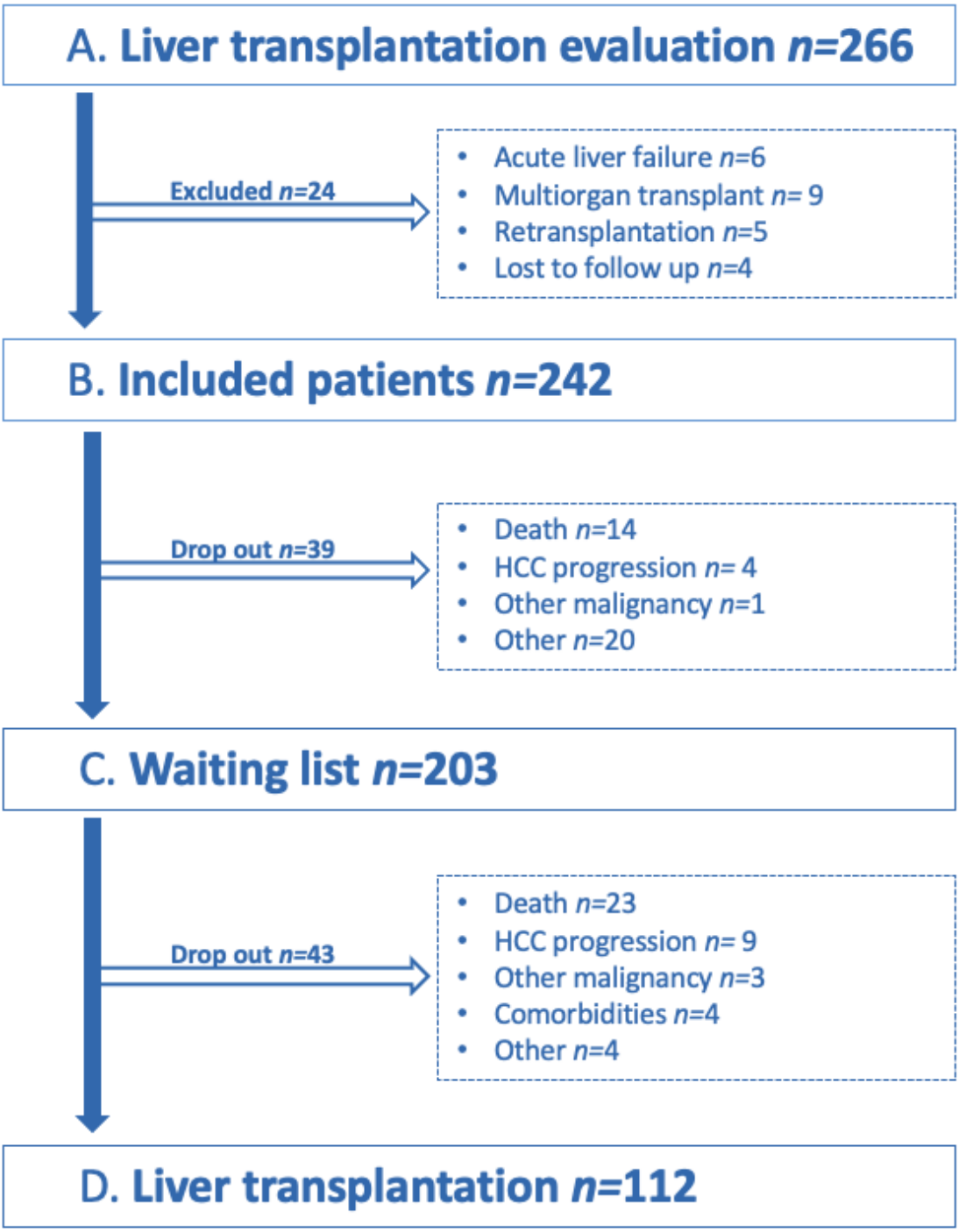

Figure 1. Patient flow chart

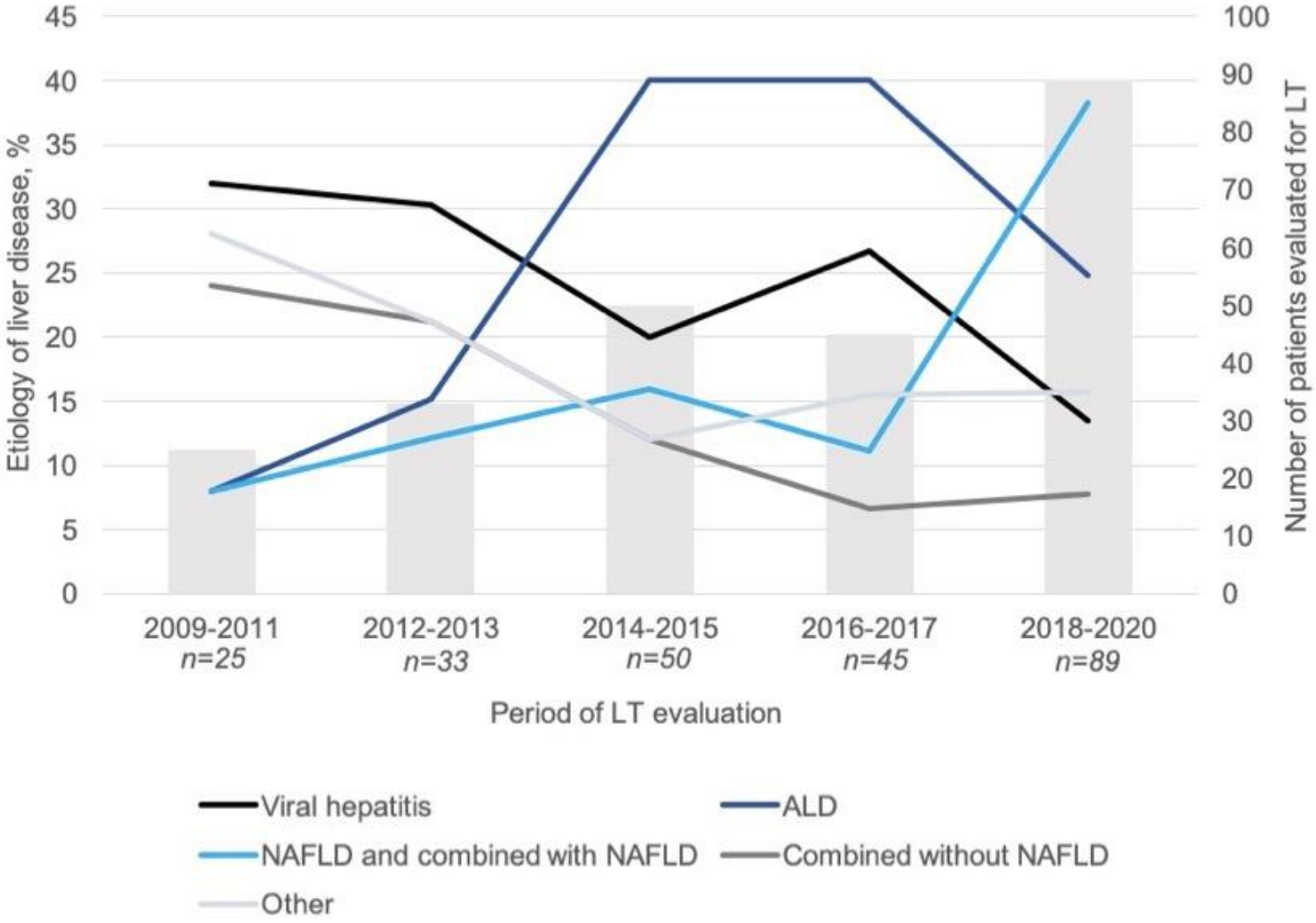

Figure 2. Aetiology of liver disease among patients evaluated for liver transplantation between January 2009 and March 2020.

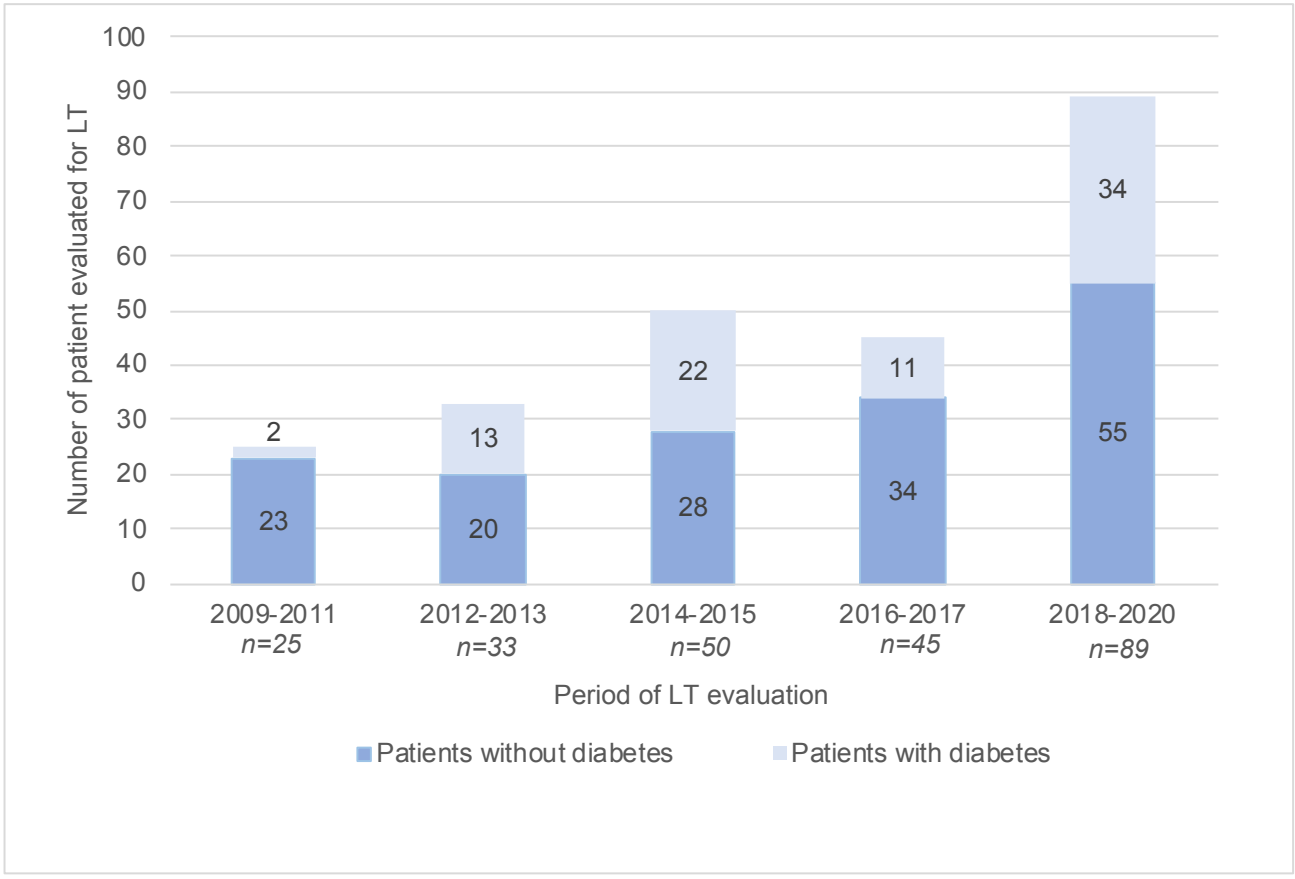

Figure 3. Evolution of BMI distribution over time in patients evaluated for liver transplantation.

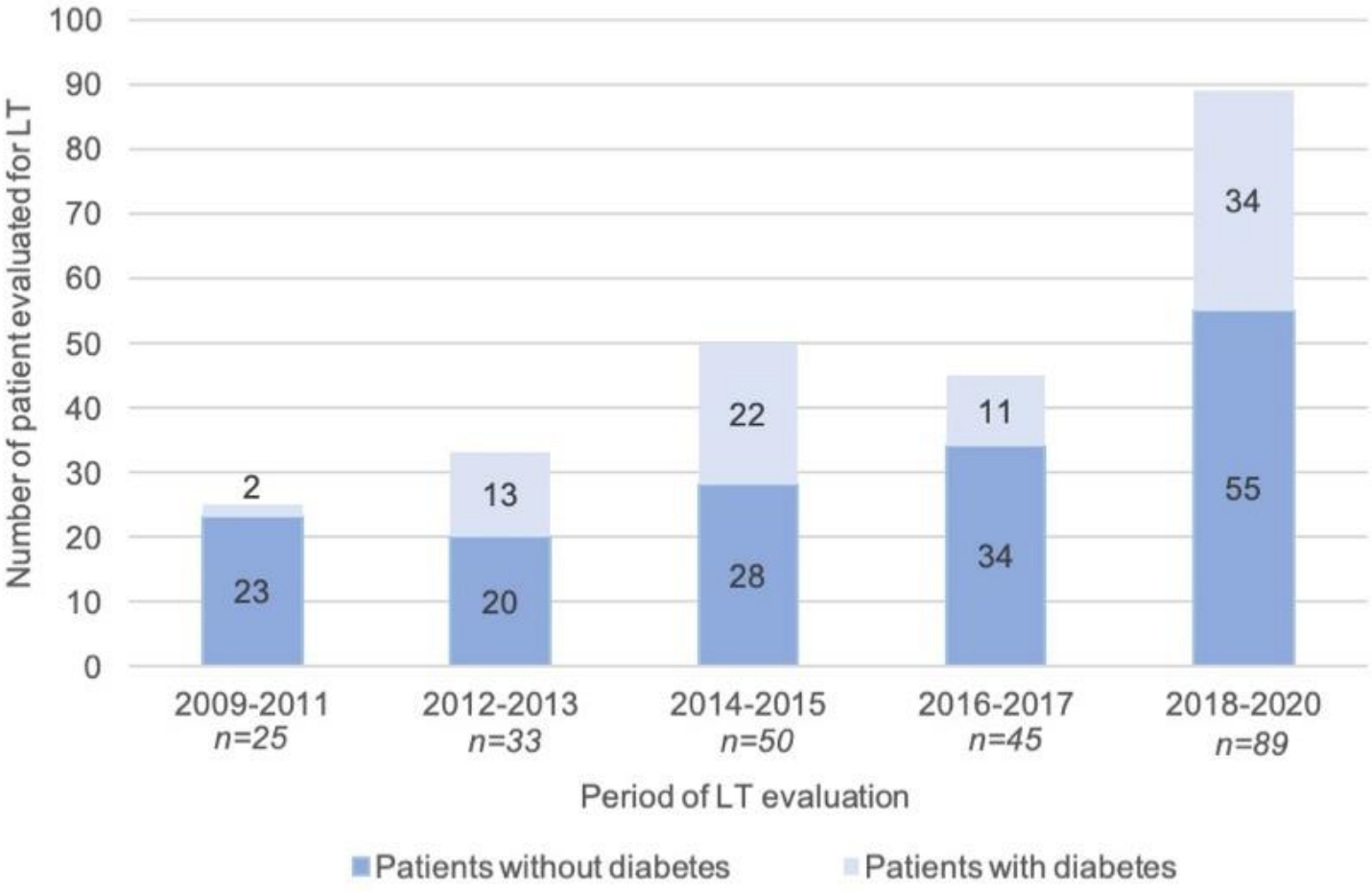

Figure 4. Evolution of T2DM prevalence over time

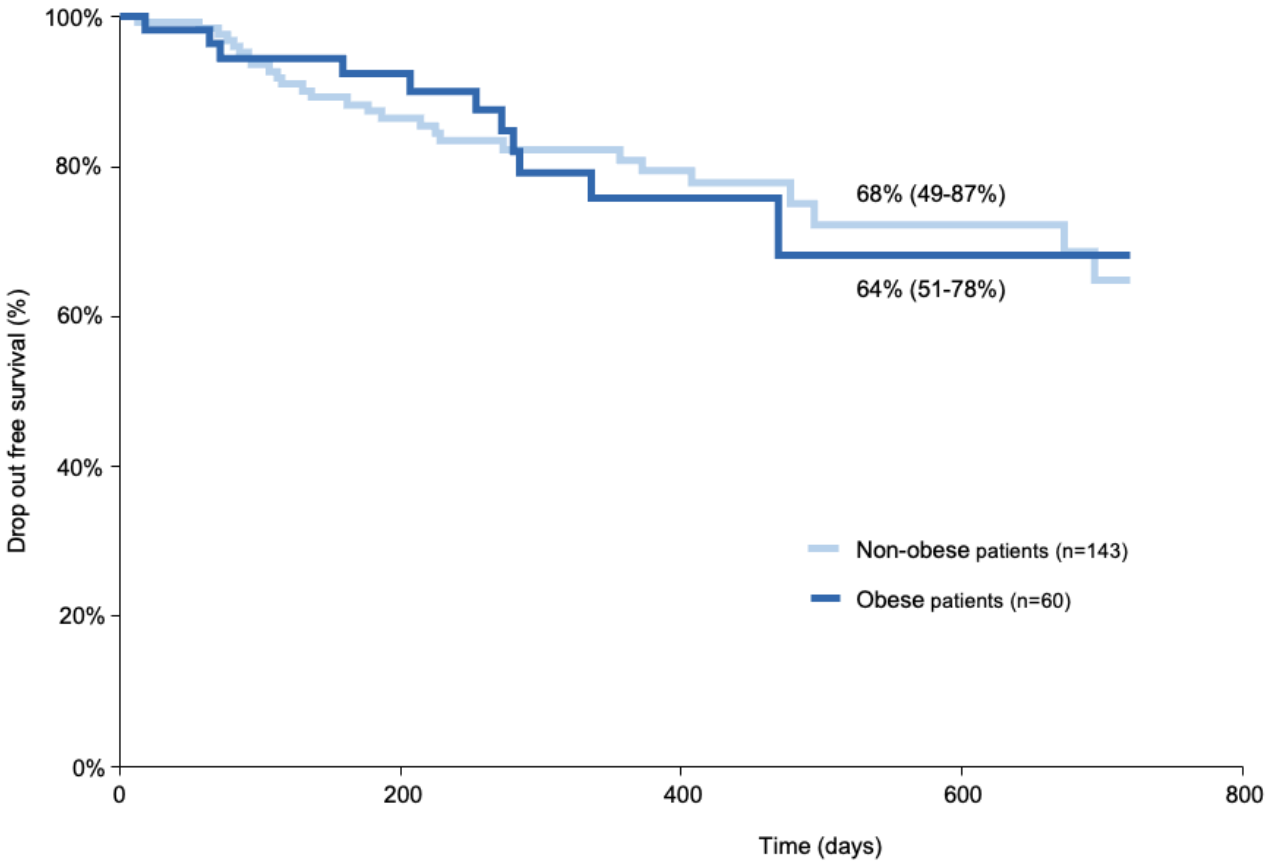

Figure 5. Drop-out curves for obese and non-obese patients over time

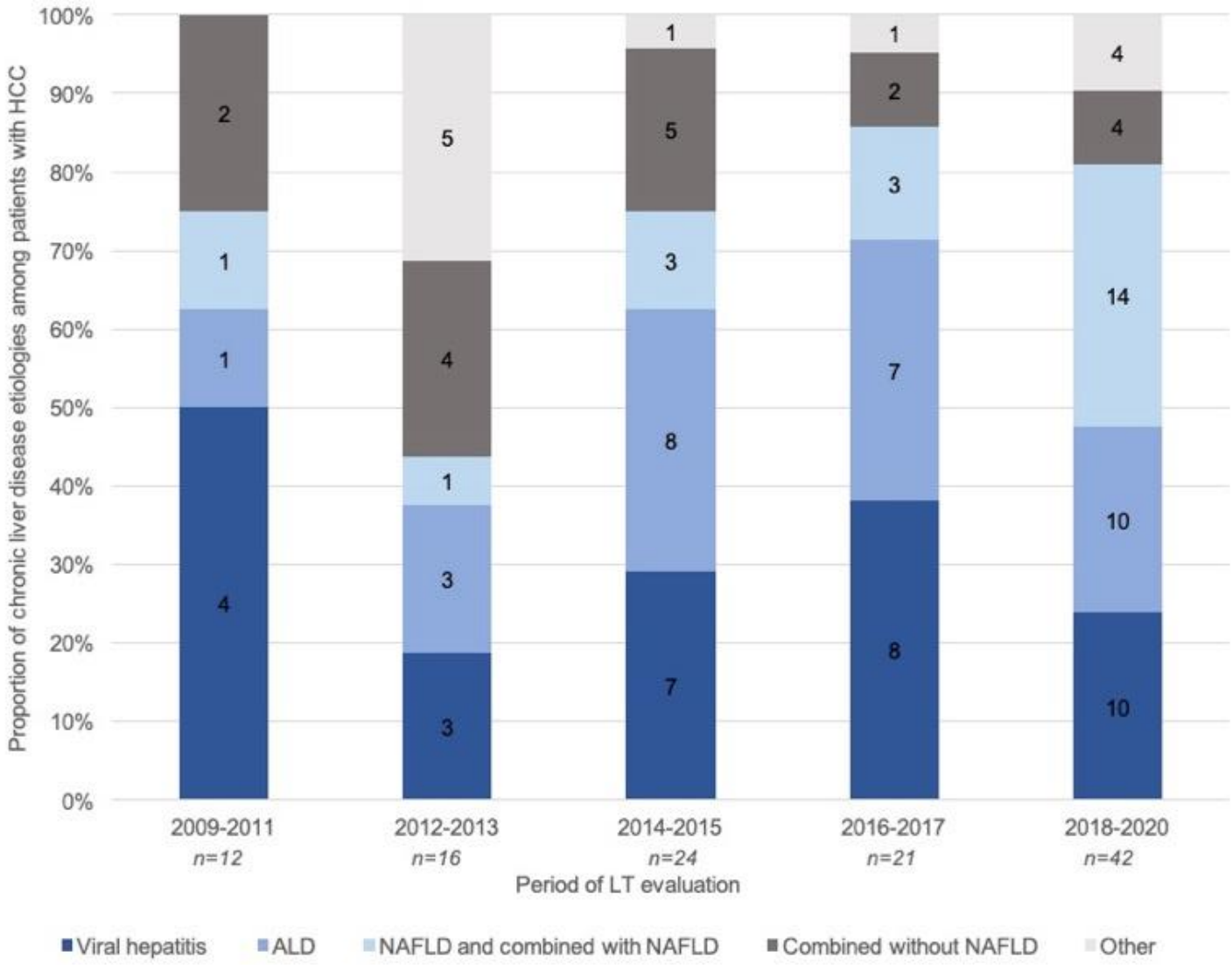

Figure 6. Causes of chronic liver disease among patients with hepatocellular carcinoma (HCC)

Sophie Kasmi

03.08.1994, Lausanne (VD)
Originaire de Lausanne (VD)
sophie.kasmi@ehc.vd.ch ; 078/712.39.51

Formation

2020-*2022*	**Médecin assistante** – Médecine interne (Hôpital de Morges)
	- Tournus : Etage, Urgences, SMUR, CTR
2019-2020	**Médecin assistante** – Chirurgie générale (Hôpital de Morges)
2019	**Diplôme Fédéral** de Médecine Humaine (UNIL)
2013-2019	**Master en Médecine Humaine** – Ecole de Médecine (UNIL)

Recherches

2019- *(en cours)*	**Doctorat** en gastroentérologie (CHUV)
2020 - *(en cours)*	Arsenic and gastrointestinal cancer: a systematic review
	Supervision : Prof. P. Bofetta, Dr I. Labgaa
2018-2019	Travail de Master - Chirurgie générale (CHUV)

Compétences

2021	Congrès **SGG/SSG** (Interlaken) – Présentation orale
	Increasing prevalence of obesity among patients evaluated for liver transplantation in a Swiss tertiary center : a 10 year restrospective analysis
2019	Congrès **SGC/SSC** – Présentation orale
	Does the fluctuation in paramedical personal influence the morbidity of patients?
2021	Advanced Cardiovascular Life Support (**ACLS**)
2021- *(en cours)*	Point of Care Ultrasonography (**POCUS**)

Intérêts

Littérature française	**Prix littéraire** Françoise Conod (2013) et publication littéraire (2013)
	« Un des thèmes les plus riches de l'existentialisme est certainement la critique de l'aliénation, ou la personne se vide ou s'étourdit dans un milieu extérieur, se fait chose et ne se renonce comme personne » - Commentaire philosophique
Enseignement	**Enseignante** à l'Ecole de Médecine Complémentaire Veillon, Lausanne (2020)
	Tutrice en anatomie pour les BMed2 et BMed3 (2015-2017) et en histologie pour les BMed1 (2016) - UNIL
Sports	

Lausanne, le 12 janvier 2022

Centre hospitalier
universitaire vaudois

Service de gastro-entérologie et d'hépatologie

Dre Montserrat Fraga Christinet
Médecin adjoint, MER-clin.

Tél.: 021 314 44 51
Fax : 021 314 47 18

www.gastro-hepato.ch

Professeur
John Prior, PhD MD
Vice Directeur de l'Ecole Doctorale
Faculté de Biologie et Médecine
Université de Lausanne
Amphipôle – Bureau # 324
Quartier UNIL - Sorge
CH-1015 Lausanne

Lausanne, le 01.01.2022

Concerne : Soutien de la candidature de Mme Sophie Kasmi au titre de MD

Cher Professeur,

J'ai le privilège de soutenir la candidature de Madame Sophie Kasmi pour un titre de MD pour son travail intitulé :

« Increasing prevalence of obesity among patients evaluated for liver transplantation: a 10-year retrospective analysis »

Madame Sophie Kasmi est une jeune collègue talentueuse avec un fort intérêt dans les maladies hépatiques.

Elle a effectué ses études de médecine à l'Université de Lausanne et obtenu son titre de médecin en septembre 2019. Elle poursuit actuellement sa formation clinique post-grade en médecine interne générale depuis novembre 2019, à l'hôpital de Morges.

Après une formation approfondie en Médecine Interne générale, Madame Sophie Kasmi rejoindra le Service de Gastroentérologie et Hépatologie pour une formation en gastroentérologie et hépatologie.

Madame Sophie Kasmi a effectué son travail de thèse MD sous ma supervision. Ce travail s'est concentré sur l'évolution de la prévalence de l'obésité et du diabète chez les patients évalués pour une transplantation hépatique dans notre Centre.

L'obésité est en passe de devenir la première cause d'hépatopathie chronique ainsi que la première indication à la transplantation hépatique. De plus, la stéatohépatite non alcoolique du foie (NASH), est associée à un risque accru de carcinome hépatocellulaire même en l'absence de cirrhose constituée.

Dans ce contexte, Madame Kasmi a étudié les aspects démographiques et cliniques de 242 patients consécutifs, évalués dans notre Service, conjointement avec le centre de Transplantation d'Organes entre 2009 et 2020, pour une transplantation hépatique.

A l'occasion de ce travail, elle a élaboré le protocole de recherche de son projet qui a été validé par la CER-VD. Elle a ensuite effectué de manière autonome la récolte rétrospective des données et mis sur pied une base de données, incluant une caractérisation démographique, clinique, biologique et radiologique des 242 patients inclus dans l'étude. Elle a fait preuve d'une grande autonomie et efficacité dans son travail et rendu des données de qualité pour leur analyse statistique.

Partant de cet important travail, elle a ensuite participé à l'analyse statistique des données et rédigé un article qui était récemment accepté pour publication dans *Swiss Medical Weekly*.

Les conclusions suivantes peuvent être retenues de ce travail de thèse :

- En premier lieu, ce travail de thèse met en lumière l'importante augmentation de l'activité « pré-transplantation hépatique » dans notre Centre sur les 10 dernières années.

- Deuxièmement, le paysage de la transplantation hépatique en Suisse est en train de changer avec une plus forte représentation de la maladie non alcoolique du foie (NAFLD) comme indication à une greffe hépatique. En parallèle, le diabète présente également une prévalence en nette augmentation dans cette population. Le travail de Sophie vient donc confirmer les données américaines et européennes déjà disponibles dans le domaine mais jusqu'à présent non disponibles pour notre pays.

- Dans notre expérience les patients obèses n'avaient pas plus de drop-out lorsqu'ils étaient inscrits en liste d'attente pour une transplantation hépatique vis-à-vis des patients non obèses. Ceci devrait donc encourager nos cliniciens à ne pas fermer la porte à un tel projet aux patients obèses. Il s'agit d'un message important puisque les recommandations européennes et américaines se montrent, à l'heure actuelle, défavorables à un projet de transplantation en cas d'obésité de grade II selon l'OMS.

- Finalement, ce travail démontre que la NAFLD est la première cause de carcinome hépatocellulaire (CHC) chez les patients inscrits en liste d'attente pour un CHC dans notre Centre. L'épidémiologie actuelle de l'obésité et de diabète, laissent suspecter une augmentation marquée des CHC en lien avec la NAFLD également en croissance.

En conclusion, le travail de Sophie met en évidence l'important challenge que pose l'obésité dans la prise en charge médicale des patients évalués pour une greffe hépatique. Elle suggère, face l'épidémiologie actuelle de l'obésité dans notre population, une augmentation des des indications à la transplantation hépatique pour carcinome hépatocellulaire et cirrhose décompensée dans le contexte de la NAFLD.

Son travail a été accueilli très favorablement par le comité scientifique du Congrès Annuel de la Société Suisse de Gastroentérologie et d'Hépatologie qui s'est tenu à Interlaken en Septembre 2021. Il y a fait l'objet d'une présentation orale en date du 10.09.2021.

Concernant les crédits ECTS, ce même travail, a également fait l'objet d'une présentation orale en colloque de formation post-graduée de gastroentérologie dans notre Service.

Sophie est déterminée à poursuivre ses efforts pour une carrière académique, probablement dans le domaine de la Gastroentérologie et de l'Hépatologie. Elle s'est montrée extrêmement réactive, fiable et impliquée dans ce travail de thèse. Je suis personnellement convaincue qu'elle dispose de tous les talents nécessaires pour pouvoir atteindre un tel but.

Ainsi, je soutiens Sophie Kasmi pour l'obtention de son titre MD par la Faculté de Biologie et de Médecine avec grand enthousiasme et sans aucune réserve.

Je vous remercie de bien vouloir me contacter si vous deviez avoir des questions et vous adresse mes cordiales salutations.

Dre Montserrat FRAGA
Médecin adjointe, MER-Clin

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Swiss Confederation

Eidgenössisches Departement des Innern EDI
Département fédéral de l'intérieur DFI
Dipartimento federale dell'interno DFI
Departament federal da l'intern DFI
Federal Department of Home Affairs FDHA

DIPLÔME

Sophie Najat Kasmi

originaire de Lausanne VD

se voit décerner le diplôme fédéral de

MÉDECIN

l'examen fédéral ayant été réussi selon la loi fédérale du 23 juin 2006 sur les professions médicales universitaires.

Berne, le 25 septembre 2019
GLN 7601007850822

Le chef du Département fédéral
de l'intérieur

Le président
de la commission d'examen

UNIL | Université de Lausanne
FBM - Ecole doctorale
bâtiment Amphipôle bureau 304
CH-1015 Lausanne

CHECKLIST POUR PRESENTATION DU TRAVAIL DE THESE MD A LA COMMISSION

Le dépôt de thèse se fait selon les articles 8 et 9 du règlement pour l'obtention du grade de Docteur en médecine.

Nom & Prénom du doctorant / de la doctorante : Kasmi Sophie

Directeur/directrice de thèse : Dre M. Fraga

Inscrit au doctorat en médecine depuis *(Minimum 2 semestres requis)* **:** Novembre 2019

Travail de thèse :

☐ **Manuscrit** (sera transmis à un expert du domaine avant passage en Commission MD)

☒ **Article publié** (merci de bien vouloir cocher toutes les cases concernées)

☒ **1er auteur.e**	☐ **Case-report**
☐ **Co-auteur.e**	☐ **Revue de la littérature**
☒ **Revue avec Impact factor**	☒ **Article Peer-Reviewed**

Les documents suivants doivent être transmis au secrétariat des thèses en médecine :

1	**Un exemplaire du travail de thèse relié par une simple agrafe** - Page de titre (disponible sur notre site rubrique « formulaires ») - Résumé en français (max. 1 page A4) - Article sous le même format que la publication	X
2	**Un Curriculum vitae mis à jour**	X
3	**Une lettre du directeur / de la directrice de thèse** décrivant la participation exacte du doctorant	X
4	**Une copie :** « Diplôme de médecin » **ou** attestation de l'équivalence « MEBEKO »	X
5	**Crédits ECTS** (*pour toute inscription à compter du semestre d'automne 2013,* remplir les documents trouvés sur ce lien : https://www.unil.ch/ecoledoctoralefbm/mdforms) - « Particpation forms » concernées accompagnées des attestations - « portfolio », pages 2 et 3 à remplir et signer avec votre directeur/directrice de thèse	X

Ces documents doivent être envoyés **par voie électronique** 3 **semaines avant la date de Commission, puis par courrier (**aux adresses mail et postale indiquées ci-dessous).

Portfolio
Programme doctoral MD

DIRECTIVES

Le doctorant est tenu de suivre un programme MD à la hauteur de 2 ECTS durant sa thèse.

Les crédits sont obtenus de la manière suivante :

1) En participant à des congrès nationaux ou internationaux et en y soumettant un abstract (1 crédit ECTS par congrès).
2) En présentant le travail de thèse devant un public plus large que son département (1 crédit ECTS).
3) En suivant les séries de séminaires accréditées par l'Ecole doctorale. (Le nombre de crédit dépend du séminaire suivi)
4) En participant aux cours de troisième cycle. (Le nombre de crédit dépend du cours suivi)

Le programme des cours ainsi que toutes les informations utiles sont disponibles à cette adresse : http://www.unil.ch/ecoledoctoralefbm

COMMENT UTILISER LE PORTFOLIO ?

A la fin de chaque activité, veuillez :

- Remplir un formulaire de participation (en annexe ou à télécharger depuis notre site internet : www.unil.ch/ecoledoctoralefbm) et le faire valider par l'organisateur
- Annexer les certificats et descriptifs demandés
- Joindre le tout au portfolio.

A la fin de la thèse, veuillez :

- Compléter les documents « Programme doctoral - Suivi - » et «Programme doctoral – Evaluation - » du portfolio
- Faire signer tous les documents par votre Directeur de thèse
- Transmettre le Portfolio, en annexant toutes les attestations, pour validation, à l'adresse suivante :

Secrétariat Ecole doctorale
Faculté de Biologie et de Médecine
Amphipôle – bureau 304
Quartier UNIL-Sorge
1015 Lausanne

UNIL | Université de Lausanne
Ecole doctorale

Portfolio
Programme doctoral MD – Suivi -

	Titre	Type (Séminaire, cours, congrès, présentation...)	Organisateur	Date/Endroit	Crédit(s)ECTS (Le nombre de crédits sera validé par l'ED)
1	Annual Congress of the Swiss Society of Gastroenterology	Présentation à un congrès national	Société Suisse de gastroentérologie	09.10.2021 Interlaken	1
Prière d'annexer les certificats de participation					
2	Colloque de formation post-graduée de gastroentérologie, CHUV	Présentation	Service de gastroentérologie et hépatologie, CHUV	11.11.2021 Lausanne	1
Prière d'annexer les certificats de participation					
3					
Prière d'annexer les certificats de participation					
4					
Prière d'annexer les certificats de participation					

➔ Vous trouverez les documents de participation sur notre site, à l'adresse suivante : *www.unil.ch/edfbm*

Visa Directeur de thèse		Visa doctorant		Visa Ecole doctorale	
Date		Date 21.12.2021		Date	

CHUV
Dre M. Fraga
Médecin Adjointe, MER clin
GLN 7601000866998
21.12.2021

Portfolio
Programme doctoral MD – Evaluation -

Suite à une discussion avec votre Directeur de thèse, résumez brièvement les connaissances et/ou les compétences acquises au travers des activités suivies :

- Revue de la littérature médicale en vue d'élaborer un protocole de recherche
- Rédaction d'un protocole de recherche clinique
- Création d'une base de données (identification de données d'intérêt, recherche des données, codage des données)
- Participation à l'analyse statistique des données
- Rédaction d'un manuscrit à partir des résultats obtenus
- Soumission d'un manuscrit à un journal peer review (formatage, révision)
- Présentation orale d'un travail de recherche (Congrès Suisse de Gastroentérologie, Interlaken 2021)
- D'une manière plus globale, l'immersion en recherche clinique m'a donné l'envie de poursuivre cette activité dans ma carrière

Visa Directeur de thèse		Visa doctorant Sophie Kasmi
Date 21.12.2021		Date 21.12.2021

CHUV
Dre M. Fraga
Médecin Adjointe, MER clin
GLN 7601000865998

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Doctoral School
MD doctoral program
VALIDATION FORM FOR AN ORAL PRESENTATION TO A PUBLIC LARGER THAT THE DEPARTMENT [ABOUT THE THESIS RESULTS]

Doctoral Student's name	Sophie Kasmi	**Thesis Director's name**	Dr M. Fraga Christinet

Dates	**Place (Town/Country)**	**Title of the presentation**
11.11.2021	Lausanne Suisse	Increasing prevalence of obesity among patients evaluated for liver transplantation : a 10-year retrospective analysis

Attach to this form: **1) a copy of the corresponding flyer (with the title of the congress, dates, place and organizers)**
2) a copy of the scientific programme
3) a copy of your abstract as first author
4) a copy of the certificate of participation, if provided by the organizers

	Visa Organizer or copy of the certificate
Signature	CHUV Dre M. Fraga Médecin Adjointe, MER clin GLN 7601000[illegible]998
Date	21.12.2021

Please, enclose these documents to the portfolio you received by mail.
When submitting your thesis, you will send the completed portfolio to the MD secretary's office

Please, check our Rules and Guidelines: http://www.unil.ch/ecoledoctoralefbm

Breakfast meetings 2ème semestre 2021 I CHUV I Salle BH10-301 et Webex | Jeudi de 8h00 à 9h00

REJOINDRE LA RÉUNION

Date		Sujet	Orateur | Superviseur/Hôte	Sponsor
AOUT	26	Activités du Service et JC	Pr D. Moradpour I Dre T. Shams	
SEPTEMBRE	2	CDC : Transplantation du microbiote fécal	Dre S. Henchoz (avec Dre T. Galperine, MIN)	
	16	ECCO Highlights	Drs S. Henchoz et T. Greuter, Pr A. Schoepfer	
	23	Research update	Dr J. Vlonnet	
	30	CDC : Hépatite alcoolique	Dr G.-M. Stamm | Dre J. Wakim	
OCT.	7	Etudes cliniques en cours en GLG	Tous les investigateurs	
	14	Colloque morbidité et mortalité	Coordonné par le Dr Ph. Maerten	N/A
NOVEMBRE	4	Présentations travaux de Master	A. Coukos (Dre M. Fraga), M.-L. Goertler et A. Pick (Pr Alain Schoepfer)	
	11	Présentations de thèses MD et PhD	Dre S. Henchoz (Pr A. Schoepfer) Dre S. Kasmi (Dre M. Fraga) Dre N. Oechslin (PD Dr J. Gouttenoire) Dre L. Vaillant (PD Dr D. Velin)	
	18	CDC : POEM et G-POEM	Dre T. Shams | Dr M. Robert	
	25	CDC : Cholangiocarcinome	Dre E. Romailler | Dre S. Oumrani	
DÉCEMBRE	2	TBA	Pr M. Pittet, Université de Genève | invité par Dre M. Fraga et Pr Ch. Sempoux, IPA	
	9	Controverse : Drainage percutané vs. endoscopique de la vésicule biliaire	Pr A. Denys, RAD et Dr S. Godat	
	16	CDC : Hépatite B	Dre J. Vieira Barbosa | Dre M. Fraga	
	23	TBA	TBA	

CDC = Cahier des charges attitudes thérapeutiques I JC = Journal club

En rouge = rocades/modifications par rapport la précédente version

Pour tout souhait de rocade ou autre modification, veuillez en informer malika.salhi@chuv.ch

D. Moradpour

Pr Darius Moradpour

1330-1500 *Kongresssaal*	**Hepatology Oral presentations I** Andrea De Gottardi, Lugano Darius Moradpour, Lausanne
1330-1340 *Kongresssaal*	A preclinical screening platform of patient-derived tumor organoids for drug discovery in hepatocellular carcinoma. Sandro Nuciforo, Basel
1340-1350 *Kongresssaal*	Suppression of tumorigenicity 2 (ST2) serum level for the assessment of liver fibrosis Sena Blümel, Zürich
1350-1400 *Kongresssaal*	Development of a microscopy readout to characterise drug response in hepatocellular carcinoma organoids. Lauriane Blukacz, Basel
1400-1410 *Kongresssaal*	Next-Generation Sequencing of Swiss Hepatitis E Virus Isolates Allows for Reconstitution of Functional Clones Jérôme Gouttenoire, Lausanne
1410-1420 *Kongresssaal*	Heterogeneity of Peripheral Monocytes in Patients with Cirrhosis Anne Geng, Basel
1430-1440 *Kongresssaal*	Increasing prevalence of obesity among patients evaluated for liver transplantation in a Swiss tertiary referral center: a 10-year retrospective analysis Sophie Kasmi, Lausanne
1440-1450 *Kongresssaal*	Increased serum levels of gut-derived MAIT cell stimulatory bacterial metabolites in patients with portal hypertension

ORAL PRESENTATIONS: HEPATOLOGY I

A preclinical screening platform of patient-derived tumor organoids for drug discovery in hepatocellular carcinoma.

Sandro Nuciforo[1], Lauriane Blukacz[1], Matthias S. Matter[2], Savas D. Soysal[3], Otto Kollmar[3], Stefan Wieland[1], Markus H. Heim[1,3]

1 Department of Biomedicine, Hepatology Laboratory, University Hospital and Univer- sity of Basel, Basel, Switzerland; 2 Institute of Medical Genetics and Pathology, University Hospital and University of Basel, Basel, Switzerland; 3 Clarunis University Center for Gastrointestinal and Liver Diseases, Basel, Switzerland

Background: Hepatocellular carcinoma (HCC) is an aggressive cancer and a major cause of cancer-related deaths worldwide. Most HCCs are diagnosed at an advanced stage with limited treatment options and poor prognosis. The efficacy of currently available therapies differs greatly between patients, primarily due to pronounced inter- and intratumoral heterogeneity and the lack of biomarkers that predict treatment response. Classic cell culture assays fail in adequately representing patient's tumor biology and physiological conditions. Tumor organoids have recently emerged as a novel preclinical 3D *in vitro* system that recapitulates the diversity and complexity of tumors observed in patients. We established a robust screening platform based on patient-derived HCC organoids with the aim to identify novel compounds for the treatment of HCC.

Methods: A comprehensive biobank of HCC organoids was generated from HCC tissues obtained by needle biopsy and surgical resection. Semi-automated drug screening was performed in a 384-well plate format. Plates were coated with a hydrogel layer and cells were seeded on top to allow for organoid formation. A library of 2889 FDA-approved-, investigational, and previously untested small-molecule compounds was screened on our HCC organoid biobank and hits were selected based on their activity profile.

Results: We report the identification of multiple compounds with strong activity against HCC cells using an organoid-based drug screening platform. Drug activity differed strongly between HCC organoid lines with compounds being highly active in all, only some, or individual lines, reflecting the heterogenous drug response observed in patients.

Conclusions: Tumor organoids can be used to screen drugs with throughputs comparable to standard screening platforms but with the ad- vantage of identifying hits based on physiologically relevant drug responses. Remarkably, the majority of hits resulting from the FDA library screen belong to drugs approved for indications other than cancer and thus open up new perspectives for drug repurposing.

Suppression of tumorigenicity 2 (ST2) serum level for the assessment of liver fibrosis

Florian Hildenbrand[1], Barbara Illi[1], Ansgar Deibel[1], Joanna Gawinecka[2], Arnold von Eckardstein[2], Beat Müllhaupt[1], Joachim C. Mertens[1], Sena Blümel[1]

1 Department of Gastroenterology and Hepatology, USZ; 2 Institute of Clinical Chemistry, USZ

Background: Liver fibrosis and cirrhosis are related to increased morbidity and mortality. Today's gold standard for assessing liver fibrosis remains liver biopsy. Alternatively, transient elastography (TE) and scores like the FIB4 and APRI can be used to estimate the fibrosis stage. The former is, however, available only through specialists and the latter require several serum parameters. Single serum biomarker for the assessment of liver fibrosis could facilitate outpatient care of patients suspected to suffer from advanced liver disease through general practitioners. A potential marker is soluble ST2 (sST2), which is related to hepatic stellate cell activation. We aimed to assess sST2 as a marker for liver fibrosis using patients treated for chronic hepatitis C.

Methods: Patients from the Swiss hepatitis C cohort study received treatment with direct-acting antivirals. sST2 was measured in plasma samples before and after therapy and correlated with reported values of TE, APRI and FIB-4.

Results: Overall, 176 patients were included with 126 having complete data sets pre- and post-treatment for compared data analyses. The median level of sST2 before treatment was 33.5 ng/ml and 28.4 ng/ml after treatment (P <0.0001). A positive linear correlation between sST2 and values for TE, APRI as well as FIB-4 was present with R^2 being in the range of 0.11 to 0.22. R^2 was highest for the correlation of sST2 with TE values and correlation generally improved after treatment.

Conclusion: In summary, the results of the study indicate that sST2 might be a suitable marker to assess liver fibrosis.

Development of a microscopy readout to characterize drug response in hepatocellular carcinoma organoids.

Lauriane Blukacz[1], Sandro Nuciforo[1], Matthias S. Matter[2], Savas D. Soysal[3], Otto Kollmar[3], Stefan Wieland[1], Markus H. Heim[1,3]

1 Department of Biomedicine, Hepatology Laboratory, University Hospital and University of Basel, Basel, Switzerland; 2 Institute of Pathology, University Hospital Basel, University of Basel, Basel, Switzerland; 3 Clarunis University Center for Gastrointestinal and Liver Diseases, Basel, Switzerland.

Background: Hepatocellular carcinoma (HCC) is one of the most common causes of cancer-related deaths worldwide. Treatment options are limited for patients with advanced stage HCC and drug resistance is frequent. Current methods to assess drug sensitivity in vitro mainly rely on metabolic-based viability readouts. These readouts provide a very rapid and sensitive estimation of drug responses. But, they do not provide information at the cellular level such as whether a drug acts cytostatically or is cytotoxic. However, such information could likely be very valuable in guiding pre-clinical development of candidate drugs derived from large drug screens. Moreover, metabolic activity of cancer cells can change greatly depending on the culture conditions (e.g. normoxia or hypoxia). This can complicate interpretation of assays where drug sensitivity under different culture conditions is compared. Therefore, we developed a metabolic-independent microscopy approach to detect dead and live cells to assess drug sensitivity at the cellular level.

Methods: Patient-derived HCC organoids were cultured on a hydrogel layer in 384-well plates. The Live-or-Dye NucFix staining kit (Biotium) was implemented as a dead-cell marker together with Hoechst as a counterstain for all nuclei. Samples were fixed and image acquisition automated on a spinning disk confocal microscope. An analysis pipeline to assess number of living cells and the fraction of dead cells was developed using the QuPath software.

Results: We report the development of a metabolic-independent microscopy-based readout to assess drug sensitivity at the cellular level in HCC organoids. Our analysis pipeline produces reliable numbers for living cells and the fraction of dead cells, allowing for unbiased comparison of drug sensitivity between HCC organoid lines or culture conditions. Based on these parameters, we can also determine cytotoxic or cytostatic effects of a drug.

Conclusions: We believe that the microscopy-based readout for drug sensitivity will proof very useful for in depth drug response analysis and thus benefit the translation of in vitro results into clinical application.

Next-Generation Sequencing of Swiss Hepatitis E Virus Isolates Allows for Reconstitution of Functional Clones

Jérôme Gouttenoire[1], Roland Sahli[2], Daniela Müllhaupt[1], Montserrat Fraga[1] and Darius Moradpour[1]

1 Service of Gastroenterology and Hepatology , 2 Institute of Microbiology, Lausanne University Hospital (CHUV) and University of Lausanne, Switzerland

Background: Hepatitis E acquired in Switzerland is caused primarily by a specific hepatitis E virus (HEV) subtype which has been provisionally designated as 3s and recently assigned as a distinct group to 3h (3s[p]/h). Here, we analyzed HEV from patients with severe outcomes of hepatitis E by a newly developed next-generation sequencing (NGS) protocol and assembled subgenomic replicons as well as full-length clones.

Methods: Illumina RNA sequencing coupled with HEV-specific sequence enrichment was carried out on 24 plasma samples from patients with hepatitis E acquired in Switzerland and severe outcomes (severe acute hepatitis, acute-on-chronic liver failure and neurologic complications). Viral genomes reconstituted by DNA synthesis and molecular cloning were functionally characterized in cell culture.

Results: The entire HEV genomes from plasma of 24 patients could be sequenced successfully, confirming the predominance of subtype 3s(p)/h in Switzerland. The number of reads at each nucleotide position and overall coverage allowed to establish a consensus sequence for 17 genomes. Subgenomic replicons and full-length genomes derived from some of these replicated in cell culture. Functional clones are currently being further characterized, in particular for their ability to produce infectious virus.

Conclusions: A newly developed NGS protocol and DNA synthesis allowed to successfully reconstitute functional clones of Swiss HEV isolates. These represent a rare resource and should facilitate further studies on the molecular virology and pathogenesis of hepatitis E.

Heterogeneity of Peripheral Monocytes in Patients with Cirrhosis

Anne Geng[1], Robert Brenig[1,2], Mechthild Lütge[3], Julien Roux[4], Hung-Wei Cheng[3], Oltin Pop[2,3], Patrizia Künzler-Heule[2], David Semela[2], Markus H. Heim[1], Burkhard Ludewig[3], Christine Bernsmeier[1]

1 Department of Biomedicine, University of Basel and Clarunis, University Center for Gastrointestinal and Liver Disease, Basel; 2 Liver Biology Laboratory, Division of Gastroenterology and Hepatology, Cantonal Hospital St. Gallen; 3 Institute of Immunobiology, Cantonal Hospital St. Gallen; 4 Bioinformatics Core Facility, Department of Biomedicine, University of Basel

Background: In patients with cirrhosis, we recently discovered dysfunctional monocytic subsets (CD14+HLA-DR+AXL+, CD14+MERTK+, M-MDSC) prevail over regular monocytes, associated with reduced capacity to repel microbial challenge and infection susceptibility. The underlying signaling mechanisms remain unexplored. Transcriptome wide single cell RNA sequencing (scRNA Seq) is expected to enhance the understanding of immune cell differentiation processes.

Methods: Monocytes (20,000 cells/sample) from compensated (CC n = 4), decompensated (DC n = 4) cirrhosis patients and healthy controls (HC n = 4) were prepared for scRNA Seq (10x Technology) and analysed (>4000 cells/sample) using R/Bioconductor.

Results: Our preliminary scRNA Seq data revealed 6 distinct monocyte clusters. 4 clusters represent classical ($CD14^{++}CD16^{-}$) monocytes, 2 representing intermediate ($CD14^{++}CD16^{+}$) and non-classical ($CD14^{+}CD16^{++}$) subsets. The cluster frequency of $CD14^{+}CD16^{++}$-like monocytes was reduced in CC/DC while M- MDSC-like were increased compared to HC. Differentially expressed (DE) gene analysis revealed increased RNA expression of Cd52 (T-cell suppressor) and Ca^{2+} binding S100 family members on monocytes from CC/DC, while some MHC class II members were decreased. $CD14^{++}CD16$- and $CD14^{++}CD16^{+}$-like clusters showed increased *Commd4* (NF-κ-B downregulation) and decreased Siglec5 (reduced inflammasome activity) in CC/DC. $CD14^{+}CD16^{++}$ subset showed higher levels of *Ppargc1b* in CC/DC. Timd4 (Kupffer Cell marker) was expressed in monocytes from cirrhosis only.

Conclusion: We identified 6 monocyte clusters, their prevalence differed between HC and CC/DC. DE Gene expression revealed abundance of immunemodulatory clusters in CC/DC.

Increasing prevalence of obesity among patients evaluated for liver transplantation in a Swiss tertiary referral center: a 10-year retrospective analysis

Sophie Kasmi[1], Florent Artru[1], Joana Vieira Barbosa[1†], Ansgar Rudolf Deibel[2], Lucie Favre[1], Claire Peuble[1], Anne-Catherine Saouli[1], Nicolas Goosens[3], Beat Müllhaupt[2], Manuel Pascual[1], Darius Moradpour[1], Julien Vionnet[1,4††], Montserrat Fraga[1]

1 Centre Hospitalier Universitaire Vaudois; 2 Universitätsspital Zürich; 3 Hôpital Universitaire Genevois; † Beth Harvard Medical School, Boston; ††King's College Hospital, London

Background and aims: NAFLD is the first cause of chronic liver disease in developed countries. We aimed to assess the trend in the prevalence of obesity, type 2 diabetes and NAFLD in patients undergoing liver transplantation (LT) evaluation and to assess whether obese patients were less likely to be listed or had an increased drop-out rate after listing.

Methods: We conducted a retrospective study of all consecutive patients who underwent a LT evaluation at a Swiss tertiary referring center between 2009 and 2020.

Results: 242 patients were included, 83% were male. The median age was 59 years (IQR, 51-64 years). The most common causes of end-stage liver disease were viral hepatitis (28%), alcoholic liver disease (21%) and NAFLD (17%). Obesity was present in 28% of our cohort, with a significant increase over time. Prevalence of diabetes followed this same trend (p = 0.02). The proportion of non-listed and listed obese patients was not different (21% vs. 30%, respectively; p = 0.3). When analyzing drop-out rates, there was no significant difference between obese and non-obese patients (36% vs. 32%; p = 0.9). HCC represented the primary indication for LT in approximately half of our cohort (46%), with increasing prevalence of NAFLD among patients with HCC (p = 0.03).

Conclusions: The prevalence of obesity and diabetes significantly increased over our study period. Obese patients had similar chances of being enlisted. The landscape of LT indications is shifting towards NAFLD, highlighting the urgent need to prevent NAFLD progression.

Increased serum levels of gut-derived MAIT cell stimulatory bacterial metabolites in patients with portal hypertension

Martin J. Lett[1], Tina Jaeger[1], Maxime Jacquet[1], Emanuel Burri[2], Christoph J. Zech[3], Magdalena Filipowicz Sinnreich[1, 2]

1 Liver Immunology, Department of Biomedicine, University Hospital Basel and University Basel; 2 Gastroenterology and Hepatology, Basel University Medical Clinic, Kantonsspital Baselland; 3 Radiology and Nuclear Medicine, University Hospital Basel

Background: Mucosal-associated invariant T (MAIT) cells represent the most abundant T cell type in human liver. They respond to bacterial metabolites derived from Riboflavin synthesis that are presented by MHC-like molecule MR1. The most potent stimulatory MAIT cell antigen (Ag) is 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU). Recent murine studies showed that microbiota-derived Ag is necessary for intrathymic development of MAIT cells, arguing for 5-OP-RU absorption from the gut. By analyzing sera of patients suffering from portal hypertension we investigated whether gut leakiness in humans may be associated with the presence of bacterial MAIT cell stimulatory Ags in circulation.

Methods: We examined MAIT cell stimulatory potential of peripheral blood serum obtained from 14 patients with a history of transjugular intrahepatic porto-systemic stent shunt (TIPSS), as compared to healthy subjects. Analogously, we analysed paired serum samples from portal and peripheral blood of 8 patients undergoing TIPSS. To detect MAIT cell ligands, Ag-presenting K562 cells overexpressing MR1 were exposed to serum and IFN-gamma release by MAIT cells was measured by ELISA. MR1 blocking antibodies were used to verify the MR1 dependence in MAIT cell activation. Serum Ag amounts were defined using control assays with 5-OP-RU added in the range of 0.006–25 pM.

Results: We found MR1-dependent MAIT cell stimulation by sera obtained from healthy subjects, corresponding to 5-OP-RU concentrations of 0.05–0.2 pM. Patients with a history of TIPSS showed significantly higher MAIT cell stimulatory potential than age- and sex-matched healthy control subjects. Sera from 4 out of 8 patients undergoing TIPSS strongly stimulated MAIT cells (1–2 pM 5-OP-RU equivalent) and portal serum was up to 3-fold more active than its peripheral counterpart.

Conclusions: We present first evidence for the presence of MAIT cell stimulatory gut bacterial metabolites in human blood. Our results provide rationale for the activated MAIT phenotype seen in human liver. Increased levels of gut-derived MAIT cell stimulatory ligands in the blood of TIPSS patients suffering from portal hypertension, associated with impaired intestinal barrier function, indicate that intrahepatic Ag-presentation may represent an important step in the development of liver disease. Measurement of circulating MAIT cell Ag levels could be considered as part of a diagnostic test panel for assessing gut integrity in the context of liver inflammation.

Thursday, 9.9.2021

Kongresssaal

0830–1000 **New Challenges in Hepatology**
Christine Bernsmeier, Basel | Nicolas Goossens, Genève

0830–0845 Neurological manifestations of Hepatitis E
Paolo Ripellino, Lugano

0845–0900 Immune mediated hepatitis: an update
Fraga, Lausanne

0900–0915 Hepatitis C after cure
Francesco Negro, Genève

0915–0930 Alcoholic liver disease – do we care enough?
Katharina Staufer, Wien

0930–0945 Daily aspirin – prevention of fibrosis and HCC
Tuyana Boldanova, Reinach

0945–1000 When to test for genetics in cholestasis?
Christoph Jüngst, Zürich

1000–1030 **Exhibition Area** **Coffee break**

1200–1230 **Exhibition Area** **Lunch break**

1215–1245 **Lunch Symposium Bristol Myers Squibb SA: Will small molecules change therapy in UC?**
Gerhard Rogler, Zürich | Alain Schoepfer, Lausanne
Andreas Sturm, Berlin

1250–1320 **Lunch Symposium Olympus: New features for diagnostic and therapeutic endoscopy**
Stefan Seewald, Zürich

1330–1500 **Hepatology Oral presentations I**
Andrea De Gottardi, Lugano | Darius Moradpour, Lausanne

1330–1340 A preclinical screening platform of patient-derived tumor organoids for drug discovery in hepatocellular carcinoma.
Sandro Nuciforo, Basel

1340–1350 Suppression of tumorigenicity 2 (ST2) serum level for the assessment of liver fibrosis
Sena Blümel, Zürich

1350–1400 Development of a microscopy readout to characterise drug response in hepatocellular carcinoma organoids.
Lauriane Blukacz, Basel

1400–1410 Next-Generation Sequencing of Swiss Hepatitis E Virus Isolates Allows for Reconstitution of Functional Clones
Jérôme Gouttenoire, Lausanne

1410–1420 Heterogeneity of Peripheral Monocytes in Patients with Cirrhosis
Anne Geng, Basel

1430–1440 Increasing prevalence of obesity among patients evaluated for liver transplantation in a Swiss tertiary referral center: a 10-year retrospective analysis
Sophie Kasmi, Lausanne

1430–1440 Increased serum levels of gut-derived MAIT cell stimulatory bacterial metabolites in patients with portal hypertension
Magdalena Filipowicz Sinnreich, Basel

1500–1530 **Exhibition Area** **Coffee break**

1530–1700 **Young gastroenterologists**
Jan Borovicka, St.Gallen | Gian Dorta, Lausanne

1530–1545 European Board Exam 2021
Andrea Stefanie Baur, Zürich

1545–1600 Nutrition – what you need to know
Philipp Schreiner, Zürich

1600–1615 IBD: Hard facts for European Board Exam
Fritz Murray, Zürich

1615–1630 GI-Bleeding: Basics for the Exam
Henriette Heinrich, Zürich

1630–1645 Image challenge – what the GI eye needs to know
Daniela Husarik, St. Gallen

1815–1900 **General Assembly MDLS**

Kasmi Sophie

De: Fraga Christinet Monserrat <Montserrat.Fraga@chuv.ch>
Envoyé: mercredi, 22 décembre 2021 08:27
À: Kasmi Sophie
Objet: SMW-D-21-00207R1 Increasing prevalence of obesity and diabetes among patients evaluated for liver transplantation in a Swiss tertiary referral center: a 10-year retrospective analysis - [EMID:a1b9fa1f92d27582] [HIN secured]

Indicateur de suivi: Indicateur de suivi
État de l'indicateur: Avec indicateur

De : em.smw.0.77f8ec.27ab4187@editorialmanager.com <em.smw.0.77f8ec.27ab4187@editorialmanager.com> de la part de Swiss Medical Weekly <em@editorialmanager.com>
Envoyé : lundi, 13 décembre 2021 17:17
À : Fraga Christinet Monserrat
Objet : SMW-D-21-00207R1 Increasing prevalence of obesity and diabetes among patients evaluated for liver transplantation in a Swiss tertiary referral center: a 10-year retrospective analysis - [EMID:a1b9fa1f92d27582]

SMW-D-21-00207R1
Increasing prevalence of obesity and diabetes among patients evaluated for liver transplantation in a Swiss tertiary referral center: a 10-year retrospective analysis

Dear Dr Fraga Christinet,

Thank you for your submission. It has now been re-reviewed and the referees have suggested some minor revisions.

You are requested kindly to revise the paper in the light of these comments. Please include a list of changes or a rebuttal on each point raised and highlight the changes made in the manuscript.

To submit a revision, go to https://www.editorialmanager.com/smw/ and log in as an Author. You will see a menu item called Submission Needing Revision. You will find your submission record there.

I look forward to your reply and thank you in advance.

Yours sincerely,

Francesco Negro

Professor Francesco Negro
Academic Editor
Swiss Medical Weekly
office@smw.ch
www.smw.ch

.....