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Rome, February 27th-28th, 2020

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Digestive and Liver Disease

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Oral communications: 53rd Annual Meeting of the Italian Association for the Study of the Liver – A.I.S.F. (Rome, February 27-28 2020)

OC-01

Genetic and B-cell clonality markers in HCV-related cryoglobulinemic vasculitis persisting after DAA therapy

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INTRODUCTION: HCV-related mixed cryoglobulinemic vasculitis (CV) is a lymphoproliferative disorder that can evolve into lymphoma. DAA treatment usually improves CV, but symptoms can recur after a SVR due to genetic factors and B-cell clonal expansion persistence. METHODS: Patients: Group A: SVR-CV patients with clinical response; Group B: SVR-CV patients with symptom persistence/recurrence. A SNP genetic analysis of notch4 rs2071286, hla rs9461776, baff gene rs12428930, baff promoter rs9514828, and baff receptor rs61756766 was performed. B-cell clonal expansion was assessed by flow cytometry, by nephelometric assay of Free Light Chains (κ/λ) ratio and by nested PCR to evaluate t(14;18) presence. Clonality markers were prospectively and retrospectively evaluated. RESULTS: 98 HCV-MC patients with a SVR after DAAs were enrolled (post therapy F/U: 12 months (6-24). 53/98 in Group A and 45/98 in Group B. A higher frequency was observed for notch4 T minor allele ($p = 0.02$) and TT genotype ($p = 0.006$) in Group B. Flow cytometry showed B-cell expansion in 5% of Group A and 15% of Group B, FLC ratio was abnormal in 18% of Group A and 45% of Group B (OR = 3.67, $p = 0.006$).19% of Group A and 38% of Group B were t(14;18) positive. Retrospective analysis showed t(14;18) positivity in 34% of Group A and 54% of Group B and abnormal FLC ratio in 17% of Group A and 51% of Group B (RR = 3.08, $p = 0.002$). CONCLUSION: K/λ ratio, a common routine assay, proved to be the most associated clonality marker with the persistence of CV after a SVR, in prospective and retrospective analysis; the significantly higher frequency of notch4 minor allele in group B suggests that this genetic test, after validation, could identify a reliable biomarker for CV persistence/recurrence after SVR. Genetic and B-cell clonality markers could help in the clinical, prognostic/therapeutic approach to CV relapsers after a SVR, preventing evolution into lymphoma.

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OC-02

Procoagulant imbalance in patients with non-cirrhotic Chronic hepatitis C (CHC) improves six months after eradication with direct-acting antiviral agents (DAAs) and likely correlates with liver fibrosis

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Background: Chronic hepatitis C (CHC) is an important cause both of liver and cardiovascular diseases. A procoagulant imbalance, potentially responsible for liver and cardiovascular injury, has been reported in CHC patients without cirrhosis.

Aim: to assess whether HCV eradication reduces this procoagulant imbalance and correlates with improvement in hepatic fibrosis. Method: From 2017 to 2019, 122 non-cirrhotic CHC patients (age 58.9 ± 10.5 years) were enrolled. Clinical and biochemical parameters, presence of steatosis (by ultrasound), severity of liver damage [by liver stiffness measurement (LSM) and non-invasive fibrosis scores (FIB-4 and NAFLD fibrosis score (NFS)] and coagulation balance [endogenous thrombin potential (ETP) with/without thrombomodulin and protein C (PC)/FVIII ratio], were determined at enrollment and at 6 ± 1 months after sustained virological response (SVR). Coagulation parameters at baseline were compared to those of 188 control subjects, enrolled among healthy employers. Results: Indexes of procoagulant imbalance were significantly higher in CHC patients than in controls (FVIII/PC ratio 1.7 + 0.7 vs 1.1 + 0.3; ETP ratio 0.8 + 0.1 vs 0.6 + 0.2, p < 0.0001). Pretreatment, FVIII/PC ratio was independently associated with FIB4 (coefficient 0.6, SE 0.2,p = 0.003) and NFS (coefficient 0.7, SE 0.1, p < 0.0001) at analysis adjusted for sex, BMI, diabetes and GGT. Compared to before treatment, six months after SVR, we observed a significant reduction in procoagulant imbalance (FVIII/PC 1.3 ± 0.5 vs 1.6 ± 0.6, ETP ratio 0.64 ± 0.11 vs 0.73 ± 0.1, p < 0.0001) and a decrease of liver fibrosis (LSM 5.1 ± 1.7 vs 6.5 ± 5.5; NFS 0.1 ± 1.9 vs -1.9 ± 1.2; p < 0.0001 and FIB4 1.9 ± 1.2 vs 1.6 ± 0.7, p = 0.02). At analysis adjusted for sex, BMI, diabetes, and GGT, the FVIII/PC was significantly associated with FIB4 (adjusted-coefficient 0.3, SE 0.14, p = 0.01). Conclusion: The viral eradication induced by DAA reduces the procoagulant imbalance in non-cirrhotic patients with CHC. Whether this mechanism underlies the reported reduction of fibrosis after SVR needs to be confirmed in a larger cohort of patients.

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OC-03

VIRONET-C real life experience of resistance-guided retreatment in HCV infected patients who previously failed a NS5A inhibitor-containing regimen

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Aim: To analyze Italian real-life resistance data and efficacy of retreatment in HCV infected patients who previously failed a NS5A-inhibitor containing regimen.

Materials & Methods: Within the VIRONET-C network, 530 NS5A-failures infected with different HCV-genotypes (GT) (GT1a/1b/2a-c/3a-b-g-h-k/4a-d-n-o-r-v = 114/177/41/151/47) were analyzed. Retreatment of 136 failures was investigated. Resistance-test was performed by Sanger-sequencing.

Results: Failures following seven different NS5A-inhibitor containing regimens were studied: 3D/2D (paritaprevir/ombitasvir + dasabuvir) + ribavirin (N = 93/6), daclatasvir/ledipasvir/velpatasvir + sofosbuvir + ribavirin (N = 118/144/58), grazoprevir/elbasvir + ribavirin (N = 68), glecaprevir/pibrentasvir (N = 43). 17.5% failures did not show any resistance-associated-substitutions (RAS), while 81.5% showed at least one NS5A-RAS, with multiclass-resistance in 36.8%. Considering the new regimens, 89.5% of sofosbuvir/velpatasvir patients failed a 12-week treatment, 41.2% were cirrhotic and 65.5% were infected with a non-1 GT, with NS5A-resistance of 65.5%. Regarding glecaprevir/pibrentasvir failures, 93.0% failed a 8-week treatment, 5.0% were cirrhotic and 74.4% were infected with a non-1 GT, with NS5A-resistance of 55.8%. To date, 136 failures started a retreatment: sofosbuvir/velpatasvir + ribavirin (N = 15 + 16), sofosbuvir/velpatasvir/voxilaprevir + ribavirin (N = 77 + 17), glecaprevir/pibrentasvir + ribavirin (N = 6 + 1), grazoprevir/elbasvir + sofosbuvir + ribavirin (N = 1 + 3). The prevalence of NS5A-RASs before retreatment was 79.4%, with multiclass-resistance in 35.3%. According to geno2pheno algorithm 41.2% patients were fully susceptible to the retreatment regimen chosen. Among patients completing post-retreatment follow-up (N = 121), a sustained-viral-response at week 12 (SVR12) was observed in 90.9%. SVR12 was low after sofosbuvir/velpatasvir + ribavirin retreatment (78.6%), particularly in complex patients retreated with sofosbuvir/velpatasvir + ribavirin for 24-weeks (69%). Differently, 92.6% of SVR was achieved after sofosbuvir/velpatasvir/voxilaprevir retreatment without ribavirin. Interestingly, SVR12 was 100% with sofosbuvir/velpatasvir/voxilaprevir + ribavirin and glecaprevir/pibrentasvir + ribavirin, grazoprevir/elbasvir + sofosbuvir + ribavirin. Considering the 5 sofosbuvir/velpatasvir/voxilaprevir failures: 3 GT1a with baseline RASs confirmed the same resistance profile, one GT4d with baseline NS3 + NS5A-RASs showed a new NS3-RAS at failure, one GT1b non-response failed without any RAS.

Conclusions: In this real-life setting, SVR after resistance test guided retreatment was > 90%, with the exception of the sofosbuvir/velpatasvir retreatment. Our results show how HCV resistance-test after failure can help to optimize retreatment strategies.

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OC-04

Comprehensive characterization of HBV in tumor and non-tumor liver tissues from patients with HBV related-HCC

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Background. Infection with HBV is associated with a high risk of developing hepatocellular carcinoma (HCC). HBV may contribute to HCC development through both direct and indirect mechanisms. However, it remains undefined the relative contribution of virus-induced inflammation and the impact of viral integration. In this study, we evaluated HBV replication efficiency in tumor cells and analyzed the transcriptome of HBV-related HCCs to identify transcription of viral-human gene fusions from the genomic integration sites. Methods. HBV replicative and transcriptional activities were evaluated in tumor and non-tumor liver tissues from 5 patients with HBV-related HCC under NUC treatment using real-time PCR assays to quantitate total HBV DNA, cccDNA, and viral transcripts. Moreover, tumor and non-tumor liver tissues from 3 of the 5 patients, normal liver tissues from 3 individuals who underwent liver resection for hepatic hemangioma, and HepG2 cells were subjected to whole-transcriptome sequencing. RNA-seq was performed on an Illumina HiSeq 2500 platform. A total of 930 M reads were obtained. For chimeras detection a bioinformatics pipeline based on BWA, samtools, picard, bedtools, and in house scripts was used Results. Tumor and non-tumor liver tissues showed comparable mean amounts of total HBV DNA (355 ± 235 vs 298 ± 2150, copies/cell), cccDNA (0.26 ± 0.14 vs 0.16 ± 0.25 copies/cell), and transcripts (989 ± 937 vs 370 ± 256 copies/cell). Interestingly, transcriptome-sequencing data showed that whereas HepG2 did not express NTCP, tumor tissues expressed NTCP at levels comparable with those expressed both in non-tumor and in normal liver tissues. In addition, RNA-Seq allowed the identification of 531 integration breakpoints (14 in non-tumor and 517 in tumor tissues). Among genes target of viral integration we found an enrichment of genes implicated in redox, inflammatory, and metabolic processes as well as in signal transduction, cell cycle, and cell adhesion pathways. Conclusion. HBV can be integrated and efficiently replicate in tumor cells.

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OC-05

Serum gamma-glutamyltransferase is a prognostic biomarker in primary biliary cholangitis and improves risk stratification based on alkaline phosphatase

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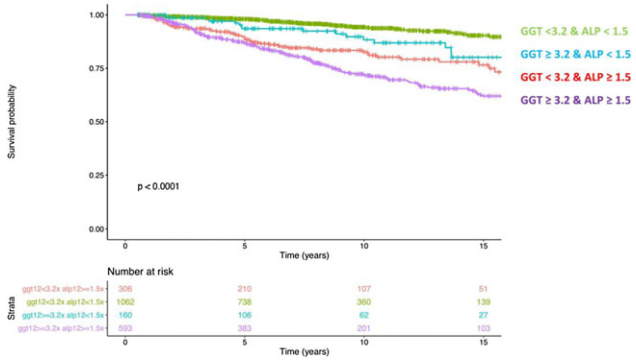
Background and Aims: Gamma-glutamyltransferase (GGT) is a serum marker of cholestasis. Its prognostic meaning in primary biliary cholangitis (PBC) is however unknown. We aimed to explore whether GGT is a prognostic marker in PBC.

Method: Data on patients from 14 centers from the Global PBC Study Group were included in the analysis. All patients with available GGT values at 12 months were selected. Levels of GGT were analyzed in different sub-populations at different time frames in relation to clinical endpoints of interest, i.e. liver transplantation (LT) or liver-related death.

Results: We identified 2129 patients, 281 (13%) experienced a liver-related clinical endpoint. Mean age at diagnosis was 53 years and 91% of patients were females. Patients treated with UDCA were 1983 (93%). Correlation between GGT and alkaline phosphatase (ALP) was strong ($r = 0.71$). When evaluated at baseline and yearly up to 5 years, higher GGT levels translated in lower transplant-free survival. When evaluated at 12 months since study enrollment, levels of GGT higher than 3.2 x upper limit of normal (ULN) best predicted the outcome at 10 years (AUC 0.70). The risk of liver-related death or LT in patients with GGT higher than 3.2 x ULN despite ALP lower than 1.5 x ULN was higher compared to those with GGT lower than 3.2 x ULN and ALP lower than 1.5 x ULN (Figure). All findings were confirmed when patients not treated with UDCA were excluded. The trend of GGT/total bilirubin over time in patients who experienced LT or death decreased before the endpoint.

Conclusion: Serum GGT can predict liver transplantation or death of patients with PBC and enhances risk stratification based on ALP only. Serum GGT might be used as surrogate end point in clinical trials and might replace ALP in patients with conditions that may spuriously alter levels of ALP, such as bone disease.



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OC-06

The metabolic plasticity of neoplastic cholangiocytes: perspective for target therapy of intrahepatic cholangiocarcinoma

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Background and Aims: Intrahepatic cholangiocarcinoma (iCCA) is a deadly cancer arising from biliary epithelial cells (BECs) lining the biliary tree. iCCA is a highly chemoresistant tumor and pharmacological therapies are generally unsuccessful. Furthermore, due to the complexity of the in vivo cellular interactions, metabolic activation pathways are largely unknown. We herein aim to elucidate the metabolic asset of both tumoral and non-tumoral primary BECs by profiling both the extra- and endo- metabolome.

Method: Primary non-tumoral BECS (NT-BECs) and tumoral iCCA BECs (iCCA-BECs) were isolated from 15 patients surgically resected at the Division of Hepatobiliary and General Surgery, Humanitas Clinical and Research Center. Both tumoral and non-affected BECs from the same donor were cultured until reaching 80% of confluence. Cells and their conditioned medium were analyzed by using mass spectrometry-based untargeted and targeted metabolomic approaches to explore the main metabolic processes. Moreover, primary iCCA BECs and Hucc-T1, human iCCA immortalized cell line, were seeded in 96-well plates to perform proliferation assay at different time point with different culture medium to detail the involvement of nutrients in iCCA-BEC proliferation.

Results: We observed that iCCA-BECs were characterized by higher mitochondrial activity compared to NT-BECs in all samples, in which glutamine and pyruvate act as metabolic sources to fuel central metabolism respectively. Importantly, iCCA-BECs exposed to different nutrient environments were able to reprogram nutrient uptake and utilization to boost central cellular metabolism. Furthermore, the proliferation assay showed that iCCA-BECs, when cultured in a different metabolic medium composition, were able to exploit the different metabolic sources to sustain cancer cell growth.

Conclusion: This observation raises the prospect that interfering with mitochondrial activity of iCCA cancer cells could make them more susceptible to cytotoxic drugs, opening new possibility to improve the outcomes of the iCCA patients.

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OC-07

Role of cellular senescence in the natural history of primary sclerosing cholangitis

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Introduction: Cellular senescence(CS) is a physiological mechanism of irreversible cell cycle arrest in response to damage that prevents uncontrolled replication of injured cells. The role of CS in the pathogenesis of human chronic liver diseases was recently reported, and few data suggest an involvement of CS in the natural history of primary sclerosing cholangitis(PSC).

Aim: To evaluate hepatic expression of CS-markers in PSC and its correlation with clinical-pathological features and prognosis.

Materials & Methods: Thirty-five PSC patients (14 males) followed-up for 12 years(0.5-29) with at least one available liver biopsy(LB) performed at diagnosis and/or during follow-up were retrospectively enrolled. Clinical/laboratory data, Mayo Risk Score(MRS) and Amsterdam-Oxford Model(AOM) at the time of LB were collected. The endpoint was survival without liver transplantation or cirrhosis decompensation. Grading and staging were assessed by 2 expert pathologists according to Nakanuma. Immunohistochemical stains for CS-markers(p16 and p21) were performed and semi-quantitatively scored by a three-tier scale based on the positivity extent in native bile duct(NBD) and ductular reaction(DR).

Results: p16 expression in NBD and DR was directly correlated with hepatitis activity($p = 0.02$ and $p = 0.05$), cholestasis-related histological lesions($p = 0.09$ and $p < 0.001$), fibrosis($p < 0.001$, both) and disease stage($p = 0.005$ and $p < 0.001$). p21 expression in NBD and DR was directly correlated with hepatitis activity($p = 0.001$ and $p = 0.03$), cholestasis-related histological lesions($p < 0.001$, both), fibrosis($p < 0.001$, both) and disease stage($p < 0.001$ and $p = 0.003$). By multivariate analysis p16 expression in DR was independently associated with advanced disease stages(HR 13.6(95%CI 2.6-72.6), $p = 0.002$). p16 and p21 expression in DR was directly related to MRS($p = 0.02$, both) and AOM($p < 0.001$ and $p = 0.007$). p16 and p21 expression in NBD was directly related to AOM($p = 0.03$, both). p21 expression in DR was independently associated with adverse outcome-free survival(HR 4.6(95%CI 1.6-13.6), $p = 0.005$).

Conclusions: In PSC, CS-markers expression is related to disease stage, clinical severity and prognosis, suggesting a role of senescence in the pathogenesis and progression of the disease.

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OC-08

Pre-existing liver disease and severity of DILI in an Italian cohort

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Introduction & Aim: Information on etiology and clinical course of drug induced liver injury (DILI) is limited in Italy.

Materials and Methods: In an observational study, we assessed prospectively all patients diagnosed with DILI at two tertiary Italian centers between 2000 and 2018. Causes and severity of DILI and pre-existing liver disease (PLD) were systematically investigated. Subjects were followed at three-month intervals for > 1 year.

Results: 295 DILI patients were enrolled. At presentation, 59% had hepatocellular damage, 27% cholestatic damage and 14% a mixed pattern. NSAIDs (30.4%), antibiotics (26.4%), immunesuppressants (10.4%), benzodiazepines (2.3%), neuroleptics (7.4%), statins (5.2%), anti-platelets (5.9%), herbal products (3,7%) and miscellanea drugs (10%) were involved. Out of 295,101 patients (34%) had PLD (NAFLD 77%, HCV 13%, HBV 4%, autoimmune hepatitis 6%). PLD patients showed a higher incidence of type 2 diabetes than non-PLD (20% vs 7%, $p = 0.001$). Cirrhosis at diagnosis was present in 7% of PLD patients (p 0.002). PLD subjects were younger than non-PLD (51.8 ± 18.6 vs 56.3 ± 16.2, p 0.04). Antibiotics and herbal products were the most frequently involved agents. Pattern of liver injury was comparable between two group, but PLD patients were more often jaundiced (61% vs 43%, p 0.04) and showed more severe hepatic injury ($P > 0.0001$). Two patients died among PLD, both had NASH cirrhosis, one with DILI due to amoxicillin/clavulanate and the other with DILI due to herbal products.

Conclusion: The etiological patterns of DILI in Italy is comparable to other countries. Pre-existing liver disease, mostly NAFLD, is frequent and associated with more severe liver damage.

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OC-09

Perception of illness in Italian patients with Primary Biliary Cholangitis referred to tertiary care units

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Introduction: Stratification of illness perception in PBC patients is an important tool to explore the personal experience on symptoms, treatment, and clinical outcome of the disease. Indeed, the standard validated questionnaire on health-related quality of life(QoL) explores the emotional aspects, but overlooks the past and present experience of patients.

Aim: To assess the perception of illness in a cohort of Italian patients with PBC referred to tertiary care units.

Materials and methods: A questionnaire assessing symptoms and their impact on QoL, treatment and perceived satisfaction toward the provided care was administered to PBC patients in 7 centers between July and November 2019. The questionnaire was previously validated in 45 PBC patients.

Results: Ninety-nine patients(89% females, median age 60 years) were enrolled. Most of patients had a high-school or higher level of education, were living as a couple and only 3% were unemployed due to PBC. The median duration of symptoms was 10 years. Fatigue, sicca syndrome, pruritus, headache and abdominal discomfort(scored $\geq$ 5/10) were present in 65%,63%,41%,48% and 80% of patients, being fatigue the most impacting on QoL. Patients reported concern or resignation in 40% of cases, otherwise 40% reported desire to react to PBC. Patients were mostly concerned about possible occurring health problems and in 25% of cases, symptoms had a negative impact on QoL. All patients were regularly followed-up, 76% were assuming UDCA alone, 13% had a second-line therapy(obeticholic acid or fibrates), 11% were untreated. 87% of patients were satisfied with effectiveness and tolerability of treatment, whereas 37% whish an improvement in the relationship with the specialist, particularly, regarding the time for each visit, the psychological support, and information concerning PBC.

Conclusions: Fatigue is the most important symptom impacting on QoL of Italian PBC patients. Due to the long natural history, important efforts on symptoms and psychological aspects of the disease should be considered

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OC-10

The weight of pre-existing cofactors for liver disease progression in patients who successfully eradicated HCV virus infection: An interim analysis in the PITER cohort

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Introduction: EASL CPG suggest that HCV patients who achieve an SVR should be maintained on follow-up if pre-existing cofactors for liver disease progression (CF) (excessive alcohol drinking, obesity, type 2 diabetes) are present.

Aim In PITER cohort, we evaluated the post-SVR real life management of patients, according to liver disease stage and presence of these CF.

Methods: Data of 4038 patients who eradicated HCV were evaluated.

Results: Of 1557 patients (mean age 57; SD: 13 years) with F1–F2 stage, 30% had a post SVR follow-up. The CF prevalence was 71% in those who continued the follow-up versus 76% in those who interrupted it ($p = 0.05$). ALT remained elevated in 2% of patients with CF compared to none in patients without. Of 473 patients (mean age 61;SD: 12 years) with F3 stage and a median follow-up of 23; range 13-35 months after SVR, 89% had CF. ALT remained altered in 4% of patients with CF compared to none in those without ($p = 0.02$). Of 2008 patients with cirrhosis, followed-up for a median of 33: range 26-41 months, the cumulative HCC incidence rate was 4.4% in patients with CF and 3.9% in those without (p = 0.7). Factors independently associated with HCC occurrence were age (HR = 1.08; 95% CI 1.04–1.12), decreased albumin (HR = 3.03 95% CI = 1.46–6.30) and genotype 3 (HR = 2.67 95% CI = 1.03-6.96). During the follow-up, 3.2% of patients with decompensated cirrhosis had a new decompensation event, whereas in 4.8% an incident decompensation was observed. Pre-treatment decompensation (HR = 7.13; 95% CI 4.51–11.27), platelets lower than 100,000 (HR = 2.01; 95% CI 1.29-3.12) and decreased albumin (HR = 1.65; 95% CI 1.08-2.54) were independent factors associated to liver decompensation after SVR.

Conclusion: Cofactors for liver disease progression are common in patients who have eradicated HCV infection. In patients with CF, during a medium term follow-up after SVR, persistent ALT elevations, but not higher liver related complications incidence were observed.

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OC-11

TM6SF2/PNPLA3/MBOAT7 loss-of-function genetic variants impact on NAFLD development and progression both in patients and in in vitro models

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Introduction: The I148 M *PNPLA3* and E167K *TM6SF2* variants alongside the rs641738 polymorphism in *MBOAT7/TMC4* locus predispose to non-alcoholic fatty liver disease (NAFLD). We previously generated a full knock-out of *MBOAT7* in HepG2, homozygous for the I148 M PNPLA3 (MBOAT7$^{-/-}$).

Aims: 1) To investigate the synergic impact of the 3 risk variants on liver injury and hepatocellular carcinoma (HCC) in NAFLD patients; 2) to mimic genetic NAFLD by silencing *TM6SF2* in HepG2 and MBOAT7$^{-/-}$ cells.

Materials and Methods: NAFLD patients ($n = 1194$), of whom 72 had HCC, were stratified according to the presence of *PNPLA3*, *TM6SF2* and *MBOAT7* at-risk variants: 0 (none), 1 (1 variant in *PNPLA3*, *TM6SF2* or *MBOAT7*), 2 (2 variants) and 3 (3 variants). The additive weight of the mutations was correlated with liver disease severity. We silenced *TM6SF2* in HepG2 (TM6SF2$^{-/-}$) and MBOAT7$^{-/-}$ (MBOAT7$^{-/-}$TM6SF2$^{-/-}$) through CRISPR/Cas9.

Results: At bivariate analysis, the co-presence of the 3 risk variants correlated with steatosis ($p < 0.0001$), lobular inflammation ($p = 0.009$), ballooning ($p = 0.004$) and fibrosis ($p < 0.0001$). At multivariate analysis adjusted for age, sex, BMI and T2D, patients carrying the 3 variants showed higher risk of fibrosis > 2 ($p = 0.002$), cirrhosis ($p = 0.02$) and HCC ($p = 0.09$). In TM6SF2$^{-/-}$ and MBOAT7$^{-/-}$TM6SF2$^{-/-}$ cells, intracellular lipid droplets and TG content were higher than in HepG2 ones ($p < 0.01$), and the expression of genes involved in lipid metabolism was altered ($p < 0.05$). Markers of endoplasmic reticulum (*XBP1*, *GRP78*), oxidative stress, lipid peroxidation and DNA damage were increased ($p < 0.05$). Cell injury was greater in MBOAT7$^{-/-}$TM6SF2$^{-/-}$ cells as they showed the highest levels of XBP1, GRP78, free radicals and higher proliferation rate compared to control ($p < 0.05$).

Conclusions: We generated an *in vitro* stable compound knock-out of genetic NAFLD. The co-presence of the 3 risk variants impacts on NAFLD development and progression *TM6SF2* silencing alone or combined with I148 M PNPLA3 and MBOAT7 knock-out contributes to hepatocellular damage and proliferation.

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OC-12

PCSK9 rs11591147 R46L loss-of-function variant protects against liver damage in individuals with non-alcoholic fatty liver

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Background and Aims: The proprotein convertase subtilisin/kexin type 9(PCSK9) plays a key role in cholesterol homeostasis, and its inhibition represents an effective therapy to lower LDL-C levels. In this study, we examined the impact of *PCSK9* rs11591147 loss-of-function(LOF) variant on liver damage in a multicenter collection of patients at risk of nonalcoholic steatohepatitis(NASH), in clinical samples and experimental models.

Methods: We considered 1,874 consecutive individuals at risk of NASH as determined by histology. The SNP rs11591147, encoding for the p.R46L variant of PCSK9, was genotyped by TaqMan assay. We evaluated 1)PCSK9 mRNA hepatic expression in human liver, 2)the effects of a NASH-inducing diet in mice with hepatic overexpression of human PCSK9, and 3)the effect of PSCK9 modulation in human HepG2 hepatoma cells and hepatic stellate cells.

Results: Carrier of *PCSK9* rs11591147 had lower circulating LDL-C levels with a protection against NAFLD(OR0.42;95%C.I0.22-0.81;$P = 0.01$), NASH(OR0.39;95%C.I.0.20-0.75;$P = 0.005$) and severity of fibrosis(OR0.44;95%C.I.0.26-0.74;$P = 0.002$) independently of clinical, metabolic and genetic confounding factors. PCSK9 hepatic expression was directly correlated with severity of steatosis($P = 0.03$). Finally, liver-specific overexpression of human PCSK9 in mice drives NAFLD and fibrosis upon a dietary challenge, and *in vitro* experiments showed that PCSK9 may contribute to increase steatogenesis, inflammatory processes and fibrogenesis.

Conclusions: In individuals at risk for NASH, *PCSK9* rs11591147 LOF variant was protective against liver steatosis, NASH and fibrosis, with this effect likely related to the ability of PCSK9 to promote fatty liver accumulation, inflammation and fibrosis. If these results translate into humans, PCSK9 inhibition may be a new therapeutic strategy to treat NASH.

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OC-13

Accuracy of metabolomics profiles to non-invasively diagnose NAFLD stages and evolution by mean of machine-learning automated algorithms

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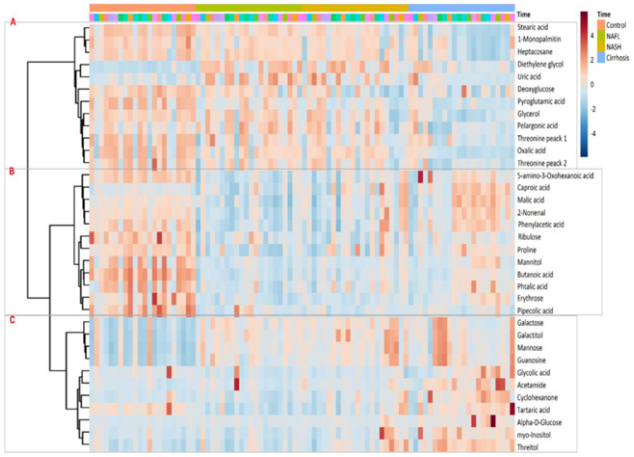
Background and Aims: Non-Alcoholic Fatty Liver Disease encompasses a spectrum of diseases ranging from simple steatosis to NASH and cirrhosis/HCC. The challenge in this field is to recognize the more severe and/or progressive pathology. A reliable non-invasive method based on biomarkers does not exist at the moment. Metabolomics technique has a great potential for this task, because it can non-invasively perform a complete "metabolic fingerprint" of a disease and, in turn, potentially detect all its evolution steps. With this aim, we performed a serum metabolomics characterization of several NAFLD forms and then tested its accuracy confronting it with an independent cohort by mean of machine-learning models' approach. Moreover, we performed a time-series analysis to verify if there were metabolomic profiles that change during the evolutionary steps of NAFLD.

Method: Metabolomic profiles were obtained by mean of gas chromatography/mass spectrometry from two cohorts of a total of 319 subjects. The first cohort, coming from the main recruitment center (University of Salerno),was composed by 69 healthy subjects (CTRL) and 144 NAFLD patients (78 NAFL, 23 NASH, 43 NASH cirrhosis) and the second, coming from the other centers, was composed by 106 subjects(40 CTRL, 34 NAFL, 10 NASH, 18 NASH cirrhosis). Ten machine learning and classification models (Partial Least Square Discriminant Analysis, Linear Discriminant Analysis, Naïve Bayes, Decision Tree, Random Forest, k-nearest neighbor, Artificial Neural Network, Support Vector Machine, Logistic regression and Deep Learning) were built and optimized for each step. Variable selection used a specifically designed genetic algorithm, while class imbalance was managed with a MetaCost approach. Moreover, thirty-four metabolites selected from the analysis of variance (ANOVA, $p < 0.05$) were included in a time series analysis to follow the evolution of these metabolites concentration during the NAFLD evolution from simple steatosis to NASH-cirrhosis.

Results: Three ensemble model was built based on the results from the individual models (CTRL Vs NAFLD, NASH Vs NAFL, and NASH Vs NASH cirrhosis). Samples from first cohort were randomly divided into 2 groups. One was used as a training set, the other one for internal cross-validation of diagnostic performance. External performance evaluation was also assessed using subjects from the second cohort. Blind analysis using the described test showed a global accuracy for NAFLD identification of 96.8% ± 2.1, 94.0% ± 4.2 for NASH and 81.2% ± 12.2 for NASH cirrhosis identification. The time-series analysis showed that ANOVA selected 3 specific metabolites patterns concentration changes during the NAFLD evolution. The first pattern (A) especially composed from fatty acids related metabolites decreased from the healthy subjects to the NASH-cirrhosis. The second (B) accounted for amino acids and related metabolites and gut microbiota related metabolites decreased in the first steps of the NAFLD (NAFL and NASH) while increased in the last (cirrhosis). The third (C), composed especially from sugars, constantly increased during the NAFLD evolution.

Conclusion: Serum metabolomics is a promising tool for an accurate and sensitive, non-invasive screening of NAFLD stages, and to forecast its evolution.



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OC-14

Noninvasive risk stratification in nonalcoholic fatty liver disease: a polygenic risk score

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Background and Aims: Identification of noninvasive biomarkers to detect patients with dysmetabolism at risk of nonalcoholic fatty liver disease (NAFLD), severe fibrosis and hepatocellular carcinoma (HCC) is a priority. Progression of NAFLD is genetically conditioned. We previously developed a polygenic risk score (GRS) based on common variants that are involved in inherited predisposition to fat accumulation, namely *PNPLA3*, *TM6SF2*, *MBOAT7* and *GCKR*. The aim of this cross-sectional multicenter study was to evaluate the accuracy of GRS to stratify the risk of NAFLD, advanced fibrosis and HCC.

Methods: A total of 2021 individuals (464 without liver disease, 1034 with histological NAFLD without severe fibrosis, 275 with NAFLD and severe fibrosis without HCC, and 248 with NAFLD-HCC) were genotyped for the rs738409 (*PNPLA3* I148 M), rs58542926 (*TM6SF2* E167K), rs641738 C > T at *MBOAT7* and rs1260326 (*GCKR* P446L). The GRS was computed for each subject. The association between GRS and disease risk was tested using multivariate logistic regression models, adjusted for age, sex, presence of diabetes, BMI and fibrosis.

Results: In the overall cohort, GRS was associated with NAFLD ($p < 10^{-11}$, OR for the upper quartile: 4.22, 95%CI 2.72–6.54) independently of confounders. In NAFLD, GRS was also an independent predictor of severe fibrosis ($p < 10^{-14}$, OR for the upper quartile 2.96, 95%CI 1.55–5.65). Moreover, GRS was independently associated with HCC ($p = 10^{-6}$, OR for the upper quartile 2.41, 95%CI 1.28–4.54) in NAFLD patients, but the association was lost after correction for fibrosis. The AUROC was 0.604, better than the single variants alone.

Conclusion: The GRS was more accurate in discriminating NAFLD, severe fibrosis and HCC compared to single variants. Genetic heritability and hepatic fat accumulation determine liver fibrosis, that remains the major risk factor for HCC, although we can not exclude a pleiotropic effect of specific variants in hepatocarcinogenesis.

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OC-15

Interplay between metabolic derangement, hepatic fibrogenesis and macrophage activation in non-diabetic patients with non-alcoholic fatty liver disease

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Introduction. The pathogenesis of Non-Alcoholic Fatty Liver Disease (NAFLD) and steatohepatitis (NASH) is likely due to the interaction between a deranged metabolic milieu and local mediators of hepatic inflammation and fibrosis.

Aim. We investigated a panel of serum non-invasive biomarkers of collagen remodelling and explored their association with metabolic derangements and liver damage to elucidate their complex interplay in non-diabetic NAFLD patients.

Materials&methods. 52 subjects with biopsy proven NAFLD underwent a double tracers oral glucose tolerance test. Using tracers data we measured endogenous glucose production (EGP) and lipolysis by glycerol rate of appearance and we calculated indexes of IR in the liver (Hep-IR = EGP x insulin) and in the adipose tissue (Lipo-IR = GlycRa x insulin and AT-IR = free fatty acids x insulin). Fibrogenesis biomarkers PRO-C3, PRO-C6 as well as macrophage activation biomarker sCD163, were measured by ELISA.

Results. Fasting CP, PRO-C3, PRO-C6 levels directly correlated with BMI and waist circumference (all $p < 0.03$). Among IR indexes, PRO-C3 and PRO-C6 correlated with Hep-IR ($r_S = 0.32$, $p = 0.025$; $r_S = 0.38$, $p = 0.006$), adipo-IR (both Lipo-IR [$r_S = 0.36$, $p = 0.010$; $r_S = 0.37$, $p = 0.007$] and AT-IR [$r_S = 0.36$, $p = 0.010$; $r_S = 0.37$, $p = 0.008$]) as well as with basal insulin ($r_S = 0.3$, $p = 0.005$ and $r_S = 0.34$, $p = 0.013$) and CP levels ($r_S = 0.51$, $p < 0.001$; $r_S = 0.55$, $p < 0.001$). On the opposite, sCD163 levels did not correlate with insulin levels but increased proportionally with adipo-IR (both Lipo-IR [$r_S = 0.28$, $p = 0.05$] and AT-IR [$r_S = 0.30$, $p = 0.032$]).Concerning histology, CP and PRO-C6 levels were able to distinguish F0/F1 from F2 ($p = 0.013$; $p = 0.05$) while PRO-C3 and sCD163 levels discriminated F2 from F3/F4 ($p = 0.009$; $p = 0.002$). By biomarkers combination, the best performance for the identification of F3/F4 was obtained with CP and sCD163 with an area under the receiver operating curve of 0.91 (PPV = 83%; NPV = 91%).

Conclusions. In non-diabetic patients with NAFLD, the combination between CP and sCD163 provides the best performance for the assessment of severe fibrosis (F3/F4). *Funded by:Horizon2020 under grant agreement no.634413,EPoS*

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OC-16

PIVKA_II a useful biomarker for hepatocellular carcinoma in caucasian HCV cirrhotic patients treated with direct-acting antivirals

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Introduction: Prothrombin induced by vitamin K absence-II (PIVKA-II) performance as hepatocellular carcinoma (HCC) marker in HCV cirrhotics treated with direct-acting antivirals (DAA) is unknown.

Aim: We evaluated PIVKA-II and AFP in DAA-treated HCV cirrhotics.

Methods: Consecutive HCV cirrhotics were tested for PIVKA-II and AFP (Fujirebio, Japan) at DAA start (baseline), end of treatment (EOT), post-treatment week 12 (PTW12) and eventually at HCC diagnosis. Patients underwent 6-month ultrasound (US)-based HCC surveillance.

Results: Overall, 692 sera (214 patients) were tested, median age 63 (28-87) years, 60% males, 19% diabetics, 87% Child A, LSM 17.5 (12.0-75.0) kPa. Median AFP levels decreased from baseline 15 (1-537) ng/mL to 8 (1-347) at EOT and 6 (2-48) at PTW12 ($p < 0.0001$), while PIVKA-II did not significantly change, being 37 (12-520) AU/L at baseline, 37 (14-867) at EOT, and 40 (20-1,192) AU/L at PTW12 ($p = 0.10$). After 42 (3-57) months of follow-up, 41 patients developed HCC, 4-year cumulative incidence being 9% (95% CI 7-12%). Median HCC size was 20 (10-30) mm, single in 68%, BCLC 0-A in 85%, AFP 7 (2-12,868) ng/mL and PIVKA-II 55 (22-15,283) AU/L. By applying PIVKA-II > 40 and AFP > 7 cutoffs, 33 (80%) HCC tested positive for at least one marker. Before HCC onset, at least one marker increased above the cutoff in 10 patients following EOT, whereas median time to HCC diagnosis by US was 39 (1-52) months. The accuracy for HCC resulted 68% for AFP > 7, 73% for PIVKA-II > 40, 95% when combining both markers. The 4-year probability of HCC resulted 41% ***vs.*** 13% in patients with PIVKA-II > or ≤40 at EOT ($p < 0.00001$), 31% ***vs.*** 20% in patients with AFP > or ≤7 ($p = 0.09$) and 45% ***vs.*** 20% in patients with or without both markers increased ($p = 0.002$).

Conclusions: In DAA-treated HCV cirrhotics, PIVKA-II levels in combination with AFP are associated with HCC.

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OC-17

Ganglioside patterns in the human cholangiocarcinoma stem cell subset

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Background and aims: Cancer stem cell (CSC) represents a critical therapeutic target in neoplastic diseases. Gangliosides (GS) are a family of sialic acid–containing glycosphingolipids, which have been associated with the malignant phenotype of several cancers (i.e. breast, melanoma, glioblastoma, ovary). Recent evidence indicates the possible involvement GS in tumor stem cell biology, but no data regarding GS composition in human cholangiocarcinoma (CCA) are available. The aim of this study was to provide a GS profiling of the stem-like subset and of their parental cells in human CCA.

Methods: Stem-like subset was enriched by sphere culture (SPH) using well-established human intrahepatic CCA cells (HUCCT1, CCLP1). CCA GS patterns were analyzed by chromatographic procedures. Assessment of GS turnover and identification of GS molecular species were evaluated using 3Hsphingosine. The role of GS in the modulation of stem features was investigated using D-threo-1phenyl-2-palmitoylamino-3-N-morpholine-1-propanol (PPMP), a GM3 synthase inhibitor. FACS-sorted $GD2^+$ SPH cells were examined for stem-like gene expression compared to $GD2^-$ SPH.

Results: In both CCA lines, the amount of total GS was markedly different comparing parental cells grown in monolayer conditions (MON) and their stem-like subsets (SPH). CCA-SPH showed enrichment in the major GS class (GM3), reduction of GM2 and the presence of GD2. This was corroborated by high expression levels of GM3 synthase as well as of GD3 and GM2/GD2 synthases in CCA-SPH. Enzymes involved in GS biosynthesis were strongly expressed in CCA-SPH compared to MON. Notably, sphere-forming ability and expression of CSC-related genes were reduced in cells treated with by PPMP. Likewise, $GD2^+$ SPH cells were enriched with CSC-markers (CD133, EpCAM, CD44) and expressed at higher levels several genes involved in pluripotency, self-renewal and epithelial mesenchymal transition compare to $GD2^-$ SPH. Notably, expression of GM2/GD2 synthases was significantly increased in tumor samples compared to paired non-tumoral tissue of CCA patients ($n = 104$) and significantly correlated with the presence of satellite nodules, lymph node invasion and recurrence.

Conclusion We show for the first time that the CCA stem-like properties may be associated with modification in the GS synthetic pathway.

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OC-18

Neoangiogenic transcriptomic signature identifies HCCs with worse response to treatment: long-term results of a prospective study

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Introduction: Hepatocellular carcinoma (HCC) is the 2nd solid tumor in males for mortality. Current therapeutic algorithms do not include molecular-signatures for choosing treatment, evaluating response and survival. We prospectively evaluated outcome of treatments performed according to SOC in relation with neoangiogenic transcriptomic signature (TS) described in doi:10.1136/gutjnl-2014-308483 (ClinicalTrials.gov:NCT01657695).

Method: 309 (80% males) consecutive HCCs underwent US-guided liver biopsy for histological, TS, miRNA evaluation (qRT/PCR) and P27 immunohistochemistry at first diagnosis and at recurrence. Physicians performing treatment were blinded to TS status. Outcome was matched with TS only after concluding follow-up.

Results: 83% of entire cohort underwent at least one treatment (14% systemic; 68% others). Overall median survival was 21 months (M ± SD:28 ± 23 months). TS + patients (27.7%) had significantly worst median survival (TS + vs. TS– : 12 vs. 41 months; $p < 0.0001$), independently from undergoing any treatment (TS + vs.

TS– : median survival: 19 vs. 44 months; p < 0.0001) or supportive therapy only (median survival: 6 vs. 22 months; p < 0.0001). A significantly different impact of cumulative therapies was observed in TS– HCCs (resection/LT survival significantly higher vs. RF vs. TACE, the latter having the worst survival, p = 0.005) but not in TS + HCCs (various therapies: p = 0.641) (Figure 1a&b). For all treatment types, survival was lower in TS + HCCs. Unexpectedly, a shift from TS– to TS + HCCs was demonstrated in sequential biopsies of recurrent HCCs undergoing TACE but not RF or resection (Figure 1c). Shift was associated with decreased survival and consensual up-regulation of a MiRNA set (linked with angiogenesis, proliferation, cell cycle progression) and with p27 nuclear/cytoplasmic translocation.

Conclusion: HCCs bearing the transcriptomic signature have an extremely aggressive clinical course that negatively influences survival despite application of all available treatments. TS– to TS + TACE-associated shift can explain worse TACE-outcome and demonstrates that transcriptomic signature is a dynamic feature, liable to be negatively influenced by therapeutic intervention.

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OC-19

Metabolic and functional recovery of tumor infiltrating NK-cells in Hepatocellular Carcinoma

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Introduction: Several immune mechanisms contribute to an immunosuppressive tumour immune milieu: regulatory immune cells, checkpoint receptors, low nutrients and hypoxia that can affect immune cells metabolism and function. Metabolic profiles rather than phenotypic characteristics seem to define the functional role of NK cells and their influence in a correct anti-tumour effect. NK-cell response is functionally impaired in Hepatocellular Carcinoma (HCC), however little is still known about NK-cell metabolism in this tumour.

Aim: To characterize metabolic NK-cell dysfunction in HCC in order to restore function targeting cellular metabolic pathways.

Materials and Methods: Liver and tumour infiltrating lymphomononuclear cells from 10 patients were derived from surgical specimens and NK-cells were purified by flow activated cell sorting in order to perform gene expression profiling. NK-cell phenotype, glucose uptake and mitochondrial polarization were defined by multi-parametric flow cytometry. Modulatory compounds were identified on the basis of gene expression profiling and employed to restore tumour infiltrating NK-cells metabolism and cytotoxic functions.

Results: Genome-wide expression profiling showed enrichment of upregulated genes belonging to metabolic pathways in HCC-infiltrating NK cells: glycolysis and oxidative phosphorylation, cell cycle, DNA damage and p38-related pathway. Higher level of phosphorylated-p38 protein was confirmed in tumour infiltrating NK cells while phenotypic characterization showed enrichment of CD49a positive and CD27CD11b double negative NK-cells that has been associated with regulatory and dysfunctional NK-cells. Functional and metabolic assessment showed defective degranulation capacity, reduced autophagy and glucose consumption. Targeting MAPK pathway by two different p38-inhibitors could restore NK-cell functions.

Conclusion: We identified an impairment of energy metabolism of HCC-infiltrating NK-cells associated with functional defects that can be rescued modulating MAPK pathway. These results provide the basis to develop new strategies to potentiate NK-cell response in HCC.

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OC-20

Adherence to Surviving Sepsis campaign 3-hour bundles improves survival in non-critically ill patients with cirrhosis and sepsis

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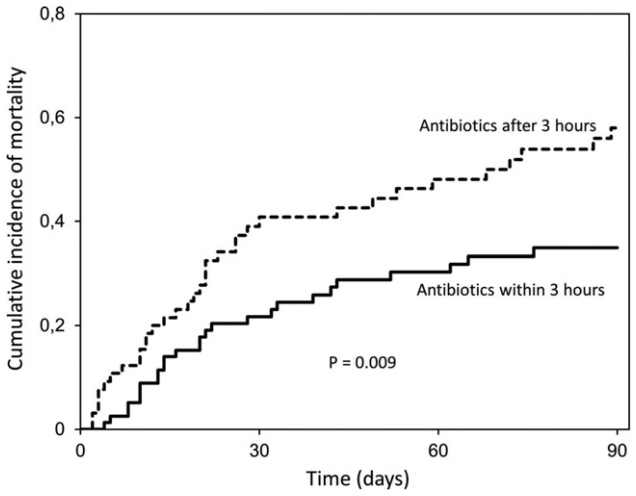
Background and Aims: Sepsis is a common and life-threatening complication in cirrhosis. Surviving Sepsis Campaign recommendations suggest early administration of treatment bundles for sepsis, which reduces mortality in general population. However, no data is currently available in patients with cirrhosis. The aim of this study was to evaluate whether the adherence to 3-hour bundles could modify clinical outcomes in patients with cirrhosis and sepsis.

Methods: From 2012 to 2019 consecutive non-critically-ill patients with cirrhosis and bacterial infections were enrolled. Clinical, laboratory, microbiological and treatment data were collected at the diagnosis of infection and during the hospitalization. Adherence to 3-hour bundles(e.g. microbiological cultures obtained before the administration of antibiotics, administration of broad spectrum antibiotics within 3 hours and assessment of blood lactates) was assessed. Patients with sepsis were identified according to Sepsis-3 criteria. Patients were followed up until death, liver transplantation or to 90 days.

Results: 144 out of 329 patients with cirrhosis and infections had sepsis and were included in the analysis(Age = 62 ± 11 years;MELD score = 23 ± 7). Microbiologic cultures were obtained before antimicrobial therapy in 98(68%)patients, broad spectrum antibiotics were given within 3 hours in 79(55%)patients while lactates were measured in 69(48%)patients. The adherence to the full 3-hour bundle was achieved in 27(19%)patients. The administration of empiric broad-spectrum antibiotics within 3 hours was associated with lower 28-day(22%vs39%;$p = 0.024$) and 90-day cumulative incidence of mortality(35vs58%;p = 0.009; Figure). In multivariate analysis(adjusted for age, MELD score, ascites and hepatic encephalopathy), adherence to the 3-hour antibiotic bundle(sHR = 0.46;$p = 0.019$) and culture bundle(sHR = 0.47;$p = 0.027$) were independently associated with better 28-day survival, while the measurement of lactates did not influence 28-day survival(sHR = 0.85;$p = 0.63$).

Conclusions: The adherence to the 3-hour antibiotic and culture bundles was associated with lower mortality in patients with cirrhosis and sepsis. The adherence to these bundles was not opti-

mal and strategies are needed to improve the adherence to sepsis bundles in cirrhosis.



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OC-21

Acute kidney injury is associated with reversible platelet dysfunction in hospitalized patients with decompensated cirrhosis

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Background and aim: Recent evidence suggests that acute kidney injury (AKI) is the main predictor of post-paracentesis bleeding in patients with cirrhosis and ascites. With the hypothesis that the increased bleeding tendency in AKI is due to platelet dysfunction, we performed a prospective comparative study evaluating platelet function in patients with decompensated cirrhosis with and without AKI.

Material and methods: Platelet function was assessed using whole blood lumiaggregometry to evaluate both platelet aggregation (an *in vitro* marker of platelet response to vessel injury) and platelet secretion (an *in vitro* marker of granule release). Platelets were stimulated with collagen 1 μg/mL, collagen 5 μg/mL, ADP 10 μM and thrombin 50 μM. In patients with AKI, platelet function was re-evaluated after AKI resolution. Inpatients with AKI but without liver disease were included as controls.

Results: Eighty patients with decompensated cirrhosis were recruited (40 each with and without AKI). As shown in the table, Child class, type of decompensating event and platelet count were comparable in both study groups. Patients with decompensated cirrhosis and AKI had lower collagen-induced aggregation and lower collagen-, ADP-, and thrombin-induced secretion, indicative of a more severely impaired platelet function. With AKI resolution (n = 23/40), both aggregation and secretion recovered and became comparable to values in patients with cirrhosis without AKI. The impairment in platelet function in patients with cirrhosis and AKI as well as the significant improvement after AKI resolution were confirmed after adjusting the analysis for the severity of thrombocytopenia. Compared to healthy individuals, controls with AKI but without liver disease (n = 10) had significantly lower platelet secretion and aggregation.

Conclusion: In patients with decompensated cirrhosis, the presence of AKI is associated with significant platelet dysfunction that is fully reversible upon AKI resolution. These abnormalities likely contribute to the increased bleeding risk in these patients.

	AKI (n=40)	No AKI (n=40)	
Age (years)	56 (52-65)	57 (52-64)	
Male gender (%)	60	73	
Child-Pugh^	10 (7-13)	10 (7-12)	
Ascites (%)	83	85	
MELD score	25 (20-29)	18 (11-26)	
Previous decompensation (%)	90	85	
Total bilirubin, mg/dL	2.9 (1.9-4.7)	2.6 (1.5-5.8)	
INR	1.7 (1.4-1.8)	1.5 (1.3-1.8)	
Creatinine, mg/dL	1.8 (1.6-2.5)	0.8 (0.7-0.9)	
			p value
Platelet aggregation, Ω			
Collagen 1	12 (7-18)	16 (10-22)	0.03
Collagen 5	15 (11-20)	22 (15-27)	0.002
ADP	14 (9-18)	12 (9-18)	0.8
Platelet secretion, nmol			
Thrombin	0.28 (0.20-0.40)	0.57 (0.40-0.70)	<0.001
Collagen 1	0.12 (0.00-0.24)	0.34 (0.21-0.41)	<0.001
Collagen 5	0.22 (0.14-0.33)	0.48 (0.32-0.63)	<0.001
ADP	0.20 (0.10-0.27)	0.38 (0.26-0.61)	<0.001

Median values reported with 25th and 75th percentile values in parenthesis. ^Median (range). Abbreviations: MELD: Model For End Stage Liver Disease; ADP: adenosine diphosphate.

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OC-22

Factor VIII/Protein C and not ADAMTS13/VWF:Ag ratio is a prognostic risk factor for patients with cirrhosis and low MELD score

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Introduction: Hemostasis has been postulated as a mechanism of liver damage in cirrhosis. Low ADAMTS13/Von Willebrand Factor antigen (VWF:Ag) and high factor VIII/protein C ratio (FVIII/PC) mark platelet hyperaggregation (primary hemostasis) and hypercoagulation (secondary hemostasis), respectively. Aim: To explore the association of such parameters with the severity of the liver disease measured by Child-Pugh, MELD, MELD-Na and their prognostic role on clinical outcome.

Methods: We investigated 123 cirrhotics (age 62 ± 12, 58% in-hospital, Child-Pugh:8.2 ± 2.2, MELD:15.6 ± 7.7, MELD-Na:16.3 ± 6.6). The main etiologies were virus (40%), alcohol (30%), virus + alcohol (15%). Hemostatic parameters included: VWF:Ag, ADAMTS13 activity, the pro-(FVIII, FII) and anti-(antithrombin,

PC) coagulant factors. Their correlations with indexes of severity were tested by Pearson coefficient. Patients were followed up to 12 months. Decompensation requiring hospitalization, death or transplantation were retrospectively collected and presented as cumulative risk. The prognostic role of the hemostatic parameters was tested by logistic regression and expressed as risk of adverse outcome predicted by the model.

Results: A pro-hemostatic imbalance was resumed by ADAMTS13/VWF:Ag of 0.21 + /-0.14 and FVIII/PC of 6.0 + /-6.5. Hemostatic parameters correlated with all the markers of cirrhosis severity ($p < 0.05$). Adverse outcomes occurred in 74 patients: 35(28%) decompensations, 23(19%) deaths, 16(13%) transplantations. MELD-Na had the highest prognostic accuracy (AUC = 0.809), compared to MELD (AUC = 0.774) and Child-Pugh (AUC = 0.771). FVIII/PC was the only variable associated with the composite clinical end-point at logistic regression (OR:1.215;95%-CI:1.05-1.38;p = 0.006). A prognostic model including MELD-Na and FVIII/PC led to a slight increase of the AUC vs MELD-Na alone (AUC 0.815 vs 0.809). A FVIII/PC≥2.78 (the lowest tertile in our series) identified patients at higher risk of adverse outcome, primarily in patients with MELD-Na < 15 (45% vs 27%) compared to MELD-Na≥15 (83% vs 75%).

Conclusions: Markers of primary and secondary hemostasis correlate with common indexes of liver disease severity. FVIII/PC ratio may have a relevant prognostic role in patients with MELD-Na < 15.

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OC-23

Effective albumin concentration and albumin function improve after long-term albumin therapy in patients with decompensated cirrhosis

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Background/Aims: Human albumin (HA) carries several functions supporting its pleiotropic activity. The ANSWER trial[1] showed that long-term HA administration in cirrhosis with uncomplicated ascites improves survival and reduces the incidence of complications. Such benefits were associated to an increase in serum albumin concentration (SA). This ancillary study to the ANSWER trial aimed to assess whether long-term HA administration has any effect on structure and function of the circulating HA pool and on the pro-inflammatory state that characterized decompensated cirrhosis.

Methods: Patients from the ANSWER cohort with available plasma samples at baseline and 6-8 months after randomization were included. HA structural microheterogeneity was evaluated by liquid chromatography/electrospray ionization mass spectrometry. Effective albumin concentration was defined as the amount of SA with fully preserved molecular structure. Binding efficiency (BE) and detoxification efficiency (DTE) were determined by electron paramagnetic resonance spectroscopy. A panel of circulating cytokines was measured by Luminex assay.

Results: Twenty-seven patients from the standard medical treatment (SMT) and 31 from the SMT + HA arms were included. Baseline characteristics were comparable between the two groups. SA increased after 6-8 months of HA treatment (from 3.1 [2.8-3.5] to 4.1 [3.8-4.4] g/dL, $p < 0.001$) but not in the SMT arm (from 3.0 [2.8-3.4] to 3.1 [2.6-3.8] g/dL, $p = 0.846$). Significant rises of the effective albumin concentration (from 0.77 [0.55-1.05] to 0.93 [0.65-1.26] g/dL, $p = 0.015$) as well as both BE (+16.8 [3.7-31.12] %, $p < 0.001$) and DTE (+15.4 [5.5-41.7] %, $p < 0.001$) were only found in the SMT + HA arm. Circulating pro-inflammatory cytokines, such as interleukin (IL)-6 and IL-33, were reduced only in patients from the SMT + HA arm.

Conclusions: Long-term HA treatment increases the amount of the effective albumin concentration, corresponding to the fraction of the circulating albumin pool with a fully preserved structure. This finding was associated with an improvement of the albumin binding/detoxification dysfunction and systemic inflammation. [1]Lancet2018;391:2417-29.

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OC-24

Oncostatin M, a novel profibrogenic mediator, is involved in the progression non-alcoholic fatty liver disease and stimulates migration of myofibroblasts

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Introduction Hepatic myofibroblasts (MFs) can originate from hepatic stellate cells, portal fibroblasts or bone marrow-derived mesenchymal stem cells and can migrate towards the site of

injury by aligning with nascent and established fibrotic septa in response to several molecules. Oncostatin M (OSM) is known to orchestrate hypoxia-modulated hepatic processes involving the hypoxia-inducible factor 1 (HIF-1) and has been recently proposed to act, although indirectly, as a pro-fibrogenic mediator.

Aims This study has been designed to further investigate the possible pro-fibrogenic action of OSM in relation to experimental and human NAFLD/NASH and in order to elucidate whether this cytokine may also act directly on LX2 cells (as a model of activated human MFs) by modulating and sustaining selected pro-fibrogenic phenotypic responses.

Materials and Methods In vivo and in vitro experiments were performed in order to analyze the expression of OSM and related receptor (OSMR) in two different murine model of progressive NAFLD/NASH (MCD and CDAA diets) and in human NASH patients. Moreover, the action of recombinant human OSM was tested on phenotypic responses of human LX2 cells.

Results OSM and OSMR expression increases in two murine models of NAFLD as well as in patients with NASH. OSM stimulates migration in LX2 cells involving an early intracellular ROS generation and activation of Ras/Erk, JNK1/2, PI3K/Akt as well as of STAT1/STAT3 pathways and involvement of HIF-1α; apocynin inhibited OSM-dependent migration, suggesting NADPH-oxidase as a major source of intracellular ROS; OSM-dependent motogenic action is exerted through a biphasic mechanism requiring early ROS generation and late HIF1-dependent expression and VEGF release.

Conclusions OSM can be considered as a mediator potentially able to trigger and/or sustain MFs activation and likely the fibrogenic progression of NAFLD.

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OC-25

Prognostication of hepatocellular carcinoma under sorafenib: external validation of the PROSASH-II model

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Introduction: Prognostic classifications for patients treated with sorafenib for hepatocellular carcinoma (HCC) are a tool to facilitate stratification in trials and inform clinical decision making. Labeur and colleagues developed the PROSASH-II model, which performed better than others in predicting the overall survival (OS) of sorafenib-treated patients. As this study included a 4-center training set and a single-center validation, further validation in multicenter cohorts are needed to understand the full potential of PROSASH-II. Aim of our study was to verify the stratification performance of PROSASH-II, comparing it with other existing prognostic models.

Materials and Methods: We analyzed a large retrospective-prospective database gathering data of 552 patients from 7 Italian centres, who were prescribed with sorafenib between 2008 (date of licence in Italy) and 2017. The PROSASH –II score was calculated as proposed by its creators [(-0.0337 x albumin in g/l) + (0.315 x Ln(bilirubin in μmol/l) + (0.295 x macrovascular invasion, where 0 = No and 1 = Yes) + (0.181 x extrahepatic spread: 0 = No, 1 = Yes) + (0.0336 x Largest tumour size in cm) + (0.0703 x Ln(AFP U/L)). It was categorized as follows: ≤-0.0760 (risk group 1), > -0.0760 to ≤0.355 (risk group 2), > 0.355 to ≤0.858 (risk group 3) and > 0.858 (risk group 4). PROSASH-II performance was compared with those of BCLC, ALBI, HAP and SAP score.

Results: The PROSASH-II stratification significantly discriminated patients, with a median OS of 21.5, 15.3, 9.3 and 5.0 months respectively for risk group 1, 2, 3, and 4. Using risk group 1 as a reference, hazard ratio was 1.52, 2.04, and 3.0 for risk groups 2,3, and 4, respectively. PROSASH-II showed improved discrimination (C-index 0.61) compared with existing prognostic scores (C-index≤0.57).

Conclusion: Our results validate the PROSASH-II as an effective prognostic classification model in a large Italian population of sorafenib-treated patients. We also confirm a slightly better performance of the PROSASH-II compared with the HAP and SAP scores.

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OC-26

Diagnostic and prognostic role of presepsin in patients with cirrhosis and bacterial infection

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Introduction Diagnosis of bacterial infection (BI) in cirrhosis is often difficult due to the low accuracy of the available biomarkers, which poorly correlate with prognosis. Presepsin (PSP), a 13kDa molecule produced by monocytes phagocytic activity, has been recently introduced as a potential biomarker for early diagnosis of BI.

Aim To prospectively evaluate PSP levels in cirrhotics with and without BI, its accuracy for the early diagnosis of BI in comparison with other commonly used biomarkers (C-reactive protein (CRP), procalcitonin) and its prognostic role in terms of 28-d mortality.

Materials and Methods All cirrhotic patients admitted at Multivisceral Transplant Unit, Padua University Hospital were consecutively enrolled between 3.2016-6.2019. For each patient, demographic and clinical features, and presence of BI at admission were evaluated. PSP was measured by Pathfast technique

(Chemiluminescent enzyme immune-assay); its accuracy for early diagnosis of BI was evaluated by ROC curve, in comparison with that of commonly used biomarkers. A multivariable analysis was performed to evaluate predictors of 28-d mortality.

Results 278 cirrhotic patients (M/F 179/99, mean age 56 ± 11 years) for a total of 448 hospitalizations were analyzed. Prevalence of BI was 28.3%. Mean ± SD PSP value WAS significantly higher in patients with BI than in patients without (2486 ± 4068 vs. 1277 ± 2399 pg/mL;$p = .001$). Sensitivity and specificity of PSP for diagnosis of BI was 0.66 (95%CI 0.57-0.74) and 0.63 (95%CI 0.57-0.68), respectively. The accuracy was lower than CRP (AUC-ROC 0.68 vs. 0.77;$p = 0.002$) but similar to procalcitonin (p = ns). Considering the whole cohort, age, ACLF at presentation, PSP (HR 2.37; 95%CI 1.29-4.34), but not CRP nor BI, were independent predictors of 28-d mortality.

Conclusions PSP showed a suboptimal accuracy for the early diagnosis of BI in hospitalized cirrhotic patients but it was an independent predictor of short-term mortality, likely reflecting the importance of pro-inflammatory state as prognostic marker in cirrhosis.

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OC-27

Sarco-model, a novel score to better predict the risk of death in cirrhotic patients awaiting liver transplantation

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Introduction: Sarcopenia has been recently proposed as a useful tool for predicting death in cirrhotic patients waiting for liver transplantation (LT). However, the creation of a model integrating sarcopenia with the conventional scoring systems is needed, with the intent to identify patients not efficaciously captured by these allocation models.

Aim: The study aimed at developing a score integrating sarcopenia and MELDNA able to predict the risk of death in cirrhotic patients enlisted for LT.

Material and methods: 1,082 patients enlisted in the Roman Liver Transplant Consortium (Training Set; $n = 855$), and in Modena University (Validation Set; $n = 232$) during the period Jan2013-Dec2018 were investigated. Exclusion criteria were: a) age < 18 years, b) non-cirrhotic liver disease. At-listing cross-sectional psoas muscle area at the level of L3 was used for evaluating the sarcopenic status.

Results: Sarco-Model was built using a competing-risk analysis of the cause-specific hazards, being based on the equation: 12*((0.069*MELDNA) + (0.027*age) + (0.056*BMI)-(0.039*psoas sum cm^2)-(0.561*albumin mg/dL)). At external validation, Sarco-Model showed an $AUC = 0.70$ ($P = 0.001$) respect to MELD ($AUC = 0.59$; $P = 0.1$) and MELDNA ($AUC = 0.68$; $P = 0.002$). When investigated only in the patients with MELDNA score ≤19, Sarco-Model showed a markedly superior diagnostic ability ($AUC = 0.80$; $P < 0.0001$). The Sarco-Model score ranged 6-40 like the MELDNA, consenting to calculate how many additive points should be added to the patient with the intent to "balance" the risk of death on the list.

Conclusion: Sarco-Model should represent a useful predictor of mortality, mainly in enlisted patients in which the mortality risk is underestimated by MELD (i.e., severe ascites). Sarco-Model can identify the "high-risk" patients not conventionally captured by the MELD determinants, therefore being a useful tool for reducing the waiting list mortality and for improving the allocation process.

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OC-28

Recent trends and intention-to-treat survival of liver transplantation for nonalcoholic steatohepatitis: an Italian liver transplant registry study

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Introduction and Aim: A recent European Liver Transplant registry study showed that the proportion of liver transplants performed for nonalcoholic steatohepatitis (NASH) in Europe has increased from 2002 through 2016, and that the post-transplant outcome in patients with NASH is comparable to that of other disease indications. There are few data on recent trends in waiting list inscriptions/dynamics, and on intention-to-treat transplant survival of NASH patients, however.

Methods: We analysed data from adult patients listed for primary LT for chronic end-stage liver disease between January 2012 and December 2018 using the Italian Liver Transplant Registry database. We evaluated annual trends of waiting list inscriptions according to main liver disease aetiologies. Moreover, we compared data of patients with NASH with that of other aetiologies in terms of patient characteristics and intention-to-treat survival outcome.

Results: Among 8,567 adults listed for first LT in Italy in the study period, 494 (5.8%) had NASH. The proportion of NASH patients significantly increased from 3.6% in 2012, to 8.9% in 2018 (p < 0.001). The proportion of patients with alcohol related–liver disease similarly increased from 11.6% in 2012, to 19.2% in 2018 ($p < 0.001$). Conversely, the proportion of hepatitis C patients significantly decreased from 46.8% to 33.5% ($p < 0.001$), while that of hepatitis B patients remained stable during the study period around 13%. NASH patients were older than no-NASH patients (59 vs.

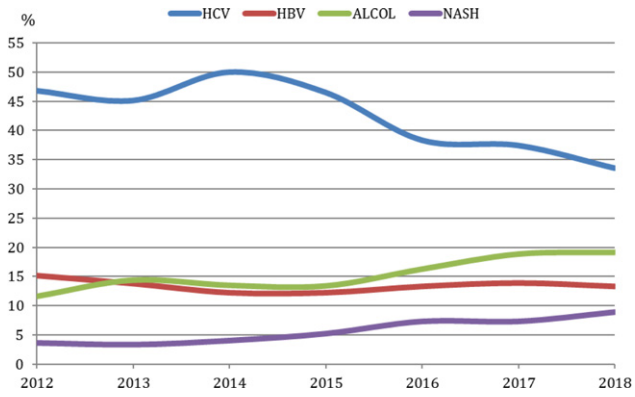

Figure 1. Recent trends of waiting list inscriptions for LT in Italy according to main liver disease etiologies.

55 years, $p < 0.001$), and more often had associated hepatocellular carcinoma (51% vs. 45%, $p = 0.005$). The 1-, 3- and 5-year intention-to-treat survival rates were 81%, 70% and 65% in the no-NASH group vs. 74%, 64% and 56% in the NASH group, pâ€¯= â€¯0.004. The presence of NASH was a significant risk factor for death (hazard ratio [HR] 1.30; 95% CI 1.07 - 1.56) also at multivariable Cox survival analysis. Figure 1

Conclusion: The proportion of NASH patients listed for LT in Italy has significantly increased from 2012 to 2018. This preliminary analysis suggests a significant negative impact of NASH aetiology on intention-to-treat transplant survival.

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OC-29

A novel nomogram based on liver stiffness to predict the comprehensive complication index after liver resection in patients with hepatocellular carcinoma

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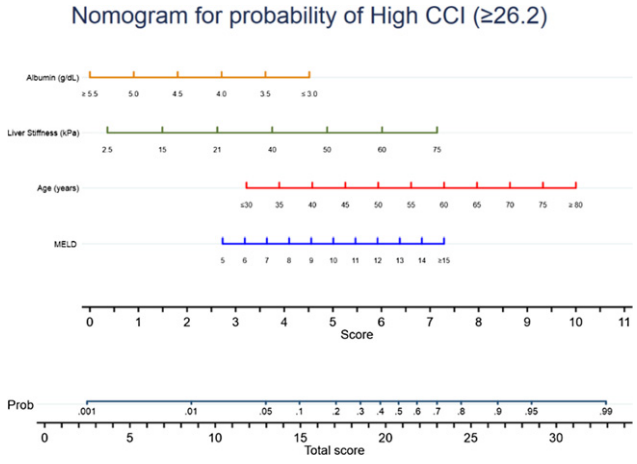
Introduction: Liver stiffness measurement (LSM) assessed by transient elastography (FibroScan®) has been demonstrated to predict post-hepatectomy liver failure (PHLF) in patients undergoing hepatic resection for hepatocellular carcinoma (HCC). However, other complications, besides PHLF, can be related to the underlying grade of liver fibrosis. Aim: This study aimed to identify predictors of postoperative complications calculated by the comprehensive complication index (CCI) and to build and develop a novel nomogram able to identify patients at risk of developing severe postoperative complications.

Material and Methods: Data of patients treated by hepatectomy for HCC between 2006 and 2016 at two referral centres, were retrospectively reviewed. All surgical complications were recorded and scored using the CCI, ranging from 0 (uneventful course) to 100 (death). A CCI ≥26.2 was used as a threshold to define patients having severe complications.

Results: During the study period, 471 patients underwent hepatic resection for HCC. Among them, 50 patients (10.6%) had a CCI≥26.2. Age, MELD score and LSM values together with serum albumin were independent predictors of high CCI. The nomogram built on these variables was internally validated and showed good performance (C-statistic = 0.797). A regression equation to predict the CCI was also established by multiple linear regression analysis: [LSM (kPa) × 0.254] + [age(years) × 0.118] + [MELD score(pt.) × 1.050]-[albumin (g/dL) × 2.395]-3.639.

Conclusion: This novel nomogram, combining LSM values, age and liver function tests provided an excellent preoperative prediction of high CCI in patients with resectable HCC. This predictive model could be used as a reference for clinicians and surgeons to help them in clinical decision-making. Figure:



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OC-30

Liver transplantation in patients with ACLF. Preliminary experience of 6 Italian centres

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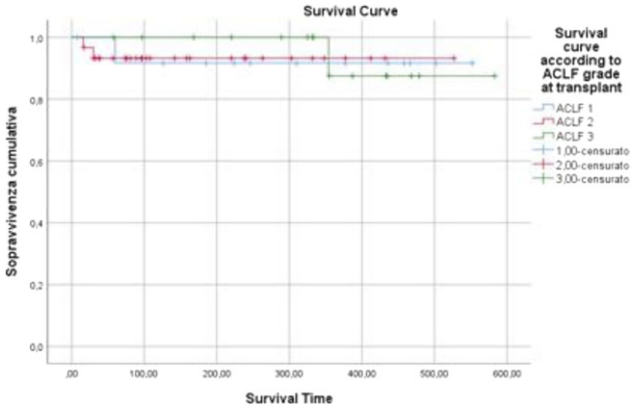
Background Liver transplantation (LT) for patients with acute on chronic liver failure (ACLF) is progressively expanding. We here report the results of LT in patients with ACLF in Italy.

Materials and Methods 73 consecutive patients with ACLF listed in 6 different Italian centers (Bergamo, Bologna, Niguarda, Padua, Palermo, Turin) from January 2018 to June 2019 were retrospectively analyzed.

Results A total number of 59 patients was transplanted for ACLF during the study period. Other 14 patients with ACLF died during the waiting list period for sepsis. Of 59 patients receiving a LT, 13 patients had ACLF grade 1 (22%), 30 ACLF 2 (50.8%) and 16 ACLF 3 (27.2%). The most common precipitating factor was bacterial infection (59%), followed by severe acute alcoholic hepatitis (19%), gastrointestinal hypertensive bleeding (7%); the precipitating factor remained unknown in 15%. Patients with ACLF grade 2 and 3 received a LT after a median time of 6 days compared to 26 days of patients with ACLF 1 ($p = 0.053$). The 1-year overall survival was 90%, independently from ACLF grade at LT (see Figure 1). However, 69% of patients with ACLF grade 3 developed a major complication immediately after LT compared to around 30% of patients with ACLF grade 1 and grade 2 ($p = 0.063$). The most common complications were prolonged mechanical ventilation (12 patients), bacterial or fungal infections (9 patients), continuous renal replacement therapy (8 patients) and surgical complications (4 patients). The median ICU and hospital stays were 6 days (1 - 88) and 26 days (8 - 153) respectively, without any difference among ACLF categories.

Conclusion This preliminary Italian experience shows that the survival of patients transplanted with ACLF is extremely favourable independently of ACLF grade. A rapid decision-making process is needed because of the short “transplantation window”.



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T-01

A genetic risk score predicts de novo hepatocellular carcinoma in hepatits c cirrhotic patients treated with direct-acting antivirals

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Background: Several single nucleotide polymorphisms (SNPs) have been associated with hepatocellular carcinoma (HCC) in hepatitis C virus (HCV) cirrhotics, however their role in patients cured by direct-acting antivirals (DAA) is still undefined.

Aim: We assessed the association between a genetic risk score (GRS) combining 4 SNPs (PNPLA3, MBOAT7, TM6SF2, GCKR) and HCC in DAA-treated patients.

Methods: Consecutive HCV cirrhotics receiving DAA in a single Center were genotyped. Cirrhosis was defined histologically or non-invasively (Liver stiffness measurement ≥12 kPa). HCC was diagnosed according to international recommendations. GRS was calculated as already described.

Results: 509 patients were analyzed: median age 64 (28-87) years, 58% males, LSM 19.4 (12.0-75.0) kPa, 87% Child-Pugh score A. Genotypes distribution was PNPLA3 CC (46%), CG/GG (54%); MBOAT7 CC (29%), CT/TT (71%); TM6SF2 CC (91%), CT/TT (9%); GCKR CC (26%), CT/TT (74%). Overall, median GRS score was 0.3 (0-1.1). Patients' clinical features were similar across SNPs genotypes. During a median follow-up of 43 (3-57) months after DAA start, 36/452 (8%) patients developed de novo HCC, with a 4-year cumulative probability of 9% (95% CI 7-12%). Male sex (Hazard Ratio [HR] 2.54, p = 0.02), diabetes (HR 2.39, p = 0.01), albumin (HR 0.35, p = 0.001) and GRS score >0.6 (HR 2.30, p = 0.04) were independent predictors of de novo HCC. Indeed, 4-year cumulative rates of HCC resulted 6% *vs.* 12% in males *vs.* females (p = 0.01); 17% *vs.* 7% in diabetic *vs.* non-diabetic (p = 0.001); 21% *vs.* 7% in patients with albumin ≤ or >3.5 g/dl (p < 0.001); 16% *vs.* 7% in patients with GRS > or ≤0.6 (p = 0.01) and 20% *vs.* 5% in patients with or without two different risk factors, respectively (p < 0.0001).

Conclusions: In a large cohort of HCV cirrhotic patients treated with DAA, GRS was associated with de novo HCC. Combination of clinical and genetic predictors could allow better individual HCC risk stratification.

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T-02

Impact of HBV infection in HCV/HBV coinfected patients treated with DAAs IN Northern Italy

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Background and AIMS: Several small series have described the incidence of HBV reactivation during direct -acting antivirals (DAAS), so far. However, many key issues remain unresolved. Aims of the present study was to evaluate both the incidence and the clinical impact of HBV reactivation in a large cohort of HCVHBV co-infected- patients treated in North Italy Methods: Between January-2015 and December-2018 data from a common web based program (NAVIGATORE), 16.161 patients treated with DAAs in Veneto and Lombardia were collected. After the first data extraction, centers were asked to provide further details on both the clinical course and outcome of HBV reactivation.

Results: Overall, the prevalence of HBV/HCV co-infection was - 1.39% (226/16161). HCV/HBV co-infection was more frequent in male ($p < 0.01$), and in HIV positive vs HIV negative patients (28.3% vs 12.7%, $p < 0.01$). HBV/HCV co-infected patients had more severe liver disease compared with HCV mono-infected (F3-F4 65.9% vs 57.1%, $p < 0.01$). HCV/HBV co-infected patients were comparable with HCV mono-infected in term of HCV baseline viral load, and SVR 12 (96.0% vs 96.6%). The incidence of HCC during follow-up was more frequent in HBV/HCV co-infected than in HCV mono-infected patients (2.2% vs 0.8%, $p < 0.05$). HBV-DNA was serially monitored during and after treatment with DAAS in 160 (70%) patients. HBV reactivation (increment of HBV-DNA > 2 log from baseline) was observed in 9 cases (5.6%). None of the patients in treatment with NUCs (as part of treatment of HIV infection or those treated prophylactically with Tenofovir, Entecavir or Lamivudine) showed HBV reactivation during the follow-up period. Only one of the the nine cases which reactivated HBV showed transient mild hepatitis (ALT >2 normal value). In additional 2 cases HBV reactivation was observed after the withdrawal of NUCs at the end of DAAs treatment (lamivudine) and after 12 weeks from DAAs suspension (Entecavir).

Conclusion: In a large series from Northern Italy HBV reactivation after DAAs in HCV/HBV co-infected patients appears to be lower than previously reported- Prophylaxis or therapy with NUCs can avoid reactivation. However, the timing of withdrawal of NUCs prophylaxis remains to be clarified. Moreover, HBV positive patients must be closely monitored for the increased residual risk of HCC, after HCV eradicatio

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T-03

The HSD17B13 rs6834314 variant is associated with liver stiffness measurement in untreated HCV-3 patients with cirrhosis

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Introduction: Recently, the single-nucleotide polymorphism (SNP) rs6834314 near to the 17-beta hydroxysteroid dehydrogenase 13 (HSD17B13) gene has been associated with NAFLD histology. Particularly, the minor G allele of the rs6834314 variant correlated with increased steatosis but decreased inflammation.

Aim: To analyzed the correlation between the rs6834314 genotypes and liver stiffness measurement (LSM) in chronic hepatitis C (CHC) patients.

Materials and Methods: 410 Caucasian CHC cirrhotic patients were retrospectively enrolled in a single Hepatology centre: median age 64 (28-87) years, 57% males, BMI 25 (16-40) Kg/m^2, ALT 75 (10-770) U/L, LSM 17.5 (12-75) kPa, and 19% with diabetes. HSD17B13 rs6834314 was analyzed by endpoint genotyping assay.

Results: HSD17B13 rs6834314 genotype was AA in 251 (61%), AG in 143 (35%) and GG in 16 (4%). Overall, the rs6834314 variant showed no association with median baseline LSM values: 17.8 (95%CI 17,2-19,1) kPa in AA *vs* 17.0 (95%CI 15,4-18,3) kPa in AG/GG, ($p = 0.24$). Stratifying patients according to hepatitis C virus (HCV)-genotypes, we found that in HCV-3 patients ($n = 41$) median LSM values significantly differed according to rs684314 genotypes: 25.8 (95%CI 18.5-28.3) kPa in AA *vs* 15.4 (95%CI 13.1-20.3) kPa in AG/GG ($p = 0.014$). Moreover, in the HCV-3 subgroup the prevalence of patients with increased risk of significant portal hypertension (i.e. those with LSM $\geq$25 kPa) was higher in AA than in AG/GG carriers (56% *vs.* 17%, $p = 0.01$). Multivariate binary logistic regression analysis confirmed that in HCV-3 cirrhotics, the minor G allele of rs6834314 reduces the risk of exceed the LSM 25 kPa cut-off more than nine fold (OR 0.11, 95%CI 0.02-0.62, $p = 0.013$) independently of gender, BMI, ALT, diabetes and PNPLA3 rs738409 polymorphism.

Conclusion: In untreated HCV-3 cirrhotics, the rs6834314 variant was associated with lower LSM values suggesting that the

correlation between HSD17B13 SNP and liver disease severity might be triggered mainly by virus-mediated steatosis.

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T-04

C-THRU: Tracking of HCV patients lost to follow up-a Retrospective database review study

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Background and aims: In Sicily over 30.000 people live with chronic C virus hepatitis (HCV).Treatment of all people with chronic HCV infection is a primary goal of all national healthcare systems for eradicating the infection before 2030.Despite the fact that Direct Antiviral Drugs (DAAs) achieve 95% SVR, there are still many patients who are lost to follow-up (LTFU) and there is a need to characterize them to develop measures or programs to link them back to care. The Sicily Region has activated a Network for the management of HCV infection through a web-oriented model (RESIST-HCV). This is a retrospective cohort study implemented through the regional HCV database. The primary objective is to assess the number/proportion of diagnosed chronic hepatitis C (CHC) patients who are not linked to care. The secondary objective is to assess the characteristics of the CHC patients who are not linked to care at last documented visit.

Methods: The web-based RESIST-HCV platform includes 30 centers that manage the diagnosis, record antiviral therapies, and verify virologic and clinical outcomes of HCV liver disease. Our study evaluated retrospectively the demographic and virologic characteristics, the stage of liver disease and the co-morbidities of the patients with a diagnosis of CHC that are included in the RESIST-HCV and did not received treatment with DAAs during the study period March 2015-April 2018. Lack of linkage to care was defined as no follow-up visits 12 months or longer following CHC diagnosis. Descriptive statistics were conducted to examine patient characteristics.

Results: Among 15.270 patients included in RESIST-HCV from March 2015 to April 2018, 12.959 (84,7%) already received therapy, while 2.311 (15,3%) had not yet received therapy and were lost to follow-up. Patients LTFU were more frequently male (59,3%), bornbefore1960 (60,2%) and infected with genotypes 1b (60,2%). Liver fibrosis was evaluated in 12.218/15.270 patients (80%) by Fibroscan. In patients LTFU the stiffness value was >10 kPa, 7-10 kPa and < 7 kPa in 36,8%, 25,6% and 36,7%, respectively. Diabetes and arterial hypertension were present in 17,3% and 26,3% of patients LTFU, respectively. Patients LTFU who received a liver transplant were 0,2%.

Conclusions: The proportion of diagnosed CHC patients LTFU was 15,3%. An important proportion of patients was male, born before 1960, infected by HCV genotype 1b and was affected by an advanced liver disease (stiffness value >10 kPa), having an urgent need for HCV treatment. Thus, we suggest to plan a more active and close follow-up for monitoring patients with those characteristics.

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T-05

Quantitative HBeAg varies across the different phases of HBV infection, and can predict treatment outcome in the setting of HBV-reactivation driven by iatrogenic immunosuppression

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Introduction and aim: Qualitative HBeAg is a marker of active HBV-replication and HBeAg-loss is an important clinical/therapeutic end-point. Here, we quantify HBeAg-levels in different phases of HBV-infection, their correlation with virological/biochemical markers and their role in predicting virological-response to anti-HBV therapy.

Methods: This study includes 86 eAg+patients: 20 with acute infection (AI) (HBcIgM+, median[IQR]HBV-DNA:8.3[7.9-8.7]logIU/mL, ALT:1556[142-2027]U/L), 14 with HBeAg+chronic infection (CI) (median[IQR]HBV-DNA:8.1[4.7-8.5]logIU/mL, ALT< 40U/L), 23 with HBeAg+chronic hepatitis (CH) (median[IQR]HBV-DNA:8[6.8-8.5]logIU/mL, ALT:85[62-179]U/L) and 29 patients with immunosuppression-driven HBV-reactivation (HBV-R) (median[IQR]HBV-DNA:6.8[5.5-8]logIU/mL, ALT:143[40-528]U/L, pre-reactivation status HBcAb+/HBsAg-). 15/29 patients with HBV-R were monitored for >12months after starting TDF/ETV (median[min-max] months of follow-up:21[12-54]). Quantitative HBeAg (qHBeAg) is assessed by DiaSorin-LIAISON assay. Association of qHBeAg at HBV-R with HBeAg-loss achievement after starting TDF/ETV is assessed by Fisher-Exact test.

Results: qHBeAg is higher in patients with HBV-R and AI (median[IQR]:930[206-1945] and 754[210-3379]PEIU/mL) and decreases in patients with CI and CH (median[IQR]:655[0.9-1773] and 412[17-1850]). qHBeAg positively correlates with qHBsAg in all subsets of patients (Rho = 0.61 for HBV-R, Rho = 0.78 for AI, Rho = 0.71 for CI and Rho = 0.75 for CH, P = < 0.001-0.003) and with HBV-DNA in CH (Rho = 0.59, P = 0.005). Moreover, qHBeAg negatively correlates with ALT in AI and CH (Rho = -0.59, P = 0.035; Rho = -0.42, P = 0.044), reflecting a modulation in HBeAg-production by immune-response. Focusing on 15 patients with HBV-R starting anti-HBV therapy for >12 months, ALT-normalization is achieved in 93% of pts while virological-suppression and HBeAg-loss in 60% and 53.3%, respectively. The combination of qHBeAg >2000PEIU/mL+qHBsAg >52000IU/mL at HBV-R is the only factor predicting no HBeAg-loss dur-

ing anti-HBV therapy (HBeAg-loss in 0% patients with qHBeAg >2000PEIU/mL + qHBsAg >52000IU/mL vs 72.7% patients without this combination, P = 0.01, result not significant considering qHBeAg and qHBsAg separately).

Conclusions: HBeAg-levels differ during the natural history of HBV-infection and according to the extent of immunological pressure. In the setting of HBV-reactivation, HBeAg-levels can help in predicting virological-response to anti-HBV therapy under iatrogenic immunosuppression.

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T-06

Long term renal safety of HCV direct acting antivirals in HCV positive kidney transplant recipients

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Introduction and aim: General transplant outcome of HCV kidney transplant recipients (KTRs) is worse than that of non-infected one. Direct acting antivirals (DAAs) resulted efficacious also in KTRs. Drug interactions between Calcineurin inhibitors (CNI) and DAAs had been described. Immunological rejection is the Achilles heel of kidney transplantation. Thus, the impact of DAAs on CNI levels and the effect on renal function need to be evaluated.

Patients and methods: Thirty-five HCV-RNA + KTRs were treated for 12 weeks with DAAs after median time from KT of 96 months. Median age: 57 yrs; 54% males. Overall, 57% of them had stage 3 CKD and median liver stiffness value was 6.6 KpA. Eleven patients had ultrasound signs of advanced liver fibrosis. Genotype 1 was detected in 68.5% of cases. CNI inhibitor: 57% TAC, 22% CsA, 21% mTOR. SOF-based regimen was used in 93%. Trough levels (TL) of IS and eGFR were collected at baseline, end of treatment and 12, 24 and 48 weeks after therapy. In all patient trough levels (TL) of IS and eGFR were collected at baseline, at the end of treatment and 12, 24 and 48 weeks after therapy. Proteinuria, glycaemia, cholesterol and platelets were assessed before and after treatment.

Results: Overall SVR was 97,1%. without difference between patients with mild vs those with advanced fibrosis (fibrosis F0-F2 vs F3-F4 100% and 91% respectively; (p = 0.73). Bonferroni's post-hoc analysis showed a significant decline in TAC levels between baseline and 12 months (6.85 vs 5.48 ng/ml respectively; (p = 0,004). Uptitration of CNI was needed in 22.8% of patients. Notably, neither decline in eGFR nor impairment in 24/hr proteinuria was noted during 12 months f-up (eGFR: 60.6 vs 57,7 ml/min; 0 = 0,28).

Conclusions: Eradication of HCV in KTRs is a feasible option. The significant decline in Tac concentrations is not associated with kidney graft dysfunction. DAA in KTRs must be managed under strict collaboration between nephrologists and hepatologist.

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T-07

Long-term liver fibrosis and outcomes in HCV-infected solid organ transplant recipients after DAAs-induced viral eradication

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Background and Aims: Hepatitis C virus (HCV) infection is associated with faster liver fibrosis progression and higher mortality in solid organ transplant (SOT) recipients compared to the non-transplanted population. Excellent safety and efficacy of direct acting antivirals (DAAs) after SOT were reported worldwide. Our aim was to evaluate long-term impact of viral eradication on fibrosis progression and patient survival after SOT.

Methods: All consecutive HCV-infected patients treated with DAAs after SOT in a single transplant center between 08-2014 and 01-2019, included in the Veneto-NAVIGATORE platform or treated within the Compassionate Use Program, were considered. Clinical and virological features were registered at baseline, during treatment and up to 3-years after end of treatment (EoT). Liver fibrosis was assessed by liver biopsy and/or transient elastography (TE) at baseline and during the follow-up.

Results: 110 patients treated with DAAs after SOT (liver = 93, kidney = 14, heart = 1, heart-kidney = 1, liver-kidney = 1) were included. 55% (n = 61) showed F3-F4 liver fibrosis at baseline. Median follow-up after DAAs was 47 months (IQR 31-54). Sustained virological response rate (SVR12) was 80% and 96% after retreatment. Patients with SVR12 showed a significant improvement in bilirubin (p< 0.001), ALT (p< 0.001) and platelet count (p = 0.006) from baseline to SVR48. During the follow-up liver fibrosis measured by TE and APRI improved in patients who achieved SVR12 (p< 0.001, p< 0.001); this result was confirmed in cirrhotic patients (p = 0.001, p< 0.001). Patient survival at 12, 24 and 36 months after DAAs was 96%, 91% and 86%, respectively. Patients with F3-4 pre-treatment fibrosis who achieved SVR had similar survival to those with F0-2 (p = 0.087). Patients with F3-4 pre-treatment fibrosis who relapsed showed lower survival compared to other groups (p < 0.001).

Conclusions: Long-term follow-up data demonstrated that DAAs-induced HCV eradication after SOT was associated with improved hepatic function, liver fibrosis and post-SOT survival, even in patients with F3-4 pre-treatment fibrosis.

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T-08

Diabetes and DAAs

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Background and aims: HCV infection is associated with an increased risk of diabetes. To date, few dates are available regarding the metabolic profile after HCV clearance with direct acting antiviral agents (DAAs) in diabetic patients.

Method: 413 SVR patients after 12 weeks of DAAs were enrolled and were followed for a mean period of 10.6 ± 2.8 months.

Results: 12,6% had type 2 diabetes (34 patients were F4 according to METAVIR with FibroScan) while 87,4% had no type 2 diabetes (132 patients F4). Diabetic patients had a higher CV risk assessed with SCORE system compared to non-diabetics; in particular 67% F4 diabetic patients had a previous CV event. At baseline, F1-F3 diabetic patients showed a better lipid profile with significant lower values of total cholesterol (TC) (p = 0.006) and LDL (p = 0.022), due to a higher use of statins (p = 0.012); no significant differences were documented in F4 diabetics. At T1, in the diabetic a significant improvement of transaminases (p = 0.001), albumin (p = 0.014) and liver stiffness (9.3 to 7.4 kPa, p = 0.068) was found both in F1-F3 and in F4 (p < 0.001 and p = 0.028, respectively); in F4 diabetic patients a significant increase of TC (at T1 157 ± 27, p = 0.018) and LDL (at T1 94 ± 30, p = 0.017) was found without modifications in the glucose profile. Also, in the non-diabetic SVR an improvement in transaminases, albumin, GGT and liver stiffness (all p < 0.001) was documented. Regarding the lipid profile a significant increase in TC (p < 0.001) and LDL (p < 0.001) values was found in F1-F3; no significant differences were shown in F4.

Conclusion: After DAAs, in SVR patients an improvement in liver profile was observed, while a slightly worsening in lipid (especially for LDL) was found in F4 diabetic and F1-F3 no diabetics. Our results suggested an attention on CV risk factors in all patients in particular in F4 diabetics.

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T-09

The combined usage of accurate virological and serological HBV markers can help to identify HBsAg-negative/anti-HBc-positive patients at higher risk of HBV-reactivation and to optimize prophylaxis duration in oncohematological setting

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Introduction: Prevention of HBV-reactivation (HBV-R) in patients undergoing immunosuppressive therapy is still challenging. We investigate the role of HBV markers in predicting HBV-R in HBsAg-negative/anti-HBc-positive oncohematological patients.

Materials & Methods: HBV-R rate is estimated in 107 HBsAg-negative/anti-HBc-positive patients (42 receiving rituximab [RTX], 40 hematopoietic stem-cell transplantation [HSCT], 25 other chemotherapeutics [chemo]). All patients received lamivudine-prophylaxis for >18months after stopping immunosuppression and were prospectively monitored every 3-6 months during/after prophylaxis completion. The role of HBV markers in predicting HBV-R is evaluated by testing 629 serum samples for highly-sensitive-HBsAg, FujiRebio (HS-HBs; lower limit of quantification[LLOQ]: 5 vs 50mIU/ml of routinely-used assays), HBV-DNA (Roche, LLOQ: 20IU/ml), quantitative anti-HBs and anti-HBc (FujiRebio, LLOQ: 1COI). HBV-R is defined as HBV-DNA >20IU/ml.

Results: At baseline, all patients have undetectable HBV-DNA and 67.3% is anti-HBs positive (median[IQR]: 152[47-976]mIU/ml]. HBV-R occurs in 13/107 patients with the highest 5-year cumulative reactivation-rate in HSCT (38% vs 21%[RTX] and 10%[other chemo]). At HBV-R, median(IQR) HBV-DNA is 42(23-5831)IU/ml and ALT >ULN for 46% (median[IQR]: 95[81-986]U/L). Among HBV-R cases, 5 occurs during and 8 after completing prophylaxis (median[min-max] months after completion: 3[1-27]). The on-monitoring analysis of serological markers reveals that anti-HBc >3COI combined with anti-HBs persistently or declining to < 50mIU/ml correlates with a higher risk to develop HBV-R (53% of patients with anti-HBc >3COI + anti-HBs< 50mIU/ml vs 16% without this combination experiences HBV-R, P = 0.01, OR[95%CI]: 5.9[1.6-21.5]). Furthermore, by monitoring virological markers, the positivity, confirmed in at least 2 time-points, to HS-HBs (detection failed by routinely used HBsAg-assays) and/or to HBV-DNA (detected below LLOQ) is another risk factor for HBV-R (45.5% of patients positive to HS-HBs and/or HBV-DNA vs 5.6% never positive to these markers experiences HBV-R, P< 0.001, OR[95%CI]: 14.2[3.2-62.9]).

Conclusions: HBV-R frequently occurs in anti-HBc-positive/HBsAg-negative oncohematological patients, particularly after completing antiviral prophylaxis. The combined usage of accurate HBV-markers can guide the identification of patients at higher HBV-R risk who need an extended prophylaxis.

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T-10

Analysis of resistance and phylogenetic clusters in HCV-2c infected patients within the Italian network Vironet C

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Introduction: HCV-genotype 2 (GT2), particularly subtype c, is the most prevalent GT in Italy after GT1b. Few data are available regarding the resistance-associated-substitutions (RASs) to direct-acting antivirals (DAA) in GT2c. Aim of this study was to investigate the prevalence and role of RASs and presence of phylogenetic clusters in GT2c.

Method: Within the VIRONET-C network, 248 GT2 infected patients (204 DAA-naïve and 44 NS5A-failures), were analyzed. NS3/NS5A/NS5B resistance-test was performed by Sanger-sequencing. RAS and polymorphisms in NS3 (N = 167) and NS5A (N = 197) were analysed. Cluster analysis was performed on NS5A-sequences by Bayesian analysis.

Results: 92% of patients were Italians, 56% males with a median (IQR) age of 69 years (54-78); 2.5% were HIV co-infected and 25% cirrhotics. Phylogenetic analysis classified sequences as GT2a-2b-2c (4%-< 1%-96%), respectively. Interestingly, 11 transmission clusters (7 with 2 sequences and 4 with >3 sequences) were identified among GT2c infected patients. In particular, 9 clusters involved 23 patients from North Italy (all SVR, except one), 1 pair from Center (both SVR) and 1 pair from North-South (both DAA-failures). 84 GT2c DAA-naïve with SVR and 40 DAA-failures were treated with the following regimens: glecaprevir/pibrentasvir (18/20), sofosbuvir/velpatasvir ± ribavirin (54/8), sofosbuvir /daclatasvir ± ribavirin (12/7), and with suboptimal-regimens for misclassified-genotype par-

itaprevir/r + ombitasvir + dasabuvir ± ribavirin (N = 0/3), grazoprevir/elbasvir (N = 0/2). A different distribution of NS5A-RASs was found among DAA-SVR versus DAA-failures, particularly among those exposed to suboptimal-regimens. Only the pattern F28C + L31 M was statistically significant associated with glecaprevir/pibrentasvir failures. No GT2c-naïve nor no GT2c-failures showed Y93FHNRS-RASs. Considering NS3, >95% of DAA-naive and DAA-failures showed 80G and 56F. NS3-RASs D168A/V and/or F56H/Y were detected only at failure (N = 4/25, 16%).

Conclusion: In this cohort of GT2 patients, the most prevalent subtype was the unusual GT2c. The majority of GT2c-failures with recommended-regimens did not show specific RASs at failure. Further structural and phenotypic analyses should investigate the role of the polymorphisms observed in GT2c.

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T-11

Genetic variants do not predict the development of hepatocellular carcinoma in cross-sectional and longitudinal studies including caucasian compensated hbv cirrhotics treated with nuc for 10 years

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Introduction Signal transducers and activators of transcription (STAT4), Epidermal Growth Factor 1 (EGF1), Tolloid like 1 gene (TLL1), Myeloid-epithelial-reproductive tyrosine kinase (MERTK) and for domain II (MERTK2), Patatin-like phospholipase-3 gene (PNPLA3) and Membrane Bound O-Acyltransferase Domain Containing 7 (MBOAT7) genetic variants have been associated with the development of hepatocellular carcinoma (HCC) in Asian and Caucasian HBV patients.

Aim To assess if these variants predict the HCC onset in HBV cirrhotics long-term treated with NUCs.

Materials and Methods NUC-treated Caucasian HBV cirrhotics were consecutively enrolled in longitudinal ($n = 258$) and cross-sectional case-control ($n = 111$) studies. At baseline longitudinal cohort were: age 61 (43-77) year, 82% males, 88% HBeAg negative, 12% diabetics, spleen length 11 (7-20) cm, 14% with esophageal varices, when transverse were: age 64 (51-77) year, 87% males, 93% HBeAg negative, 19% diabetics, spleen length 11 (7-20) cm, 24% with esophageal varices. Seven SNPs mapping on genes above cited (*rs7574865, rs4444903, rs17047200, rs4374383, rs6726639, rs738409* and *rs641738*) were analyzed by TaqMan genotyping assay.

Results In the cross-sectional case-control study, no significant difference in minor allele rate was found between HCC ($n = 51$) and controls ($n = 60$): 24% vs 27% for STAT4 ($p = 0.63$), 52% vs 74% for EGF (p = 0.09), 33% vs 30% for TLL1 ($p = 0.75$), 75% vs 77% for MERTK ($p = 0.80$), 57% vs 63% for MERTK2 ($p = 0.53$), 52% vs 40% for PNPLA3 (p = 0.33), 67% vs 62% for MBOAT7 ($p = 0.72$). In the longitudinal study, 45 (17%) patients developed an HCC after 56 (18-129) months with a 10-year cumulative HCC incidence of 20%. The 10-year HCC incidence was similar among different SNPs. The only independent baseline predictors of HCC were age (HR 1.09, 95%CI 1.0-1.1, $p < 0.001$) and spleen length (HR 1.33, 95%CI 1.1-1.5, $p < 0.001$).

Conclusions In Caucasian HBV cirrhotics treated with NUC, none of the 7 different genetic signatures predicted the development of HCC.

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T-12

Microelimination of HCV in residual populations of coinfected HIV/HCV: real-life data from an hospital setting in Southern Italy

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Background and Aims: Despite antiretroviral treatment, HIV remains independently associated with advanced liver disease in HCV + patients. Thus, HCV treatment in HIV + patients should be a priority. With the availability of HCV direct-acting antivirals (DAAs), efficacy and adverse event rates are similar in HIV + /HCV + and in mono-infected HCV patients. Despite that, in clinical practice some factors can delay HCV treatment in these patients. In order to to understand reasons delaying the anti-HCV treatment, we analysed a cohort of HIV + /HCV + patients from "D.Cotugno" Hospital, Naples, Southern Italy.

Method: Electronic database were consulted in order to identify the study population and to collect available data. The source population was represented by all HIV + patients who was in charge to our Medical Division in the study period. As the electronic database include data from 1997, thus 1997-2018 was the study period. We considered lost-to-follow-up all patients with no access for at least 3 years. Reasons for not treatment were classified as: due to epidemiological and social characteristics of the patients (e.g. poor compliance, irregular follow-up, frequent imprisonments); clinical reasons (co-morbidities, drug-to-drug interactions); other reasons (e.g. patient's refusal).

Results: In the study period, 254 HIV + /HCV + patients (males 92%, median age 59) were included in this study. Among these, 39 patients were lost to follow-up, and 38 were persistently not-viraemic. Among the remaining 177 patients, 154 (88%) were treated (54 with IFN-based therapy and 100 with DAAs). Almost all patients (21/23) not treated were persons who inject drugs (previously or still actively). Reasons for not treatment were due to epidemiological and social characteristics in 11 patients (mainly poor expected compliance); to clinical reasons in 4 (all with severe psychiatric disorders); to other reasons in 8 (mainly refusal of treatment). Those not treated for epidemiological and social characteristics showed an advanced liver diseases (F3-4 fibrosis in 64%) more frequently than those not treated for clinical or for other reasons (F3-4 fibrosis in 0% and 37%, respectively).

Conclusion: Despite DAA availability, a residual population of HIV + /HCV + patients with factors hampering the HCV treatment still exist, even if true clinical contraindications are rare. In the context of HCV global eradication, special attention should be given to these difficult-to-treat populations. An approach integrating psychological and social support should be promoted, in order to realize micro-elimination programs.

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T-13

Retreatment with glecaprevir/pibrentasvir and sofosbuvir in patients with viral failure at DAA

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Introduction and Aim: Development of direct-acting antiviral (DAA) agents revolutionized the treatment of patients with chronic HCV infection and DAAs are currently the standard of care. Combination regimens of DAA agents targeting different viral proteins to halt viral replication are frequently used and often? >?95% of patients achieve SVR 12 weeks post-treatment (SVR_{12}). Nevertheless, a small proportion of patients experience HCV relapse. Various virological factors [HCV genotypes, HCV with resistance associated amino acid substitutions (RAS), advanced liver cirrhosis and/or poor drug adherence) may contribute to cause treatment failure. Patients with hepatitis C virus (HCV) who have virological failure (VF) after treatment containing a nonstructural protein 5A (NS5A) inhibitor have limited retreatment options.

Materials and Methods: We performed a retrospective observational study. We enrolled patients with chronic HCV and past VF on at least one NS3 protease and/or NS5A/NS5B inhibitor-containing therapy to evaluate the number of patients with SVR 12 post *off-label* regime with glecaprevir/pibrentasvir and sofosbuvir for 12 weeks

Results: 9 patients with compensated liver disease , 6 (66%) male, 1 HIV positive have been enrolled . HCV genotype were 1b (3/9, 33%), 1a (3/9, 33%), 3 (2/9, 22%), 4 (1/9, 12%). Most patients were F3-F4 (56%). RAS in NS3 were present in 55% (Q80K and 168A with Voxilaprevir resistence), RAS in NS5A in 100% (93H, 93N, 30R,31 M), RAS in NS5B in 55% (159F with Sofosbuvir reduced susceptibility)

Conclusions: Twelve weeks of G/P and sofosbuvir treatment achieved 100% (9/9) of SVR12 rate in patients with HCV infection and past failure to regimens containing either NS5A/NS5B inhibitors or NS3 protease inhibitors. No adverse event was occurred.

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T-14

Liver steatosis detected by controlled attenuation parameter (CAP) increases after HCV eradication with direct-acting antiviral therapy: preliminary data

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Background and aims: Liver steatosis in patients with chronic hepatitis C (CHC), for all genotypes but 3, has been considered mainly due to metabolic alterations. The effect of direct-acting-antiviral-agents (DAAs) in reducing liver fibrosis is well demonstrated, while data about hepatic steatosis are still controversial. We aimed to compare hepatic steatosis (by controlled attenuation parameter (CAP) before and after DAAs and its associated factors.

Methods: 95 patients (mean age 64 ± 5, 51% male) with CHC, (6% with type 3 genotype), after 6 months from sustained viral response (SVR) to DAAs were enrolled. All parameters were collected at baseline and after SVR. All patients underwent ultrasound for steatosis and fibroscan providing CAP and liver stiffness measurement (LSM). CAP values ≥ 248, considered diagnostic for steatosis, significantly correlated with ultrasound steatosis ($p = 0.02$).

Results: mean CAP increased significantly after SVR (254 ± 57.2 vs 239 ± 48.2($p = 0.005$)). A significant difference was observed among patients with loss, equal or gain weight after SVR (227 ± 56, 239 ± 35 and 277 ± 61 respectively, $p = 0.01$). After SVR the number of patients with CAP ≥ 248 significantly increased with 21 new-onset steatosis, similarly to BMI (28 ± 3.9 vs 26.7 ± 4.3, $p = 0.005$). At multivariate analysis, post SVR-CAP (adjusted for age, sex, baseline and after SVR BMI, type of DAAs and baseline CAP), was independently associated with baseline BMI (-0.74, SE 4.3, p = 0.02), post SVR BMI (1.2, SE4.4, $p < 0.0001$) and baseline CAP (0.27, SE0.13, p = 0.01). As expected, LSM decreased after HCV eradication from 7.8 kPa to 5.4 kPa ($p < 0.0001$).

Conclusions: CAP values increase in CHC patients after SVR along with weight gain possibly reflecting a change in patients' lifestyle. However it cannot be ruled a possible direct effect of DAA on liver steatosis. Longer follow up of a larger number of patients are necessary to evaluate the evolution of steatosis.

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T-15

Efficacy of 8 weeks elbasvir/grazoprevir regimen for naïve-genotype 1b, HCV infected patients with mild-moderate fibrosis, with or without glucose abnormalities: interim results of the EGG18 study

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Background and Aim: Antiviral treatment by Direct Acting Antivirals (DAAs) achieves the highest rate of sustained viral response (SVR) in patients with genotype 1b (G1b) Hepatitis C virus (HCV) infection. Reducing treatment duration can simplify the management and improve adherence of therapy.

Patients and Methods: The study evaluates the efficacy of 8 weeks of the NS5A inhibitor elbasvir 50 mg/d (EBR) and protease inhibitor grazoprevir 100 mg/d (GZR) in 75 treatment-naïve (TN), G1b patients with mild-moderate fibrosis (Liver Stiffness by Fibroscan® < 9.5 kPa). Preliminary analysis included the first 66 patients enrolled in EGG-18 trial who completed the 8 weeks short regimen. The primary end point was the proportion of patients with HCV RNA not detectable by using Roche TaqMan RT-PCR (LLOQ < 15 IU/ml) at the end of treatment (EOT) and at 12 weeks after treatment (SVR12).

Results: Mean age was 61.8 ± 14.8 years, 45% were male, viral load higher than 800.000 IU/ml: 44/66 (67%); mean ALT: 51.0 ± 39.9

U/l, mean LS by Fibroscan®: 6.0 ± 1.4. Diabetes was present only in 6/66 patients (9.1%) but 23/66 patients (34.8%) had an HOMA > 2.5. At the time of this analysis, all 66 patients were evaluable for EOT and 53 patients were evaluable for SVR12. By the end of treatment (EOT) at 8 weeks, 64 out of 66 patients (97.0%) had HCV-RNA undetectable, while in two case HCV-RNA was detectable but with viral load < 15 IU/ml. Both patients were females, had a baseline viral load higher than 800.000 IU/ml and LS lower than 6 kPa. Both achieved SVR at 12 weeks of follow up. All 53 patients but one (98.1%) who have completed the 12 weeks of follow up achieved SVR. This male patient is 85 years old, had a baseline viral load of 3660000 IU/ml, a LS of 5.7 kPa and HOMA score of 1.3. His HCV viral load was undetectable both at 4th week and at the end of therapy. All patients concluded the indicated DAA regimes and no severe adverse events were observed. Four patients reported mild headache during therapy.

Conclusion: In naïve, genotype 1b HCV infected patients with mild or moderate liver fibrosis, short course of 8 weeks of EBR/GZR appears to achieve high efficacy regardless of features of insulin resistance. Further confirmation of these results will be available at the conclusion of the study.

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T-16

Changes in bone mineral density during monotherapy with tenofovir disoproxil fumarate: a 6-year real life longitudinal cohort study in chronic hepatitis B caucasian patients

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Introduction: In chronic hepatitis B (CHB) patients, treatment with tenofovir disoproxil fumarate (TDF) may impair bone mineral density (BMD). Aim of the study was to evaluate the BMD changes in 138 CHB NUC-naïve patients (56 yrs, 29% females, 30% compensated cirrhosis, 83% with 25(OH)-vitamin D < 30 ng/mL) treated with TDF monotherapy.

Material and Methods: BMD was assessed by dual X-ray absorptiometry (DEXA) at the lumbar spine (LS) and femoral neck (FN) at baseline (TDF start) and every two years during treatment. Reduced BMD was defined as the presence of osteoporosis (T score < -2.5) or osteopenia (T score between -1 and -2.5) at LS and/or at FN.

Results: At baseline, 73 (53%) patients had osteopenia and 19 (14%) osteoporosis at either LS or FN. Older age (57 vs 52 yrs, p = 0.006) and lower BMI (24 vs 25 kg/m^2, p = 0.001) were associated with reduced BMD. After a median of 70 (14-121) months of TDF and 357 DEXA performed (2.6 per patient), 24 (52%) of 46 patients with normal BMD at baseline progressed to osteopenia (5 at LS, 16 at FN and 3 at both LS and FN) and 1 (2%) to osteoporosis at LS. Among the 73 patients with baseline osteopenia, 8 (11%) progressed to osteoporosis (5 at LS, and 3 at FN) and 8 (11%) normalized BMD. Among patients with normal DEXA or osteopenia at baseline, 65% maintained stable BMD, 7% improved and 28% worsened. Overall, median LS and FN BMD reduced by 2.9% and 3.8%, respectively and a >3% BMD decrease was shown in 52% and 58% of patients at the LS and FN, respectively.

Conclusion: Osteopenia and osteoporosis are highly prevalent in untreated CHB patients starting TDF. As BMD further worsened during treatment in approximately ¼ of patients, alternative treatment strategies, such as Tenofovir alafenamide, should be considered.

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T-17

HBsAg clearance in HBeAg negative infection and treated chronic hepatitis B is associated with different HBsAg kinetics

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Introduction and Aim: Predictive markers of HBsAg clearance in carriers of HBeAg negative infection (ENI) and chronic hepatitis (CHB) treated with nucleos(t)ide analogues (NAs) remain an unmet need. We investigated whether the kinetic profile of HBsAg decline could predict this end point.

Materials and Methods: HBV-DNA and HBsAg were measured at baseline (BL) and every 6 months thereafter in 89 ENI, 63 Low Viremic Carriers (LVC, HBV-DNA ≤ 20.000 IU/mL) and 90 CHB under NAs (55 with cirrhosis, CI). Individual HBsAg kinetics were plotted in semi-log scale and fitted with the exponential function y = aâ^TM expb̂x, with -1 < b < 1. Statistical analyses were performed by χ^2, Kruskal-Wallis, Spearman correlation test and logistic regression analysis.

Results: The overall rate of HBsAg clearance was similar in ENI, LVC and CHB (9.0% vs 7.9% vs 6.7%, p = 0.846). Median BL HBsAg (LogIU/mL) was lower in ENI vs LVC vs CHB [3.07 (-0.86/4.62) vs 3.36 (1.24-4.69) vs 3.52 (1.12/4.71); p = 0.003). Median follow up was longer in CHB and LVC vs ENI [81.0 (11.6/204.6) vs 85.8 (33.1/226.7) vs 65.3 (25.2/155.9) mos., p = 0.004]. HBsAg < 100 UI/mL was reached within the end of follow up (EOF) in 63 (28.8%) of 219 cases with BL HBsAg >100 IU/mL: 15/72 (20.8%) ENI, 9/59 (15.3%) LVC and in 19/88 (21.6%) CHB (p = 0.608). Three HBsAg kinetic patterns were observed: Steady, S = 54 (22.4%); Monophasic, M = 146 (60.3%) and Biphasic, B = 42 (17.4%) decline (figure). S pattern was more often observed in ENI and LVC than in CHB (29.2% and 34.9% vs 6.7%); M pattern was similarly distributed (57.3% vs 52.4% and 68.9%); B pattern was more frequent in CHB than in ENI and LVC (24.4% vs 13.55% and 12.7%; p < 0.001). HBsAg clearance occurred in 9/146 (6.2%) with M and in 10/42 (23.8%) with B patterns (p < 0.001). In M pattern the exponential decline was slower in LVC vs ENI vs CHB (median b = -0.009 vs -0.011 vs -0.014; p = 0.016). In B pattern, the 2nd phase exponential decline tended to be faster in LVC vs ENI vs CHB (median b = -0.108 vs -0.087 vs -0.040; p = 0.053). HBsAg clearance was independently associated with BL HBsAg Log IU/mL (OR = 0.521, 95%CI = 0.284-0.956, p = 0.035) and its Delta Log decline at 36 months (DLog36m) (OR = 26.94, 95%CI = 4.386-165.481, p < 0.001). EOF HBsAg predicted by DLog36m showed a good correlation with measured EOF HBsAg in the whole cohort (r = 0.897), stronger in ENI (r = 0.964) and CHB without CI (r = 0.900)

than in LVC (r = 0.883) and CHB with CI (r = 0.748). Overall DLog36m identified carriers who achieved EOF HBsAg< 100 IU/mL with 78.7% Se, 99.4% Sp, 98.0% PPV, 93.0% NPV and 94.0% DA.

Conclusions: The lack of HBsAg decline was more frequent in untreated ENI and LV carriers (29.2% and 34.9%) than in NAs treated CHB (6.7%). The predominant pattern was a monophasic exponential decline, faster in CHB than in ENI and LVC. HBsAg clearance, however, occurred more frequently in biphasic (23.8%) than monophasic (6.2%) patterns, and was independently associated with BL HBsAg and Delta Log decline at 36 months, which identified carriers who achieved EOF HBsAg< 100 IU/mL with 98.0% PPV.

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T-18

Directly acting antivirals are safe and effective in HCV elderly patients: a multicenter real life study

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Treatment of chronic Hepatitis C (HCV) with directly acting antivirals (DAAs) can lead to sustained virologic response (SVR) in nearly 95% of patients. However, treatment efficacy and safety in elderly patients has not been extensively studied. We retrospectively analyzed efficacy and safety of DAAs in HCV patients of 80 years or older, consecutively treated in two centers between 2015 and 2019. DAAs were given following the EASL recommendations. During the study period, 129 patients older than 80 received DAAs. Their mean age was 82,4 years (80-89), 83 patients were female (64.3%). The most prevalent HCV genotypes were 1b (78 patients, 60.5%) and 2 (49 patients, 38.0%). Advanced fibrosis (F3-F4) defined by transient elastography >10 KPa was present in 72 patients (55.8%), 13 patients had CPT score >A5 and 24 (18.6%) had previously failed IFN based treatment. Sofosbuvir based therapies (SOF/LDV, SOF/VEL and SOF + RBV) were given to 72 patients (55.8%), G/P in 30 (23.3%), Grazoprevir/Elbasvir in 19 (14.7%), PAR/OMB/RTV was used in 3 (2.3%), PAR/OMB/RTV + Dasabuvir in 6 (4.7%). Concomitant medications were common in our cohort with 124 patients (96%) taking at least 1 drug and 82 (63.6%) taking 4 or more concomitant drugs. In 10 cases, concomitant therapy had to be modified to start DAA treatment for potential significant drug interactions. Four patients had to discontinue treatment prematurely (2 SAE, 1 AE and 1 self-discontinuation). In total, 35 patients (27%) reported mild side effects. SVR was achieved in 126/129 (97.7%) patients, 2 patients had a post-treatment relapse and 1 patient was lost to follow-up). Mean follow-up after therapy start was 16 months (range 4-48). Our study shows that DAA treatment in HCV patients older than 80 is safe and effective. Due to high rate of comorbidities, DDI should to be carefully assessed before starting treatment.

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T-19

THE "CASERTA MODEL". AN HCV WAY OUT IN PERSONS WHO USE DRUGS (PWUD) IN ITALY

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Background: The aim was to evaluate the efficacy of a simplified model to eliminate HCV infection in PWUD population.

Methods: between January 2018 and April 2019 a prospective, interventional, before and after study, based on the cooperation between all the 6 Caserta Services for the Dependence (SerD) starting from the Teano one and the units of Infectious Diseases (ID) in Caserta, Campania, Italy, was performed. The intervention included periodic audits conducted in the SerD to improve the knowledge on HCV infection and on the need to treat. The ID consultants shared a diagnostic simplified pathway for HCV infection diagnosis, access to DAA treatment and follow up. The outcomes were to test the efficacy of the model. The pre-intervention period was defined as January-December 2017; the post-intervention period as January-September 2018

Results: in this setting, in the 6 SerD, the linkage to care model, resulted in an increase of 506% of rates in DAAs treatment. PWUD followed up by the Teano one in 2017 and in 2018 were 318 and 275, respectively. The Figure shows the HCV cascade in the two periods. Compared with the pre-intervention period the number of subjects tested for HCV increased, but no significantly, in the post-intervention period (78% vs. 72%, p 0.1). Compared with the pre-intervention period the number of subjects HCV Ab positive tested for HCV RNA increased (91% vs 27% p< 0.05). Of the 75 HCV-RNA-positive subjects identified in post-intervention period 65 (86%) were linked to care to Infectious Disease Unit and started DAA regimen, a prevalence clearly higher than that observed in the pre-intervention period (17%, p < 0.05). In post-intervention period. Conclusion: This innovative procedures **for micro-elimination of HCV infection** is very effective in PWID with rates of diagnosis and **linkage to care.**

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T-20

Safety and efficacy of up to 76 weeks 10 mg/day (high dose) bulevirtide monotherapy in compensated cirrhotics with delta hepatitis

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Introduction: Treatment with Bulevirtide (BLV) 10 mg/day + TDF is effective in HDV hepatitis in 48-weeks clinical trial.

Aim: To assess BLV effectiveness and safety beyond 48 weeks, and the kinetics of virological/clinical relapse after discontinuation in a real-life setting.

Materials and Methods: Three compensated HDV-cirrhotics were treated with BLV 10 mg/day + TDF for >76 weeks (Case 1: 69 years, female, HDV-RNA 23,600 IU/mL, ALT 140 U/L; Case 2: 51 years, male, AIH features, HDV-RNA 392,000 IU/mL, ALT 232 U/L; Case 3: 58 years, female, autoimmune thrombocytopenia, HDV-RNA 5,900,000 cp/mL, ALT 244 U/L). HDV-RNA by RoboGene (LOD 6 IU/mL) or by in-house RT PCR (LOD 100 cp/mL).

Results: In Case 1, HDV-RNA became undetectable by week 36 and ALT normalized by week 20, both markers remained negative up to week 52 when BLV was withdrawn. Thereafter, HDV-RNA turned detectable after 2 weeks, progressively increased up to week 16 (24à13,655 IU/mL) and then declined. Similarly, ALT progressively increased from week 14 to week 30 (41à333 U/L), and then declined, without any lab/clinical decompensation. 38 weeks after discontinuation: HDV-RNA 431 IU/mL, ALT 70 U/L, HBsAg 0.20 IU/mL (22 IU/mL at EOT). In Case 2 and Case 3, BLV was continued for 76 weeks, obtaining and maintaining a biochemical/effective virological response. At week 76: HDV-RNA < 6 IU/mL and 150 cp/mL, ALT 33 and 35 U/L, respectively, with no significant changes of HBsAg. In Case 2, a significant improvement in portal hypertension features and liver function tests were documented, and a reduction of plasma cell infiltration and histological activity (liver biopsy at week 72). BLV was well tolerated in all 3 patients, without any drug-related adverse events except for an asymptomatic increase in bile acids.

Conclusions: Up to 76 weeks of Bulevirtide 10 mg/day is safe and effective in HDV compensated cirrhotics.

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T-21

Nailfold capillaroscopy: a useful instrument for early diagnosis of systemic sclerosis in patients with primary biliary cholangitis

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Introduction: Primary Biliary Cholangitis (PBC) is a cholestatic autoimmune disease affecting small bile ducts. PBC is often associated with Systemic Sclerosis (SSc). SSc prevalence is about 5–12% in PBC patients and diagnosis is often delayed due to lack of specific recommendations. Aim: We assessed the utility of Nailfold Capillaroscopy (NC) in anticipating SSc diagnosis in PBC patients.

Materials and methods: We performed NC in 56 of the 76 PBC patients of our Centre. Raynaud phenomenon (RP) was evaluated in each patient. Patients with a previous SSc diagnosis were excluded from the study. Patients with NC minor abnormalities were advised for capillaroscopic follow-up. Patients with major abnormalities and those with scleroderma pattern were suggested to undergo screening for SSc-specific auto-antibodies and were followed-up with NC. VEDOSS and 2013 ACR/EULAR criteria were used for the SSc diagnosis.

Results: NC abnormalities were found overall in 31 patients (55%): 11 (20%) presented NC minor abnormalities, 17 (30%) showed major abnormalities, 3 (5%) presented a scleroderma pattern. Auto-Ab screening showed the following positivities: 1 for anti-ENA screening, 4 for anti-SSa/Ro, 1 for anti-PML and 1 for anti-U1RNP. Among the ones with scleroderma pattern, 2 patients were newly diagnosed with SSc. The first patient presented antinuclear Ab (ANA) and anti-SSA. The second presented ANA and anti-U1RNP. The third patient was positive for ANA but did not fulfil SSc diagnostic criteria despite strong clinical suspicion. All patients diagnosed with SSc presented RP. Nobody among those without RP was diagnosed with SSc. The SSc prevalence estimated in our Centre is consistent with literature data.

Conclusions: Performing NC in PBC patients is helpful in anticipating SSc diagnosis. The presence of RP should always be checked in PBC patients and, if present, should prompt the gastroenterologist to perform NC for early SSc diagnosis.

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T-22

Durable response in the markers of cholestasis through 5 years of open-label extension study of obeticholic acid in primary biliary cholangitis

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Obeticholic acid (OCA) is a selective and potent farnesoid X receptor agonist indicated for treatment of primary biliary cholangitis (PBC). POISE was a placebo-controlled, phase 3 study of the efficacy and safety of OCA in PBC, and included a 12-month double-blind phase with a 5-year open-label extension (OLE). The OLE was to assess the long-term safety of OCA and the durability of OCA effects on serum markers of cholestasis. Following the 1 year double blind phase, patients on placebo started OCA and were then pooled with OCA treated patients to evaluate the efficacy and safety of up to 6 years of OCA treatment. 146 patients (76%) completed the protocol as specified following administrative shutdown of the study. 158 patients (82%) completed 4 years of OCA treatment and 116 (60%) patients completed 5 years of OCA treatment; 52 patients who had received OCA in the double-blind phase completed 6 years on treatment. The percentage of patients meeting the primary endpoint was 46% at 12 months and 50% at 48, 60, and 72 months. Significant and durable reductions were observed for ALP, alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase throughout the study (Table). Mean total bilirubin remained stable through 72 months of OCA treatment. OCA treatment resulted in sustained improvement in liver biochemistry during up to 6 years of follow-up.

Table. Serum markers of cholestasis from baseline through 72 months of OCA treatment

Mean (SD)	Baseline (N=193)	Change from baseline	
		12 months (N=185)	72 months (N=52)
Alkaline phosphatase (U/L)	317 (120)	−105 (88)*	−118 (128)*
Total bilirubin (μmol/L)	11.5 (7.0)	−0.9 (4.1)†	−0.1 (4.5)
Aspartate aminotransferase (U/L)	51.2 (33.5)	−12.8 (24.7)*	−14.1 (18.2)*
Alanine aminotransferase (U/L)	56.7 (37.0)	−21.5 (24.4)*	−28.2 (29.4)*
Gamma-glutamyl transferase (U/L)	275.2 (306.0)	−157.7 (205.1)*	−156.1 (200.1)*
Liver stiffness (kPa)‡	11.4 (9.4)	0.5 (5.6)	1.2 (10.1)

*p<0.0001; †p=0.004; ‡Baseline N=79, 12 months N=71, 72 months N=32; kPa, kilopascal. p-values for the within-treatment comparisons were obtained using a paired *t* test.

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T-23

A novel HER2-targeted liposomal formulation reduces the risk of hepatotoxicity induced by PEG-based anticancer drugs

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Introduction: Stealth immunoliposomes (SILs) are nanosystems obtained by conjugating monoclonal antibodies or antibody fragments to fractions of poly-ethylene-glycol (PEG)-phospholipids present in stealth liposomes. The aim is to improve the pharmacokinetic and toxicological profile of encapsulated drugs and permit targeted therapy. However, It has been shown that these nano-sized materials can accumulate into the liver, causing drug-induced-liver-injury (DILI).

Aim: to assess the pharmacokinetic and toxicological profile of two HER2-targeted SILs obtained by conjugating trastuzumab Fab' with classic PEG-phospholipids (SIL) or with a novel mPEG-branching-$(phospholipid)_2$ ($SSIL_2$), both loaded with doxorubicin, examining in particular the risk of DILI occurrence.

Methods: 2.5 mg/kg of doxorubicin equiv. SIL or $SSIL_2$ was administered via caudal vein to Sprague-Dawley rats ($n=6$ per group). Vehicle-administered rats were used as controls. Rats were sacrificed 48 hours after treatment. Hepatotoxicity was assessed by 1) standard histological analysis (H&E) performed on liver sections; 2) full blood count and plasma liver function tests; 3) hepatic mRNA level for IL-1beta, TNF-alpha, IL-10, CCL2 and CXCL2; 3) reactive oxygen species (ROS) production in liver tissue.

Results: $SSIL_2$ showed an improved pharmacokinetic profile compared to SIL, since elimination half-life increased ($p<0.05$), while systemic clearance of doxorubicin tended to drop. SIL caused hepatotoxicity, as indicated by the decrease of plasma albumin ($p<0.05$ *vs* controls), the presence of several hepatic granulomatous lesions, granulocytes, confirmed by increased hepatic CXCL2 mRNA levels ($p<0.001$ *vs* controls), and macrophages. Accordingly, IL-1beta and TNF-alpha mRNA expression and ROS concentration increased significantly ($p<0.001$) in these rats. At variance, histological analysis revealed only few isolated granulomas in $SSIL_2$-treated animals, and the other parameters were similar to those of controls.

Conclusion: The conjugation of SILs with mPEG-branching-$(phospholipid)_2$ represents an effective strategy to improve the

[a] Employed at Intercept Pharmaceuticals, Inc., San Diego, CA, USA, at the time the study was conducted.

pharmacokinetics of drugs and prevent the hepatoxicity associated to PEG-derived nanosystems, thus improving the efficacy and tolerability of innovative cancer therapy.

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T-24

Autoantibody study in Primary Biliary Cholangitis and possible relation with therapeutic response

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Background and aim: Among the stratification risk parameters in Primary Biliary Cholangitis (PBC), there is still poor evidence of serological markers. In this study we evaluated the autoantibody typing of our patients and the possible association with therapeutic response.

Material and methods: 119 patients with PBC referred to our Centre were evaluated but only those with serum frozen at diagnosis were included in the study. 72 patient's sera, 55 (9 M and 46F; median age 66) responders (R) and 17 (3 M and 14F; median age 61) non-responders (NR) to ursodeoxycholic acid were analyzed by Euroimmun blot contains the PBC associated antigens. The positivity has been confirmed by IFI on Hep-2 cells and on rat tissue. The same sera were analyzed by EIA testing for specific ENA antibodies.

Results: As expected 93% of the patients (50/55R and 17/17NR) were AMA positive in IFI and anti M2 and M2-3E in blot. Anti-gp210 antibodies (confirmed by IFI) were positive in 26% of the patients and were equally represented in both groups, respectively 15/55R and 4/17NR; anti-sp100 (confirmed by IFI) and PML were more represented in the R group: 14/55R vs 1/17NR ($p = 0{,}0625$) and 9/55R vs 0/17NR ($p = 0{,}0594$) respectively. From the ENA study, positivity for SS-A and SS-B appeared to be more present in NR than R group (4/17 vs 1/55) with statistical significance ($p = 0{,}0022$). Only one patient had Sjögren syndrome (in NR group).

Conclusions: In our case the positivity for anti-sp100 and PML was more represented in the R group. Conversely, the positivity for SS-A and SS-B was significantly increased in the NR group to suggest a possible association with a more aggressive or more therapy-resistant form of the disease. Our current objective is the widening of the case and the identification, on the same serum, of possible positivity for anti-kelch-like12 and anti-hexokinase-1.

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T-25

Risk factors for disease progression in non – cirrhotic patients with Primary Biliary Cholangitis

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Background: Despite ursodeoxycholic acid therapy, a subgroup of patients with primary biliary cholangitis(PBC) will develop cirrhosis. Identification of baseline factors related to a high risk of disease progression may assist in selecting patients who are most likely to benefit from non UDCA-based therapies.

Aims: To identify among non-cirrhotic PBC patients, at the time of starting UDCA, demographic and clinical features linked to progression to cirrhosis

Methods: 111 consecutive, histologically proven PBC patients without cirrhosis, treated with UDCA, were included. Development of cirrhosis was defined as: *de novo* appearance of esophagogastric varices or ascites or of US signs of portal hypertension, plus liver stiffness by TE >12.5 kPa **or** platelets< 130.000/mL. Table 1 shows predictive factors assessed. Cox proportional hazard assumption was used to assess the risk.

Results: Over a mean follow-up of 67,1 months, the biochemical response rate to UDCA was 84%. Twelve patients developed cirrhosis. By multivariate Cox regression analysis, only male sex (HR:4.3;$p < 0.041$) and FIB-431.21 at baseline (HR:6,88;$p < 0.046$) were independently associated with progression to cirrhosis. Failure to respond to UDCA was not related to a higher risk of progression.

Conclusions: In our cohort of non-cirrhotic PBC patients, progression to cirrhosis was observed in about of 10% over > 5 years follow up. Male sex and baseline FIB-4 were independently associated with a worse outcome, but we were unable to find a protective effect of UDCA. This suggests that patients with noncirrhotic PBC could be selected for non UDCA-based therapy based on personalized risk profiles rather than on the failure to respond to UDCA.

Table 1

Baseline factors	No progression (99)	Progression to cirrhosis (12)	HR (CI95%)	p value
Age (SD)	55(10.9)	58.7(11.5)	1.04(0.97-1.10)	0.16
Gender (F)	91(91.9%)	9 (75%)	0.18(0.05-0.69)	0.013
ALP > 1.5	67(67.7%)	9 (75%)	1.32(0.28-6.25)	0.73
GGT (x ULN)	7.2 (9.4)	12.2 (10.8)	1.02(0.98-1.05)	0.33
FIB-4 > 1.21	50 (50.5%)	9 (75%)	7.95(1.05-67.33)	0.02
UDCA responder*	86 (89.9%)	8 (67%)	0.57(0.17-1.89)	0.36

*Calculated after 1 year of UDCA

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T-26

Antioxidant and anti-inflammatory effect of oleuropein in hepatic steatosis

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Introduction: Nonalcoholic fatty liver disease (NAFLD), or liver steatosis, is a common hepatic disease in which oxidative stress plays a main role in causing liver damage. Fat metabolism is dependent on mitochondrial activity that generates ATP but also reactive oxygen species (ROS). Oleuropein (Ole) is a phenolic compound with significant antioxidant and anti-inflammatory properties.

Aim: The aim of this study was to investigate if, in the presence of hepatic steatosis, Ole may improve liver damage by restoring the redox balance.

Materials and Methods: We evaluated the effects of Ole in female and male mice fed normal diet (ND) or high fat diet (HFD) for 8 weeks, either adding or not Ole for the following 8 weeks.

Results: Ole was able to induce a decrease in body weight, as well as in liver and heart weight, in HFD mice. Administration of Ole has an anti-inflammatory effect in HFD mice, decreasing the inteleukin1-alpha, interleukin-2, tumor necrosis factor-alpha and granulocyte- colony stimulating factor cytokines in the serum of HFD mice, but the effects on inflammation of this phenolic compound were higher in female than in male reaching a statistical significance for IL-2 and G-CSF. SOD1 and SOD2 belong superoxide dismutase family bind to the superoxide transforming them to hydrogen peroxide. In our mouse model, SOD2 and catalase are involved in Ole-dependent liver damage protection. SOD2 expression and activity was significantly increased either in ND or HFD female mice, whereas Ole administration was effective only in HFD male mice. The liver tissue damage reflects the SOD2 activity. Sirtuin 1 and 3 seem to have a key role in the Ole dependent protection on the liver damage induced by unhealthy diet.

Conclusion: Our results indicate Ole as an effective and promising antioxidant nutriaceutical compound. In presence of unhealthy diet, Ole seems to overcome gender-related differences.

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T-27

Additive beneficial effects of Fibrates combined with Obeticholic acid in the treatment of patients with Primary Biliary Cholangitis and inadequate response to second-line therapy: data from the Italian PBC Study Group

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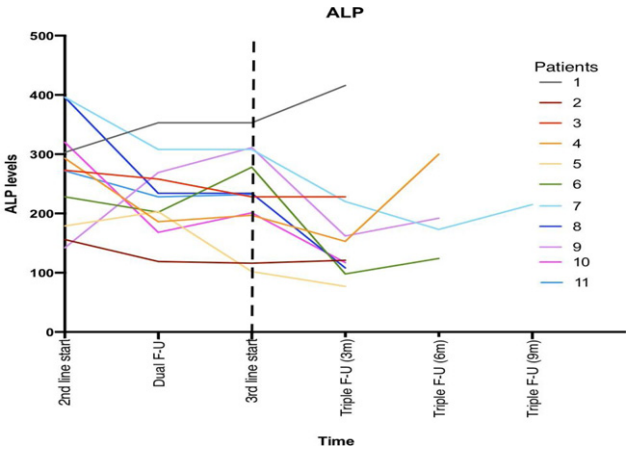
Obeticholic acid (OCA) and fibrates are the only therapies, which have shown biochemical benefit in PBC patients with inadequate response to ursodeoxycholic acid (UDCA). However, the efficacy of their combination is unknown. Aim of our study was to investigate the efficacy of a combined therapy with OCA and fibrateson the liver biochemistry in high-risk PBC patients, i.e. those with inadequate response to UDCA. This is a proof-of-concept retrospective cohort study. Patients with PBC treated with at least 12 weeks with combination therapy of UDCA (13-15 mg/kg/day), OCA (5-10 mg/daily) and fibrates (bezafibrate 400 mg/daily or fenofibrate 200 mg/daily) were included. Demographical, clinical and biochemical data were collected and analysed before starting the second line therapy, before starting the third line therapy and after 3-6 months of triple therapy. Eleven PBC patients from three liver centres in Italy were included. Median ALP level at the start of the second line therapy was 273U/L (interquartile range, IQR 203,311) with a median reduction of 22%[-0.9,35]. The median ALP level at the start of the third line therapy was 232U/L[199,293] with a median reduction of 29%[22,48] (Figure 1). Eight patients experienced any reduction in ALP levels during triple therapy.The median bilirubin level at the start of the second line therapy was of 0.72 mg/dL[0.6,1] with a median reduction of 13%[-36,20]. The median bilirubin level at the start of the third line therapy was 0.80 mg/dL[0.7,0.9] with a median reduction of 3%[-5,18]. One patient dropped out for persistently abnormal transaminases secondary to introduction of bezafibrates. Triple therapy with UDCA, OCA and fibrates improves liver biochemistry and increases the rate of ALP normalization in patients with PBC and an inadequate response to OCA/UDCA or fibrates/UDCA dual therapy. A randomized clinical trial to assess the efficacy and safety of triple therapy in high-risk PBC patients is warranted.



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T-28

Real-world data on the treatment of primary biliary cholangitis with obeticholic acid in Italy: the CLEO-AIGO OCA cohort

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Introduction: Obeticholic acid (OCA) has been recently approved for patients with Primary Biliary Cholangitis (PBC) and non-response to ursodeoxycholic acid (UDCA).

Aim: To evaluate first real-world results of OCA treatment in patients recruited at centres belonging to "Club Epatologi Ospedalieri" (CLEO) and "Associazione Italiana Gastroenterologi Ospedalieri" (AIGO).

Methods: CLEO and AIGO centres were invited to participate to the study and to collect the required data for all their OCA-treated PBC patients.

Results: Fourteen centres were enrolled throughout Italy, with 87 patients started with OCA based on the following criteria: ALP≥1.5XULN and/or 1 > total bilirubin< 2 mg/dL after ≥ 1 year of UDCA treatment. They were 77 females (88.5%), mean age 60.2 ± 10.3 years, median BMI 23.9 (22.1–27.4) kg/m^2, 78 (89.7%) AMA-positive, 13 (14.9%) overlap PBC/autoimmune hepatitis, 34 (39.1%) staged as cirrhotics based on clinical and/or histological and/or elastographic findings, with a median duration of disease of 9 (5–15) years. Sixty-six patients had completed 6 months and 42 patients 12 months of OCA therapy, for a median treatment duration of 10.6 (6.0–15.2) months. Liver biochemistry is reported in Table 1). All liver enzymes were significantly reduced at months 6 and 12, while bilirubin was unchanged. Permanent OCA discontinuation was reported in 14 patients (16.1%): 5 patients, de novo pruritus; 3 patients, worsening pruritus; 2 patients, worsening liver enzymes/function; 2 patients, anemia; 1 patient, headache; 1 patient, abdominal pain. Any adverse event was reported in 32 patients (37%), mostly pruritus (26 patients, 29.9%). The response according to Poise criteria at 6 and 12 months were 35% and 52% (intention-to-treat), and 39% and 64% (per-protocol), respectively.

Conclusions: These first real-world Italian data confirm the efficacy of OCA treatment in reducing liver enzymes and stabilizing bilirubin levels of PBC patients non-responder to UDCA. Pruritus is confirmed as the most frequent adverse event and the main cause of OCA permanent discontinuation.

Table 1).

Duration of OCA therapy (months)	Number of pts	AlkPhos /UNL	% variation	P value
0	87	2 (1.7-2.6)		
6	66	1.5 (1.2-1.9)	-22.7	< 0.001
12	42	1.3 (0.9-1.6)	-31.9	< 0.001
Duration of OCA therapy (months)	**Number of pts**	**Bilirubin (mg/dL)**	**% variation**	**P value**
0	87	0.9 (0.6-1.1)		
6	66	0.7 (0.5-1.1)	-0.8	0.187
12	42	0.8 (0.6-1)	-7.1	0.102
Duration of OCA therapy (months)	**Number of pts**	**GGT /UNL**	**% variation**	**P value**
0	87	3.4 (1.8-5.5)		
6	66	1.7 (0.9-2.8)	-51.3	< 0.001
12	42	1.4 (1-2.3)	-58.3	< 0.001
Duration of OCA therapy (months)	**Number of pts**	**ALT /UNL**	**% variation**	**P value**
0	87	1 (0.6-1.4)		
6	66	0.6 (0.5-0.9)	-29.6	< 0.001
12	42	0.6 (0.5-0.8)	-32.5	< 0.001
Duration of OCA therapy (months)	**Number of pts**	**AST /UNL**	**% variation**	**P value**
0	87	1 (0.6-1.4)		
6	66	0.9 (0.6-1.2)	-18.4	0.036
12	42	0.7 (0.6-1)	-24.2	0.007

Continuous variables expressed as medians (IQR).

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T-29

The economic cost and health burden of non-alcoholic steatohepatitis in the EU5 countries

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People with advanced liver fibrosis due to non-alcoholic steatohepatitis (NASH) (fibrosis stages F3 – F4) have a high risk of rapid progression to end-stage liver disease (ESLD). This study estimates the prevalence of NASH and the socioeconomic burden associated with its treatment in the EU5 countries (France, Germany, Italy, Spain and UK) during 2018. The socioeconomic burden of NASH per country was estimated using cost-of-illness methodology applying a prevalence approach to estimate the number of adults with NASH, and the economic and wellbeing costs attributable to diagnosed NASH in a base period (2018). Wellbeing costs were estimated using the WHO burden of disease methodology, which includes societal wellbeing measures e.g. disability-adjusted life years (DALYs). The analysis was based on extensive literature review and consultations with clinical experts, health economists and patient groups. Epidemiological data were derived from two modelling studies (upper and lower bound). Resource-use estimates were based on literature and expert opinion. Unit costs were sourced from the literature and local fee schedules. Only a small subset of adults living with any-stage NASH were diagnosed due to the low probability of being diagnosed at < F3 stage (where there is usually minimal symptomatology). Of the 0.9 – 2.0 million adults estimated to have advanced liver fibrosis due to NASH, only 37.8 – 39.1% were diagnosed. Direct costs due to NASH were estimated at €619 – 1,292 million/year; 95% of these costs were incurred from the diagnosis and monitoring of patients with advanced liver fibrosis due to NASH. Adults with NASH experienced between 311,944 and 660,451 DALYs. Total wellbeing costs ranged from €41,536 to 90,379 million, primarily driven by the high rate of premature mortality in patients with NASH. Prevention of progression to ESLD and appropriate management of adult NASH patients could result in reduced economic impact and improvements in wellbeing.

Table: Prevalence of NASH in adults in the EU5 countries

	Percentage of adult population (%)			
	Estimated		Diagnosed	
	All stages NASH	F3 – F4 NASH	All stages NASH	F3 – F4 NASH
EU5	1.89 – 4.03	0.37 – 0.79	0.22 – 0.51	0.15 – 0.33
France	2.20 – 3.60	0.33 – 0.56	0.12 – 0.20	0.08 – 0.14
Germany	1.40 – 4.10	0.27 – 0.79	0.35 – 0.99	0.18 – 0.53
Italy	1.70 – 4.40	0.36 – 0.95	0.06 – 0.16	0.05 – 0.14
Spain	2.20 – 3.90	0.47 – 0.84	0.04 – 0.07	0.02 – 0.04
UK	2.20 – 4.10	0.46 – 0.86	0.45 – 0.83	0.35 – 0.64

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T-30

High rate of misclassification of fibrosis stage using Transient Elastography in patients with Primary Biliary Cholangitis

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Objective: Liver biopsy is no longer considered necessary for the diagnosis of primary biliary cholangitis (PBC) according to the current EASL guideline. Noninvasive staging of fibrosis by transient elastography (TE by FibroScanâ) has been evaluated in this setting, a TE cut-off value of 9.6 kPa being related with a high risk of outcome events (1). We aimed to assess the reliability of TE in comparison to biopsy in discriminating the stage of PBC at the time of diagnosis.

Methods: 92 consecutive patients (91% female, median age: 56 years) with an histological diagnosis of PBC (staged according to Scheuer's score for PBC) (2) underwent TE within 1 months from. A receiver operating characteristic (ROC) curve was set to assess the performance and the misclassification rate of TE, using biopsy as a "gold standard".

Results: Twenty-seven patients out of 92 (29.3%) had histological features of severe fibrosis or cirrhosis (Stage 3–4). The AUROC of TE for diagnosis of stage 3-4 was 0.87. TE values $\leq$ 9.6 kPa were found in 64 patients (69.6%). Ten of them were in Scheuer's stage $\geq$ 3, with a false negative rate (FNR) of 15.6% (sensitivity 71.4%, NPV 84.4%). 28 patients (30.4%) had TE values > 9.6 kPa. Eight of them had stage 1–2 disease at biopsy, with a false positive rate (FPR) of 28.6% (specificity 84.4, PPV 71.4%) and a misclassification rate of 19.6%.

Conclusions: At the time of diagnosis, TE by Fibroscan misclassifies Scheuer's stage of PBC in one every five patients, mostly by an overestimate of fibrosis.

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T-31

Overall Health, Daily Functioning, and Quality of Life in Acute Hepatic Porphyria Patients: ENVISION, a Phase 3 Global, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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Objectives: Acute Hepatic Porphyria (AHP) is a family of rare genetic diseases leading to an enzyme deficiency in the heme biosynthesis pathway, causing accumulation of neurotoxic heme intermediates, resulting in neurovisceral attacks and chronic manifestations. Givosiran, an investigational RNAi therapeutic, is being evaluated for its ability to reduce the levels of neurotoxic intermediates thus decreasing attacks and disease manifestations.

Aim: ENVISION (NCT03338816), a Phase 3 global, multicenter, randomized, double-blind, placebo-controlled trial, evaluated the efficacy and safety of givosiran in AHP.

Methods: The primary endpoint was composite annualized attacks over six months. Secondary endpoints included worst daily pain, and the QoL Physical Component Summary, Short Form-12 (PCS SF-12). Exploratory endpoints included EuroQoL Visual analog scale (EQ-VAS), Patient Global Impression of Change (PGIC), Porphyria Patient Experience Questionnaire (PPEQ), and missed days of work.

Results: Ninety-four AHP patients enrolled. Givosiran significantly reduced composite attacks relative to placebo ($p = 6.04x10^{-9}$), as well as the cardinal symptom of pain ($p = 0.0493$). Givosiran led to greater change in PCS SF–12 scores from baseline (givosiran = 5.4; placebo = 1.4, $p = 0.0216$), and to higher change in EQ-VAS scores (givosiran = 5.2; placebo = –1.3). More givosiran patients (89%) reported greater improvements in overall health since study-start, as measured by PGIC, than placebo (37%). Givosiran led to greater improvement in PPEQ (traveling, social activities, planning future events, household chores, exercise, and treatment satisfaction) and fewer missed work days, compared to placebo.

Conclusions: In a Phase 3 study, givosiran treatment resulted in clinically meaningful efficacy and marked improvements in AHP patients' overall health status, daily functioning, and quality of life.

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T-32

Primary biliary cholangitis: histological and clinical liver progression in non responders to ursodeoxycholic acid

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Background and aim: In several patients with Primary Biliary Cholangitis (PBC) abnormally elevated levels of alkaline phosphatase persist despite ursodeoxycholic acid (UDCA) therapy. The aim of this study is to analyze the progression of liver fibrosis in non responder patients (NR) to UDCA.

Material and methods: This study evaluated 119 patients with PBC referred to our Center between 2004 and 2018. Those with an inadequate response to UDCA were evaluated for liver biopsy which then was compared to that obtained at diagnosis. Patients without biopsy but with a clinical diagnosis of cirrhosis were considered as an histological stage IV according to the Ludwig's classification.

Results: Of the 119 total patients, 3 died (2 for PBC progression) and 10 were lost at follow-up. Of the remaining 106 patients, 26

were NR to UDCA. Out of these we considered only the 14 patients who were cirrhotic or had a biopsy at diagnosis and at follow-up and we compared the progression of fibrosis. At baseline, 7 were histologically assigned with a low severity fibrosis stages (I or II). After UDCA treatment, with a median follow-up of 8.5 years (CI95 % 6 – 15), an histological fibrosis progression was observed in 8 patients (57.1 %), while a progression from low to severe fibrosis was seen in 6 (42.9 %). Progression was associated with a longer follow-up trend (11.5,CI6–26 vs 6.5,CI6–13 years, in progressed and not-progressed fibrosis respectively).

Conclusion: PBC is a cholestatic progressive disease and an adequate response to therapy is essential to prevent fibrosis progression. In our study we observed that in NR patients there was a histological progression of the disease, however this progression seemed to be slow. Due to the limited number of patients enrolled, further multicentric studies are needed.

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T-33

New and old therapy against Carbapenemase-Producing Klebsiella pneumoniae (kpc) infections in the cirrhotic patient: a retrospective analysis

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Introduction: Infections by Klebsiella pneumoniae carbapenemase-producing (KPC-Kp) in cirrhotic patients are of great concern. The choice of an appropriate therapeutic approach to fight KPC-Kp infections remains an important challenge. Ceftazidime-Avibactam (CAZ-AVI), the new standard of care, shows great promise compared to older regimens, such as Colistin or double-carbapenem. There is little data comparing the different antibiotic therapy in cirrhotic patients.

Aim: Compare clinical outcomes of different therapeutic strategies in cirrhotic patients with KPC infections.

Material and Method: This is an observational retrospective study performed in cirrhotic patients with a proven KPC-Kp infection, divided into the 'Group A' treated with non-CAZ-AVI therapies between 2009-2017 and 'Group B' treated with CAZ-AVI, between 2018-2019. The clinical outcomes was in-hospital mortality, time to cure and length of hospital stay after infection onset. Safety was assessed by occurrence of side effects and common complications. 30 cirrhotic patients were included (28 males and 2 females), with a mean age of 60 ± 10 yrs. 38 episodes of KPC-Kp infections were observed (64 % in the Group A and 36 % in the Group B), with baseline data showing no significant differences between the groups. The most common sites were the urinary tract (46 %), respiratory tract (23 %) and blood (18 %). A univariate analysis showed no significant differences in crude mortality (31 % vs 44 %, $p = 0.442$) nor in infection-related mortality (8 % vs 28 %, $p = 0.158$) between the two groups. No significant differences were found in any other variable, except for a significantly higher rate of infection relapses ($p = 0.001$) in group A, and a longer post-infection hospital stay in group B ($p = 0.048$).

Conclusion: The lack of significant improvement in clinical outcomes when using CAZ-AVI therapy in cirrhotic patients with KPC-Kp infections invites further investigations and emphasizes the importance of implementing methods of infection-prevention. fx6

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T-34

Cost of Illness of Primary Biliary Cholangitis in Lombardia

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The burden of Primary Biliary Cholangitis (PBC) has never been characterised at population-level. We aimed to estimate the cost of illness of PBC in Lombardy Region, Italy. PBC cases were defined as individuals with at least a single episode of hospitalization attributed to code 571.6 (ICD–9 – Biliary Cirrhosis) or with a disease exemption code 008.571.6, (Biliary Cirrhosis) from year 2007 to year 2017. Case finding was further refined excluding patients not receiving ursodeoxycholic acid and those treated with antivirals for hepatitis B and C. Data are representative of the context of Lombardia Region (located in Northern Italy, with a population of about 10 million inhabitants) and costs are calculated assuming the perspective of Regional Health Service. Only health services considered clinically related to the PBC diagnose were considered, and direct costs were estimated only for services related to PBC in 2017 and subdivided as outpatient and inpatient activities. The point of view assumed in the analysis is that of the Regional Health Service of Lombardia Region. We identified 970 adult patients, 810 (83.5 %) were females, with a mean age of 61 years. Direct medical costs in 2017 were equal to € 916,763, with € 459,506 (50.3 %) deriving from inpatient activities. These were mostly due to liver transplant (30.5 %) and cirrhosis complication (20.6 %). Costs from outpatient activities were equal to € 109,090 (11.9 %). Of note, only 52.8 % were prescribed to perform biochemicals tests: of those 72 % had alkaline phosphatase checked. Cost of drugs used to manage was € 345,167 (37.7 %). The main direct costs component for PBC are inpatient activities due to the progression of disease, which might be potentially reduced as a result of the adoption of new treatments. The analysis of outpatient's activities suggests an inadequate monitoring activity of patients affected by PBC.

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T-35

Hepatocyte-specific deletion of ERK5 worsens insulin resistance in a murine model of nonalcoholic fatty liver disease (NAFLD)

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Introduction: The extracellular signal-regulated kinase 5 (ERK5) is a member of the Mitogen-Activated Protein Kinases family highly expressed in hepatocytes, macrophages and stellate cells, and we recently generated hepatocyte-specific ERK5 knock-out mice (ERK5ΔHep). The aim of this study is to investigate the role of hepatocyte ERK5 in a murine model of NAFLD.

Methods: ERK5ΔHep and control mice were fed with a high-fat diet (HFD) for 16 weeks. For glucose tolerance test (GTT) mice were injected with 1 g/kg BW glucose i.p.. Insulin tolerance test (ITT) was performed by injecting 0.8 U/kg BW of regular insulin i.p.. A murine hepatocyte cell line (MMH) was silenced using lentiviral vectors encoding shRNA for the ERK5 gene. Mitochondrial depolarization was assayed using the TMRE staining protocol. OXPHOS metabolism was measured by Seahorse.

Results: ERK5ΔHep mice exhibited impaired glucose tolerance and reduced insulin sensitivity in comparison to the control group. Body weight and food consumption were similar, while visceral fat was increased in ERK5ΔHep. MMH stably silenced for ERK5 showed reduced Akt activation following insulin stimulation. When cells were challenged with palmitic acid and then stimulated with insulin, Akt activation was completely abrogated in MMH/shERK5. In addition, measurement of mitochondrial membrane potential indicated a strong depolarization in MMH/shERK5 cells, which also showed an impairment of mitochondrial OXPHOS, indicating a profound impact of ERK5 deficiency on mitochondrial functions. In MMH/shERK5 cells, expression of peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α), a pivotal regulator of mitochondrial biogenesis and function, was upregulated. Additionally, expression of TRIB3, a negative regulator of insulin signaling (through inhibition of Akt) under the control of PGC-1α was higher in MMH/shERK5 cells, and its expression was further enhanced by palmitic acid.Increased expression of PGC-1α protein and TRIB3 was also observed also in liver tissues from HFD-fed ERK5ΔHep mice.

Conclusion: We have elucidated a novel pathway connecting expression of ERK5 in hepatocytes to the regulation of insulin sensitivity through PGC-1α, TRIB3, and Akt, which is relevant to the pathogenesis of NAFLD.

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T-36

The PSRC1 rs599839 A>G variant disentangles the risk of coronary artery disease and hepatocellular carcinoma in Italian NAFLD patients

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Introduction: Inherited variants, regulating hepatic lipid handling, increase the susceptibility to nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), fibrosis and hepatocellular carcinoma (HCC). Dyslipidemia and enhanced cardiovascular risk are hallmarks of NAFLD. The rs599839 A >G variant in PSRC1, in CELSR2-PSRC1-SORT1 locus, has been associated with coronary artery disease (CAD) and reduced circulating lipids.

Aim: To examine the impact of the rs599839 variant on metabolic traits and liver damage in patients at risk of NASH.

Materials and Methods: We studied the impact of the rs599839 variant in 1224 Italian NAFLD (Liver Biopsy Cohort (LBC)), in 500,000 individuals (UK Biobank Cohort (UKBBC)) and in 366 HCC (The Cancer Genome Atlas (TCGA)). Hepatic expressions of PSRC1, SORT1 and CELSR2 genes were evaluated by RNAseq (n = 125).

Results: The rs599839 G allele was associated with lower LDL (beta:-0.19; 95%c.i.-0.3–0.09; p = 0.0003), higher HDL (beta:0.07; 95%c.i.0.03-0.10; p = 0.0008), reduced intima-media thickness (beta:-0.06; 95%c.i.-0.1–0.01; p = 0.008), decreased carotid plaques (OR:0.23; 95%c.i.0.04-1.3; p = 0.09) and hypertension (OR:0.43; 95%c.i.0.18-0.98; p = 0.04) in LBC and with lower cholesterol in UKBBC. G allele was associated with ballooning (beta:0.26; 95%c.i.0.01-0.51; p = 0.03) and HCC risk (OR:1.92; 95%c.i.1.06-3.50; p = 0.03; N = 72 cases) in LBC, but not in UKBBC. Carriers of G allele showed increased hepatic expression of PSRC1, SORT1 and CELSR2 (p< 0.0001). PSRC1 expression negatively correlated with that of genes involved in lipoprotein release (APOB and DGAT2), while positively with that of markers of proliferation (PCNA and TP53) (p< 0.0001). In TCGA, PSRC1 expression was associated with tumor stage (beta:0.40; 95%c.i.0.05-0.27; p = 0.006), histological grade (beta:0.17; 95%c.i.0.05-0.29; p = 0.005) and tumor extension (beta:0.17; 95%c.i.0.06-0.28; p = 0.003). As in LBC, PSRC1 expression negatively correlated with that of APOB and DGAT2, and positively with SORT1, CELSR2 and PCNA (p< 0.01).

Conclusions: PSRC1 rs599839 A >G variant disentangles the risk of CAD and HCC in NAFLD patients, likely by modulating PSRC1, SORT1 and CELSR2 expressions.

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T-37

Tropifexor, a highly potent FXR agonist, produces robust and dose-dependent reductions in hepatic fat and serum alanine aminotransferase in patients with fibrotic NASH after 12 weeks of therapy: FLIGHT-FXR Part C interim results

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Introduction: FLIGHT-FXR (NCT02855164) is a phase 2 randomized, double blind, placebo-controlled, 3-part, adaptive-design study to assess the safety, tolerability, and efficacy of several doses of tropifexor (LJN452, TXR) in patients with non-alcoholic steatohepatitis (NASH). AIM: here, we present Part C prespecified interim results at W12.

Materials and Methods: the effects of higher doses of TXR on biomarkers and histology will be evaluated over 48 weeks in patients with biopsy-proven NASH and fibrosis stages 2-3. 152 patients were randomized to receive placebo (N = 51), TXR 140 μg (N = 50) or TXR 200 μg (N = 51) once daily. Endpoints at W12 included overall safety and changes in alanine aminotransferase (ALT), hepatic fat fraction (HFF), gamma glutamyl transferase (GGT), and body weight.

Results: endpoints were met for TXR 200 μg. Relative HFF reduction by ≥30% was achieved in 20%, 32%, and 64% of patients in the placebo, TXR 140 μg, and TXR 200 μg groups, respectively. Serious adverse events frequency was low and comparable across groups. Among patients with pruritus, >60% in both TXR groups and all in the placebo group experienced Grade 1 severity events. Treatment discontinuation rates due to pruritus were low (TXR 140 μg: n = 1 [2%]; TXR 200 μg: n = 3 [6%]; placebo: 0%). A dose-related increase in low density lipoprotein-cholesterol (LDL-C) was seen. None of the lipid changes led to treatment discontinuation or dose reduction.

Conclusions: in this prespecified interim analysis of Part C, higher doses of TXR resulted in robust and dose-dependent decreases in ALT, HFF, and body weight with good safety and tolerability after 12 weeks of treatment. Like other farnesoid X receptor agonists, these higher doses were associated with mild pruritus and minor dose-related increase in LDL-C. Liver histology changes from this trial, along with trials of TXR combined with other drugs will define future therapeutic options in fibrotic NASH.

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T-38

PNPLA3 rs738409 C >G variant is associated with a higher risk of liver fibrosis progression assessed by FIB-4 and stiffness by fibroscan in patients with non-alcoholic fatty liver disease

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Background&Aims: A single nucleotide polymorphism in patatin-like phospholipase domain-containing-3(*PNPLA3*) gene has been associated with a higher prevalence of NASH and severity of fibrosis, hepatocellular carcinoma and liver decompensation, but there are no data from prospective studies about fibrosis progression with this polymorphism.We investigated whether in NAFLD,PNPLA3rs738409 variant associates with fibrosis progession evaluated by noninvasive tools like FIB-4 and liver stiffness measurement(LSM) by FibroScan.

Methods: In 579 consecutive individuals with histological diagnosis of NAFLD,FIB-4 and LSM were obtained at enrollement and at last follow-up visit.According to FIB-and LSM, patients were classified as at low, medium and high risk for F3-F4 fibrosis(<1.45,1.45-3.25 and >3.25,respectively for FIB-4;< 7.9,7.9-9.6 and >9.6KPa,respectively,for LSM).Fibrosis progression was defined as transition from low to medium or high risk, or from medium to high risk.Fibrosis regression was defined as transition from high to medium or low risk, or from medium to low risk.We detected the rs738409 G >C polymorphism in DNA from blood using the TaqMan assay.

Results: FIB-4 and LSM had a good diagnotic accuracy for the diagnosis of F3-F4 fibrosis(AUC0.871 and 0.887,respectively).430patients(61.2%males,mean age 51.7years,mean BMI 30.4 Kg/m^2,50.1% with IFG/diabetes)had paired FIB-4 evaluation during a mean follow-up time of 59.5 months.At baseline 61.2%,26% and 12.8% were at low, medium and high risk of F3-F4 fibrosis,respectively.Fibrosis progression was observed in 79patients(21.1%) and independently associated with older age(OR 1.05;95%CI,1.02–1.08;P< 0.001),time of follow-up(OR1.01;95%CI,1.01–1.02;P< 0.001),PNPLA3rs738409 variant(OR1.57;95%CI,1.06–2.34;P = 0.02).Fibrosis regression was oserved in 41patients(24.6%);no variables could predict it.Similarly,342patients(64.9%males, mean age50.8years,mean BMI29.8Kg/m^2,49.4% with IFG/diabetes)had paired LSM evaluation during a mean follow-up time of 61.4months.At baseline 48.2%,14.3% and 37.4%were at low, medium and high risk of F3-F4 fibrosis,respectively.Fibrosis progression was observed in29patients(13.4%)and independently associ-

ated with IFG/diabetes(OR3.32;95%CI,1.27–8.67;P = 0.01)and PNPLA3rs738409 variant(OR1.78;95%CI,1.02–3.27;P = 0.04).Fibrosis regression was oserved in 71patients(40.1%) and independently associated with changes in ALT levels from follow-up to baseline(OR0.98;95%CI,0.97–0.99;P = 0.001).

Conclusions: Patients with NAFLD carrying *PNPLA3*rs738409G >C variant are at higher risk of fibrosis progression.

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T-39

Histological renal damage and eligibility for kidney donation are worse in patients with biopsy-proven non-alcoholic steatohepatitis compared with simple steatosis

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Introduction Non-alcoholic fatty liver disease (NAFLD) has been related with multi-organ comorbidities. Nevertheless, the relationship with kidney disease has been poorly investigated.

Aim The aim was to verify whether NAFLD patients have higher risk of kidney disease evaluated during the process of eligibility for kidney donation and histological scores of damage.

Methods This study is based on the register of Reference Center for Transplantation of Emilia-Romagna, containing data collected during the work-up for the determination of eligibility of potential donors. After having excluded patients with incomplete work-up (771), with non-NAFLD liver diseases (153) and whose liver was utilized for transplantation without biopsy (414), 722 consecutive subjects submitted to liver biopsy from 2008 to 2018 were enrolled (62y, range 18–89). Patients were classified according to the review of histological reports: healthy liver ($n = 166$: no steatosis, fibrosis or inflammation), simple steatosis ($n = 358$: steatosis involving >5% of the parenchyma, no fibrosis and inflammation), and non-alcoholic steatohepatitis (NASH, $n = 198$: fibrosis or inflammation). The risk of having kidneys not eligible for donation was assessed in these groups. Finally, 403/722 had been submitted to both liver and kidney biopsy (62y, range 18–89). Kidney damage (Karpinski score) was verified in this population.

Results Distributions of age, diabetes and hypertension were similar in the groups. NASH showed higher risk of having kidneys not eligible for donation than healthy liver. Odds ratios (OR) were: left kidney 1.9, p = 0.005; right 1.7, p = 0.017. Higher risk of histological kidney damage (Karpinski ≥ 3, Figure 1) and vascular damage involving >20% of the glomeruli (right kidney OR 1.9, $p = 0.029$) were found in NASH group (OR: left kidney 2, $p = 0.022$; right 2.6, $p = 0.002$). Simple steatosis showed the same risk than healthy liver.

Conclusion NASH is associated with increased risk of kidney damage. These findings might indirectly suggest generalized inflammatory pathway in the subset of patients developing NASH.

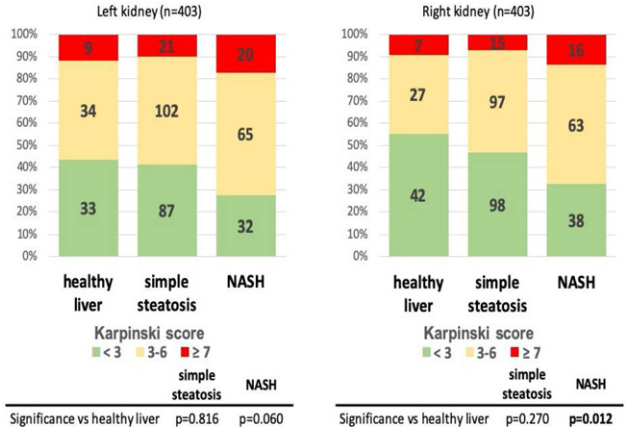

Figure 1. Distribution of Karpinski classes (Karpinski score< 3, 3-6 and >7) in patients with healthy liver, simple steatosis and NASH.

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T-40

SerpinB3 inhibition as a novel target therapy for non-alcoholic steatohepatitis

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Introduction: Nonalcoholic fatty liver disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH) are relevant public health issues and their prevalence is increasing in parallel with the increase of obesity and diabetes, but pharmacological treatments are still lacking. SerpinB3 is a serine protease inhibitor that is upregulated in the liver in relation to the extent of hepatic damage. In animal models of NASH, SerpinB3 transgenic mice display increased fibrosis and inflammation. 1-Piperidine Propionic Acid (PPA) has been identified as SerpinB3 inhibitor.

Aim: To evaluate the effect of PPA on NASH experimental models.

Method: Cell lines with different SerpinB3 expression have been incubated with PPA to assess its inhibitory activity. Recombinant SerpinB3 was added to primary monocytes in the presence or absence of PPA. SerpinB3-transgenic and SerpinB3-KO mice and their controls were fed on MCD and CDAA diets to induce experimental NASH. Starting from the second month mice were injected daily with PPA and were sacrificed at week 8 (MCD diet) and 12 (CDAA diet). Liver pathology, IHC for F4/80, Sirius red staining, fibrosis and inflammation gene expression was carried out at sacrifice.

Results: In cell lines PPA was found to inhibit SerpinB3 mRNA expression in a dose dependent manner. In monocytes SerpinB3 induced overexpression of sCD163 that was inhibited by PPA. SerpinB3-KO mice showed significantly lower steatosis, inflammation and fibrosis after both dietary regimens, while opposite findings were observed in SerpinB3 transgenic mice. Treatment with PPA reverted these features, leading to liver profiles similar

to controls. PPA significantly decreased gene expression of fibrosis and inflammation and lead to the activation of PPAR-gamma and PPAR-alpha.

Conclusion: SerpinB3 has been identified as a new druggable target for NASH and PPA proved to be an efficient compound that markedly reduces NASH through the inhibition of SerpinB3 and the activation of PPAR-gamma and alpha in the liver.

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T-41

A cholestatic pattern predicts liver outcomes in patients with nonalcoholic fatty liver disease

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Background&Aims: The expression of NAFLD(non-alcoholic fatty liver disease) in liver biochemistry has usually a "cytolitic" pattern(raised ALT,normal ALP),but a "cholestatic" pattern(low ALT, raised ALP),can also be observed.We aimed to assess the prevalence of the "cholestatic" pattern in subjects with NAFLD at different stage of fibrosis and its impact on development of liver events and death.

Methods: A cohort of consecutive NAFLD patients diagnosed by biopsy or, in the case of cirrhosis, by transient elastography and/or evidence of portal hypertension.Patients were divided into 3 groups based on the pattern of elevated liver enzymes:predominantly cholestatic pattern (C), predominantly hepatocellular pattern (H) and mixed (M) by using the formula (ALT/ALTULN)/(ALP/ALPULN).C group is defined by a ratio of less than 2;the H group with a ratio of more than 5;the M group with a ratio between 2-5.Liver outcomes(ascites,encephalopathy,variceal bleeding,jaundice and hepatocellular carcinoma),as well as total and liver deaths were recorded during follow-up.

Results: 529 patients(62.4% males,mean age49.8 years,mean BMI30.3 Kg/m^2,46% with diabetes,34.8% with F3-F4 fibrosis,21.4% with cirrhosis) with a mean follow-up time of 68.3 months were enrolled.H, M and C patterns were found in 159(30.1%),258(48.8%) and 112(21.1%)patients,respectively.The prevalence of the C pattern was significantly higher in patients with cirrhosis when compared to all the other(17.7% in F0-F1,8.4% in F2,12.7% in F3 and 46% in cirrhosis,respectively,$p < 0.001$).27(5.1%)hepatic decompensation,16(3%) HCC,17(3.2%) total deaths and 14(2.6%) and liver deaths were recorded, all occurring in patients with F3-F4 fibrosis.In the entire cohort, at multivariate Cox regression analysis adjusted for age,IFG/diabetes(not for overall mortality),PLT,albumin and F3-F4 fibrosis,C vs M vs H pattern was independently associated with a higher risk of hepatic decompensation(HR2.42,95%C.I. 1.02-5.74,$p = 0.04$),HCC(HR2.90,95%C.I. 1.01-8.34,$p = 0.04$) and liver deaths(HR3.98,95%C.I. 1.09-14.4,$p = 0.03$).Comparable results were observed in patients with F3-F4 fibrosis for liver decompensation(HR2.63,95%C.I. 1.11-6.23,$p = 0.02$),HCC(HR2.94,95%C.I. 1.03-8.41,p = 0.04)and liver deaths(HR3.98,95%C.I. 1.09-14.4,$p = 0.03$).

Conclusions: Patients with NAFLD cirrhosis have frequently a cholestatic pattern.This is associated to a higher risk of decompensation,HCC and liver death.

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T-42

Liver stiffness measurement by fibroscan predicts the occurrence of liver-related events and death in patients with NAFLD-related compensated advanced chronic liver disease

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Background&Aims: Patients with advanced fibrosis related to nonalcoholic fatty liver disease(NAFLD) are at risk of developing hepatic and extrahepatic complications. Liver stiffness measurement(LSM)by FibroScan has a good diagnostic accuracy for advanced fibrosis and can also predict the occurrence of liver-related events in patients with chronic hepatitis C.Data about the accuracy of LSM in the prediction of events in NAFLD,especially in patients with NAFLD and F3-F4 fibrosis,are scarce. We investigated whether,in a large cohort of patients with NAFLD and compensated advanced chronic liver disease(cACLD),LSM at baseline,at follow-up,and its variations are accurate for the prediction of hepatic and extrahepatic events.

Methods: We retrospectively evaluated consecutive individuals with NAFLD with histological diagnosis of F3-F4 fibrosis and/or LSM >10KPa,and prospectively followed-up for at least 6 months.LSM was measured by FibroScan using M or XL probe,and recorded at baseline and within 1year from the last follow-up visit.Difference between follow-up and baseline LSM(delta LSM)was categorized as < -20%, -20% to + 20%, > + 20%.Hepatic(liver decompensation–ascites,encephalopathy,variceal bleeding and jaundice-and hepatocellular carcinoma(HCC))and extrahepatic(cardiovascular and extrahepatic cancers)events,as well as overall and liver-related death were recorded during follow-up.

Results: 937 patients(56.5%males,mean age60.2 years,mean BMI32.5Kg/m^2,61.1%with diabetes,78.6%with cirrhosis)with a

median follow-up of 37.9months were enrolled.67(7.2%)hepatic decompensation,34(3.6%)HCC,33(3.5%)cardiovascular events, 25(2.7%)extrahepatic cancers,56(6%)all-cause deaths and 33(3.5%)liver-related deaths were recorded.By Cox regression analysis and after adjusting for age,gender(only for HCC),serum albumin and platelets,baseline LSM was independently associated with occurrence of hepatic decompensation(HR1.03,95%C.I. 1.02-1.04,$p < 0.001$),HCC(HR1.02, 95%C.I. 1.00-1.04,$p = 0.01$) and liver-related death(HR1.03,95%C.I. 1.02-1.04,$p < 0.001$).In a subgroup of 494patients with available follow-up LSM,delta LSM was independently associated with hepatic decompensation(HR1.54,95%C.I. 1.04-2.48,$p = 0.04$),together with baseline LSM(HR1.03,95%C.I. 1.00-1.05,$p = 0.01$) and with liver related death(HR1.87,95%C.I. 1.05-3.34,$p = 0.03$).

Conclusions: In patients with NAFLD and F3-F4 fibrosis baseline LSM can predict the occurrence of hepatic decompensation,HCC and liver-related death.Moreover,changes in LSM during follow-up can further help to identify patients at higher risk of hepatic decompensation and liver-related death.

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T-43

A higher dietary intake of phenolic acids is protective against insulin resistance and non-alcoholic fatty liver disease

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Background & Aims: The inverse association between non-alcoholic fatty liver disease (NAFLD) and diet rich in fruit and vegetables has been demonstrated, but the specific compounds that may be responsible for this association need to be elucidated. The aim of this study was to test the association between phenolic acids (PA) consumption, NAFLD, and insulin resistance (IR).

Methods: A cross-sectional cohort of individuals included in a metabolic screening program was studied. Liver steatosis was evaluated by ultrasonography and quantified by the HepatoRenal Index (HRI); fibrosis was assessed by FibroTest; IR by the sample upper quartile of HOMA score. Dietary intake was measured by food frequency questionnaire (FFQ). Phenolic acids food content was calculated according to Phenol Explorer.

Results: A total of 789 subjects were included (52.6% men, age 58.83 ± 6.58 years). Higher (above the upper median) phenolic acids intake was inversely associated with the presence of NAFLD, higher HRI and IR ($OR = 0.69$, 95%CI 0.49-0.98, $P = 0.036$; $OR = 0.64$, 95%CI 0.45-0.91, $P = 0.013$; OR = 0.61, 95%CI 0.42-0.87, $P = 0.007$, respectively), adjusting for age, gender, BMI, dietary and lifestyle factors. Considering specific classes of PA, higher hydroxybenzoic acids intake was independently associated with lower odds of NAFLD, higher HRI and fibrosis ($OR = 0.72$, 95%CI 0.51-0.99, $P = 0.049$; $OR = 0.63$, 95%CI 0.45-0.89, $P = 0.008$; $OR = 0.28$, 95%CI 0.12-0.64, $P = 0.003$, respectively). Higher hydroxycinnamic acids consumption was independently associated with lower odds of IR ($OR = 0.63$, 95%CI 0.44-0.90, $P = 0.012$).

Conclusion: Phenolic acids may represent food compounds that are protective against insulin resistance and NAFLD.

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T-44

Obeticholic acid (OCA) improves non-invasive markers of fibrosis in patients with non-alcoholic steatohepatitis (NASH): a secondary analysis of the phase 3 Regenerate study

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REGENERATE showed that treatment with OCA improved histological liver fibrosis in NASH patients.[1] However, liver biopsy is an impractical tool to monitor patients' response to therapy.

Here, we evaluate the potential utility of non-invasive tests in monitoring NASH patients with fibrosis during treatment. Patients with fibrosis stages 2 and 3 were randomized (1:1:1) to placebo, OCA 10 mg or OCA 25 mg QD. Change in non-invasive biomarker scores of fibrosis (FIB-4 index, AST to platelet ratio index [APRI]), FibroSure® and NASH (CK-18), and liver stiffness via transient elastography (TE, subset of patients), were assessed. At baseline, average biomarker scores and liver stiffness were similar across treatment groups (ITT; placebo $n = 311$, OCA 10 mg n = 312, OCA 25 mg n = 308; 56% F3). OCA treated patients showed improvement across several measures captured in Regenerate as early as six months after treatment initiation: fibrosis scores (APRI and FIB-4), markers of fibrosis (FibroSure), and markers of definite NASH (CK-18) (table). Improvements were generally dose-dependent and maintained over the duration of 18 months. TE, a surrogate marker for liver fibrosis, decreased from baseline in both OCA groups but increased with placebo at 18 months. Improvements in TE were dose and time dependent and were observed in both F2 and F3 patients; a greater dose-dependent response was observed in F3 patients. Treatment with OCA resulted in early and consistent improvements across several non-invasive measures of fibrosis and NASH, suggesting serum tests are useful for monitoring early treatment response. Liver stiffness as assessed by TE also improved, with a dose-dependent reduction by month 18, consistent with histologic improvement seen in REGENERATE. [1] Interim analysis results at 18 months are based on surrogate endpoints and impact on clinical outcomes has not been confirmed. The REGENERATE study is ongoing to confirm the clinical benefit of OCA.

Table: Change in Non-invasive Markers

LS Mean (SE) Change from Baseline (*p* value)	Placebo (n=311)	OCA 10 mg (n=312)	OCA 25 mg (n=308)
Early Change (at Month 6) in Serum-Based Biomarkers			
FIB-4	0.017 (0.04)	-0.099 (0.04) *p*=0.0328	-0.120 (0.04) *p*=0.0119
APRI	-0.018 (0.03)	-0.153 (0.03) *p*=0.0011	-0.209 (0.03) *p*<0.0001
CK-18 (M30), U/L	43.7 (32.56)	-127.1 (32.4) *p*<0.0001	-222.7 (32.45) *p*<0.0001
FibroSure	0.022 (0.0069)	-0.051 (0.0069) *p*<0.0001	-0.072 (0.0070) *p*<0.0001
Change at Month 18 in Transient Elastography			
Liver Stiffness by TE (kPa)	1.11 (0.54)	-0.56 (0.55) *p*= 0.0187	-1.30 (0.56) *p*= 0.0008

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T-45

Selective LXR α intestinal activation reduces hepatic inflammation and fibrosis during the development of chronic liver injury

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Introduction: Liver fibrosis is the result of the wound healing response during chronic liver injury. Liver X receptors (LXRs) exert anti-inflammatory effects, but their activation is associated with hypertriglyceridemia and liver steatosis, due to hepatic fatty acid synthesis.

Aims: Selective induction of LXRs in the gut might regulate hepatic inflammation and fibrogenesis via specific gut-liver signaling.

Materials and Methods: Mice with intestinal constitutive LXRα activation (iVP16-LXRα) were exposed to intraperitoneal injection of carbon tetrachloride (CCl_4) for 8 weeks.

Results: iVP16-LXRα mice showed reduced macrophage infiltration associated with lower expression of hepatic pro-inflammatory genes interleukin 6 (IL-6), tumor necrosis factor-α (TNFα) and NF-kB. Decreased hepatic inflammation reduced fibrogenesis, measured by immunohistochemistry for α-smooth muscle actin (α-SMA), and transforming growth factor β (TGFβ) and metallopeptidase inhibitor-1 (TIMP1) gene expression, which, in turn, lowered collagen deposition. Furthermore, gut LXR activation decreased hepatic oxidative stress, evaluated by malonildialdehyde (MDA) quantification and expression of (NADPH) oxidases. Intestinal LXR activation increased high-density lipoproteins (HDL) synthesis in the gut, shown by their plasmatic quantification and by gene expression of intestinal ATP-binding cassette transporter 1 (ABCA1). *In vitro,* HDL induced a shift from M1 to M2 phenotype of Kupffer cells (KCs) and, reduced NF-kB expression and decreased oxidative stress in hepatocytes. These beneficial effects were not associated with hepatic steatosis development, as shown by the expression of sterol regulatory element-binding protein 1 (SREBP1-c) and by the quantification of triglyceride content.

Conclusions: Intestinal LXRα activation might represent a new target for the treatment of chronic liver injury by modulating macrophages and hepatocytes response to injury, thus reducing hepatic inflammation, without the occurrence of the side effects related to hepatic LXR induction.

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T-46

The anti-inflammatory effects of hydroxytyrosol and vitamin e on paediatric NAFLD

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Introduction Nonalcoholic fatty liver disease (NAFLD) is becoming an increasing cause of chronic liver disease even in children. In the absence of approved pharmacological therapies, the use of natural supplements that may improve oxidative stress and inflammation represents together to lifestyle interventions a potential therapeutic approach for paediatric NAFLD.

Aim The aim of the study is to test the potential anti-inflammatory of a mixture of Hydroxytyrosol (HXT) and vitamin E in paediatric patients with NAFLD.

Materials and Methods We performed a randomized double-blind placebo-controlled trial. Eighty adolescents with biopsy-proven NAFLD were enrolled. Forty patients received an oral dose of HXT and vitamin E and 40 received the placebo for 4 months. Seventy patients completed the study.

Results Patients in the treatment arm showed a significantly decrease of HOMA-IR and triglyceride levels ($p < 0.05$), but not in anthropometric parameters. Moreover, in the treatment arm, there was a significant reduction of severe steatosis, while no difference on steatosis degree in placebo arm. After 4-months, the levels of IL-1β and TNF-α were reduced in both groups of treatment, while the circulating levels of IL-10 was increased and IL-6 was decreased significantly only in the treated group. It should also be noted that in the treatment arm there was a significant reduction in the levels of uric acid, triglycerides, LDL-cholesterol, as well as an improvement in HDL-cholesterol values ($p < 0.05$), compared to the placebo arm. Moreover, our data compared with the analysis of oxidative stress parameters showed that their decrease in the treatment group correlated with the increase of IL-10.

Conclusions The treatment with HXT and Vitamin E reduced the systemic inflammation with a significantly decrease of IL-6, but above all it increases the expression of IL-10, which is able to inhibit the synthesis of pro-inflammatory cytokines.

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T-47

Validation of Interleukin-32 as a new circulating fatty liver biomarker

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Introduction and Aims Efforts to manage nonalcoholic fatty liver disease (NAFLD) are limited by the absence of accurate non-invasive biomarkers. The I148 M variant in *PNPLA3* is a major determinant of the development and progression of NAFLD associated with a distinct disease pathophysiology. Aim of the study was to identify novel candidate NAFLD biomarkers by examining the hepatic transcripts associated with severe NAFLD in obese individuals in patients stratified by the presence of the PNPLA3 I148 M variant.

Methods Hepatic transcriptomic analyses were conducted in 125 liver-biopsied severely obese individuals. "Severe NAFLD" was defined as the presence of steatohepatitis, or NAS ≥ 4, or fibrosis stage ≥ 2. RNA was isolated from liver biopsies and sequenced (HiSeq4000). After reads alignment (STAR software) and count (RSEM), differential expression was investigated at gene (DESeq2) and pathway (GSEA) level. Plasma IL32 was measured in other 71 liver-biopsied obese patients (Bariatric cohort) by ELISA (R&D) 174 liver-biopsied patients (Hepatology Service Cohort).

Results Principal component analysis revealed that carriage of the PNPLA3 I148 M variant was one of the most important determinant of transcriptome variability. Indeed, carriage of the variant highly correlated with the first two principal component of transcriptome variability ($p < 0.001$, both). Consistently, differential gene expression analysis revealed overexpression of inflammatory genes together with a downregulation of metabolic genes in PNPLA3 I148 M carriers. Conversely, severe NAFLD patients overexpressed genes involved both in inflammatory response and oxidative metabolism. Importantly, IL32 showed the strongest association with severe NAFLD (adjusted $p = 1^{*}10^{-6}$). In the bariatric cohort, plasma IL32 levels were associated with both NAFLD and severe NAFLD ($p < 0.01$ both) and results were confirmed in the Hepatology Service Cohort ($p < 0.0001$ NAFLD and $p < 0.01$ severe NAFLD).

Conclusion This work highlights PNPLA3 I148 M as the major determinant of transcriptome variability and IL32 as a potential biomarker for NAFLD early diagnosis.

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T-48

Moderate alcohol consumption is associated with risk of fibrosis in patients with non-alcoholic fatty liver disease

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Introduction: The role of moderate daily alcohol consumption (<30 g for men and 20 g for women) in determining the risk of progression of non-alcoholic fatty liver disease (NAFLD) is unclear.

Aim: The aim of our study was to evaluate whether moderate drinking is associated with risk of fibrosis in patients with NAFLD.

Materials and Methods: We enrolled 169 consecutive subjects with NAFLD (January 2015-May 2019) submitted to liver stiff-

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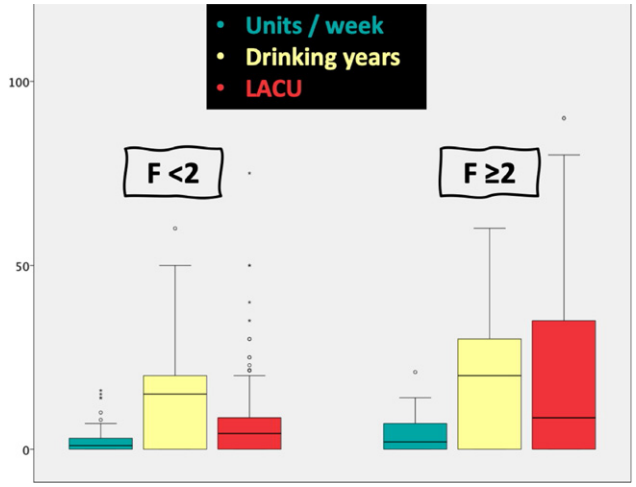
ness measurement (Aixplorer 2D shear wave elastography) and to a questionnaire on current and lifetime alcohol consumption. The interview allowed us to generate a new indicator for lifetime alcoholic cumulative units (*LACU* = drinking years x median alcohol units in a week / 7) in order to better average weekly alcohol consumption and consider time-related cumulative risk. Patients were divided in three groups according to liver stiffness: no significant fibrosis (F0/F1, < 7.1 KPa, *n* = 119), moderate or severe fibrosis (F2-F3, 7.1-12.9 KPa, *n* = 34), cirrhosis (F4, ≥13 KPa, n = 16).

Results: Median current alcoholic consumption (weekly units) was ($p = 0.098$): 1 (range 0-16) for F0/F1, 2 (0-14) for F2-F3 and 0 for F4 (0-21). Median drinking years were (p = 0.007): 15 (0-60) for F0/F1, 27.5 (0-60) for F2-F3 and 7.5 for F4 (0-40). Median LACU was ($p = 0.007$): 4 (0-114) for F0/F1, 18 (0-90) for F2-F3 and 2 for F4 (0-90). Figure 1 displays these results. Diabetes was present in 34.3% of F0/F1, 49.2% of F2-F3 and 22.9% of F4 ($p < 0.001$). LACU and diabetes resulted independent risk factors for having fibrosis F≥2 at multivariate analysis. Odds ratios were respectively 1.021 (1.007-1.035, $p = 0.003$) and 8.892 (3.824-20.676, $p < 0.001$).

Conclusion: Moderate drinking evaluated with LACU is associated with risk of significant fibrosis in patients with NAFLD, independently from diabetes. This result suggests that a quantitative threshold for alcohol consumption cannot be defined in this population.



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T-49

Risk factors for significant fibrosis differently affect patients with non-alcoholic liver disease depending on gender

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Background: Several risk factors are involved in non-alcoholic fatty liver disease (NAFLD) progression, but whether their role is different in males (M) and females (F) is unclear. The aim of this study is to verify whether NAFLD-related risk factors differently affect the disease according to gender.

Methods: We enrolled 230 consecutive patients (132 M, 98 F) with NAFLD. Patients underwent a questionnaire on lifestyle (alcohol consumption, smoking, physical activity) and metabolic risk factors (diabetes, dyslipidemia, cardiovascular disease and BMI). Drinking was evaluated with lifetime alcoholic cumulative units (LACU): drinking years x median weekly units / 7. Liver stiffness was measured with Aixplorer 2D shear wave elastography (SWE). Risk of developing significant fibrosis (F≥2 with SWE≥7.1 KPa, *n* = 74) for each potential risk factor was assessed separately according to gender.

Results: Distribution of NAFLD-related risk factors significantly differed between the genders (Table 1). F showed higher age, lower physical activity and alcohol exposure. Despite a similar distribution of fibrosis, hepatocellular carcinoma was rarer in F. Risk of F≥2 was found for age, alcohol exposure, BMI, diabetes and inactive lifestyle in M; in F only advanced age and diabetes were associated with risk of F≥2.

Conclusion: Targeting diabetes must represent the cornerstone of NAFLD management. Different vicious behaviors affect the risk of F≥2 depending on gender in patients with NAFLD: M are more prone to moderate drinking habit while F have a more sedentary lifestyle. Hence, tailored lifestyle interventions should be adopted.

	Males	Females	
Age	**52 (18-85)**	**61 (18-88)**	**<0.001**
BMI	29 (20-44)	29 (18-48)	ns
Smokers	49.5%	40.4%	ns
Drinkers	**84.1%**	**64.4%**	**0.001**
LACU	**6.1 (0-160)**	**2.9 (0-114)**	**0.003**
Physical activity			**0.022**
No	**6%**	**8.8%**	
Poor	**47.8%**	**63.7%**	
Adequate	**46.2%**	**27.5%**	
Hypertension	61.5%	56.5%	ns
Diabetes	17.0%	25.0%	ns
Cardiovascular diseases	25.3%	15.6%	ns
Dyslipidemia	66.7%	73.0%	ns
F≥2	**28.4%**	**36.5%**	**ns**
HCC	**10.6%**	**3.1%**	**0.031**
	OR for F≥2 (M)	**OR for F≥2 (F)**	
Age	**1.03 (1.03-1.06), p=0.032**	**1.11 (1.04-1.17), p=0.001**	
Diabetes	**8.67 (2.98-25.19), p<0.001**	**8.58 (2.67-27.54), p<0.001**	
LACU	**1.02 (1.00-1.04), p=0.031**	1.02 (0.99-1.04), p=0.061	
BMI	**1.19 (1.04-1.35), p=0.009**	1.05 (0.96-1.14), p=0.258	
Physical activity			
Poor vs No	**0.08 (0.01-0.80), p=0.031**	0.53 (0.12-2.40), p=0.410	
Adequate vs No	**0.07 (0.01-0.74), p=0.026**	0.26 (0.05-1.44), p=0.124	

Median and range are shown for continuous data in the upper part. The lower part display odds ratios (OR) for F≥2.

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T-50

NAFLD fibrosis score identifies not only advanced liver fibrosis but also chronic vascular complications in type 2 diabetic patients

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Introduction: In patients with type 2 diabetes (T2DM) liver fibrosis detected by either histology or FibroScan® has been related to liver-related and diabetic vascular complications.

Aim: Since liver biopsy and FibroScan® are not easily available in routine diabetes care, we evaluated whether liver fibrosis assessed by NAFLD fibrosis score (NFS), correlates with chronic vascular complications in T2DM patients.

Matherials and Methods and Results: 394 outpatients with T2DM consecutively attending five Italian diabetes centers underwent liver ultrasonography (US) and evaluation of macro-/micro-vascular diabetic complications. In US-detected NAFLD patients, liver fibrosis was evaluated by FibroScan® and NFS. Steatosis by US was present in 351 (89%) patients, of whom 58% had at least one chronic vascular complication, 19% a macrovascular (myocardial infarction and/or ischemic stroke) and 32% a microvascular one (24% chronic kidney disease; 16% retinopathy; 6% peripheral neuropathy). Prevalence of advanced fibrosis by either FibroScan® (LSM $\geq$ 8.7/7.2 kPa for the M/XL probe) or NFS ($\geq$0.676) was 14% and 18% respectively, with acceptable concordance between the methods. Prevalence of macrovascular complications and peripheral neuropathy was higher in patients with NFS $\geq$0.676 compared to those with NFS < 0.676 (31% vs. 15%, $p = 0.007$; 19% vs. 3%, $p < 0.001$). NFS was significantly associated with cardiovascular events and peripheral neuropathy (adjusted-OR 2.2, 95%CI 1.0-4.9; $p = 0.05$ and adjusted-OR 5.5, 95%CI 1.7-18.4; $p = 0.005$, respectively), even after adjustment for centre, sex, smoking, haemoglobin A1c, duration of diabetes, hypertension and use of statins or ACE-I/ARBs (age and BMI not adjusted for because included in the NFS). Similarly, LSM was also independently associated with cardiovascular events and peripheral neuropathy.

Conclusions: NFS, which is an easy and affordable non-invasive test of advanced liver fibrosis, may help clinicians in primary care in identifying patients with T2DM and NAFLD at higher risk of both hepatic and chronic vascular complications, possibly applying more intensive preventive and therapeutic strategies.

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F-01

A multidisciplinary approach to non-alcoholic fatty liver disease (NAFLD) improves cardiovascular risk factors: the experience of a tertiary liver center in UK

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Introduction and Aim: Cardiovascular (CV) disease is the leading cause of death in unselected patients with non-alcoholic fatty liver disease (NAFLD). Although the need of a multidisciplinary approach is highlighted in guidelines, there is lack of data to demonstrate its effectiveness. We assessed the efficacy of a multidisciplinary clinic through control of metabolic comorbidities and surrogate markers of liver involvement.

Materials and Methods Results: Prospectively collected data of patients referred to a multidisciplinary NAFLD clinic in a tertiary hospital in London (UK), comprehensive of a hepatological consultation, cardiovascular risk assessment and dietetic counseling, were analyzed. 273 patients were enrolled (57% males) with a mean age of 56.4 ± 12.1 years. The median follow-up was 18 months. The prevalence of obesity, hypertension and diabetes was 60%, 67% and 50% respectively, while 13.2% had a positive history of CV events. At baseline, dyslipidaemia management was suboptimal in 64 patients (25.2%), while 57 (41.9%) patients with diabetes and 36 (19.6%) patients with hypertension needed modification of their treatment. During follow-up, there were statistically significant improvements in ALT ($p = 0.013$), AST ($p = 0.013$), systolic and diastolic blood pressure ($p = 0.002$ and 0.014 respectively), total cholesterol ($p < 0.001$) and glycated haemoglobin in diabetic patients (70.2 to 62.5 mmol/mol, $p = 0.04$). 142 patients (52%) achieved weight loss during the follow-up (≥10%, ≥7% and ≥5% in 8.2%, 6% and 7.3% of the cohort respectively). The total number of patients with a QRISK3 score≥10% decreased from 156 (62.7%) to 97 (48.5%).

Conclusion: A multidisciplinary NAFLD approach was effective in improving liver-related and CV risk factors. A strong collaboration between primary and secondary care is essential to implement and maintain these improvements in the long term.

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F-02

Obeticholic Acid Treatment in Patients with Non-Alcoholic Steatohepatitis: A Secondary Analysis of the Regenerate Study Across Fibrosis Stages

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In REGENERATE, results of the 18-month interim analysis based on surrogate endpoints showed that obeticholic acid (OCA) improved liver fibrosis in F2/F3 patients.[1] This secondary analysis assessed the effect of OCA in patients with fibrosis due to NASH including those with early fibrosis but at risk of disease progression.

The full efficacy (FE) population included patients with NASH and fibrosis stages F2/F3, and F1 with at least one risk factor (BMI ≥ 30 kg/m^2, type 2 diabetes, ALT > 1.5x ULN), who were randomized 1:1:1 to placebo (PBO), OCA 10 mg, or OCA 25 mg QD. Primary endpoints were fibrosis improvement (≥ 1 stage) with no worsening of NASH, or NASH resolution with no worsening of fibrosis. The safety population included all randomized patients who received at least one dose of study treatment (F1-3, N = 1968).

The FE population included 1218 patients (PBO [n = 407], OCA 10 mg [n = 407] or OCA 25 mg [n = 404]), comprised of approximately 24 % F1 and 76 % F2/F3 patients. Overall, in the FE population nearly twice as many patients treated with OCA 25 mg met the primary fibrosis and NASH endpoints compared to placebo (PBO) (table). In addition, dose-dependent reductions in ALT, AST and GGT were observed. Overall, pruritus was the most common adverse event (AE) (19 % PBO, 28 % OCA 10 mg, 51 % OCA 25 mg). Serious AEs occurred in 11 % PBO, 11 % OCA 10 mg and 14 % OCA 25 mg patients.

OCA improved liver fibrosis, steatohepatitis and liver biochemistry in F1-F3 patients, demonstrating consistent efficacy with an overall similar safety profile to that previously reported in the REGENERATE primary efficacy analysis population (F2/F3 intention-to-treat).

	Placebo	OCA 10 mg	OCA 25 mg
Full Efficacy Population (F1-F3)	**n=407**	**n=407**	**n=404**
Fibrosis improvement + no worsening of NASH	10.6%	15.7% p=0.029	21.0% p<0.0001
NASH resolution + no worsening of fibrosis	7.9%	11.3% p=0.09	14.9% p=0.001

[1] Interim analysis results at 18 months are based on surrogate endpoints and impact on clinical outcomes has not been confirmed. The REGENERATE study is ongoing to confirm the clinical benefit of OCA.

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F-03

Mitochondrial oxidative metabolism contributes to maintain a cancer stem cell phenotype in cholangiocarcinoma

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Introduction: Accumulating evidence indicates cancer stem cells (CSC) as a key target in cancer. Although metabolic reprogramming is considered an important feature of cancer cells, little is known about metabolic regulation in CSC derived from cholangiocarcinoma (CCA). This study investigated the role of mitochondria-dependent metabolism and of the related signaling pathways in the maintenance of a stem-state in CCA.

Methods: Stem-like subset was enriched by sphere culture (SPH) in established human intrahepatic CCA cells (HUCCT1, CCLP1). Extracellular flux analysis was examined by Seahorse technology. Mitochondrial membrane potential and mitochondrial mass were assessed by MitoTracker Red and MitoTracker Green, respectively. Glucose uptake was quantified by incorporation of (U-^{14}C)-D-Glucose. Gene set enrichment analysis (GSEA) and correlation with overall survival (OS) (log rank/Mantel-cox statistics) and time to recurrence (TTR) (Gehan-Breslow Wilcoxon test) were carried out from a transcriptome database of 104 CCA patients.

Results: In contrast to parental cells grown as adherent monolayers (MON), metabolic analyses by Seahorse revealed a more efficient respiratory phenotype in CCA-SPH, due to mitochondrial oxidative phosphorylation. In addition, CCA-SPH retained high mitochondrial membrane potential and elevated mitochondrial mass, as well as over-expression of PGC-1α, a master regulator of mitochondrial biogenesis. *In vitro* targeting of mitochondrial complex I by metformin impaired the ability to form SPH, expression of CSC-associated genes, and genes related to pluripotency and epithelial mesenchymal transition. In an in vivo model in immunocompromised mice, growth of tumors derived from CCA-SPH was suppressed by metformin. Furthermore, PGC-1α silencing highly reduced the expression of stem-like markers in CCA-SPH, and reduced sphere-formation and cell invasion. Notably, GSEA analysis showed that patients with with high levels of mitochondrial complex II had a worse prognosis in terms of OS (p = 0.036) and TTR (p = 0.029). In addition, PGC-1α was significantly correlated with mitochondrial complex II and stem-like genes in CCA patients.

Conclusion: Our data indicate a pivotal role of mitochondrial oxidative metabolism in the biology of the stem-like subset in CCA.

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F-04

Care or palliation for recurrent hepatocarcinoma: a multicentric national analysis of survival

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Background and Aims: How to treat recurrent hepatocarcinoma (HCC) is still an open debate.The aim was to compare the Survival after Recurrence(SAR) of curative (RedoSurgery or ThermoAblation) versus palliative (Trans-arterial-chemo-embolization or Systemic Therapies) treatments for recurrent HCC.

Method: Data were obtained from the surgical Italian register of HCC Recurrence (He.Rc.O.Le.S. Group), which collected aggregate data between 2008 and 2017 from 16 centers. Patients with recurrence were considered for analysis, and they were divided between curative (CUR) or palliative (PAL) treatments. Inverse Probability Weighting (IPW) was performed to weight the groups and to reduce the risk of selection bias.

Results: Among 1,560 patients in the register, 421(27 %) experienced HCC recurrence and were included in this study: 156(37 %) in CUR and 256(63 %)in PAL group. Tumor burden and liver function were weighted by IPW, and two pseudo-population were obtained (CUR = 397.5 and PAL = 415.38). SAR rates at 1-, 3- and 5-years were respectively 98.3 %, 76.7 %, 63.8 % for CUR and 91.7 %, 64.2 % and 48.9 % for PAL (p = 0.007). At the multivariate analysis, palliative therapies (HR = 1.75; 95 %CI = 1.14-2.67; p = 0.01) and a recurrent HCC larger than 5 cm(HR = 1.875; 95 %CI = 1.22-2.86;p = 0.004)were the only predictors of mortality after recurrence. Time to recurrence per year of increase was the only protective factor (HR = 0.616;95 %CI = 0.54-0.69;p < 0.001). Median DFS was 43 months (95 %CI = 32-74) for CUR group, while it was 23months(95 %CI = 18-27) for PAL(p:0.017).

Conclusion: patients firstly submitted to surgery for HCC may benefit from redo curative approaches in case of recurrence, obtaining long term survival when compared with palliative treatments. Thus, surgery and thermoablation should not be avoided especially in case of limited tumor burden.

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F-05

Global characterization of tumor infiltrate of Intrahepatic Cholangiocarcinoma by single cell sequencing

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Background: Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver cancer, characterized by high resistance to chemotherapy and poor prognosis. We have previously demonstrated that the tumor immune microenvironment (TME) has a prognostic impact on iCCA patients; however, little insight exists on immune subsets involved in iCCA and precise criteria to assess tumor biology are still lacking.

Methods: we examined immune infiltrate with single cell-RNA sequencing (scRNAseq) of iCCA tumor and peritumor liver sample. scRNAseq was performed on CD45 + sorted cells isolated from tumoral and peritumoral sample of iCCA patients (n = 6) surgically resected at the Division of Hepatobiliary and General Surgery in Humanitas. Cell suspensions were converted to barcoded scRNAseq libraries with 10x Genomics Chromium Single-cell system and were sequenced on Illumina NextSeq 500. CellRanger (v3.0.1, 10x Genomics) pipeline were applied to obtain gene espression data.

For each cluster, gene average expression and marker genes were obtained. A principal component analysis (PCA) was performed both for the whole dataset and for each cluster of cells. Clusters classification by cell types was performed by comparing each single cell gene expression with public transcriptomic datasets of pure cell types by using the SingleR (v0.9) Bioconductor R package.

Results: We obtained an integrated dataset of 12 samples for a total of more than 30,000 good quality single cells with a median of 800 detected genes each. This analysis revealed that tumor samples clearly separate from peritumoral ones according to the main principal immune cells population for each patient. Key actor of these differences, identified by clustering and classification analysis, were T cells, NK cells and myeloid cells. Moreover, each of them is characterized by cell subpopulations with transcriptional differences between tumoral and peritumoral samples.

Conclusions: These results highlighted that TME strongly differs from the immune system infiltrating the peritumoral area. Further, our study provides a new approach for patient stratification and will help further understand the functional states and dynamics of TME in iCCA.

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F-06

Inhibition of isoform D of phosphodiesterase type 4 reduces cell proliferation and survival in hepatocarcinoma cell lines

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Cyclic AMP phosphodiesterases (PDEs) are enzymes that regulate intracellular levels of cAMP by controlling its rate of degradation, in contrast to adenylyl cyclases that synthesize cAMP from intracellular ATP. PDEs are classified in 11 families (PDE1-PDE11). Some of these control the intracellular levels of both cyclic nucleotides, while others (PDE4, 7, 8) are specific for cAMP degradation. Previous experiments showed that isoform D of cAMP specific PDE4 (PDE4D) was aberrantly up-regulated in HCC cells, in particular in the highly tumorigenic Hep3B and Huh7 cell lines, which also showed increased PDE4 activity. In agreement, tumor tissues displayed stronger staining for the PDE4D isoform when compared to normal liver tissues. The aim of the present study was to analyze the effects of inhibition of this isoform with the final goal of understanding its role in the development of hepatocellular carcinoma and shedding light on the mechanisms eventually involved in this process. SiRNA-mediated transient silencing of PDE4D expression reduced cell proliferation and triggered apoptosis, with an increased number of cells found in the G0/G1 phase of the cell cycle, as shown by DELFIA proliferation assay and flow cytometry experiments. In agreement, Western blot experiments revealed inhibition of cyclin D1, as well an increase in p21, p27 and p53 protein expression. The pharmacological selective inhibition of PDE4D with Gebr-7b gave similar results, with no toxicity. In conclusion, this study established a crucial role of PDE4D in the hepatic tumor phenotype. In addition to being a biomarker for diagnosis, PDE4D could represent a specific adjuvant therapeutic target for the treatment of hepatocellular carcinoma, in particular for those cases that are refractory to existing therapies.

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F-07

Epidemiological trends of hepatocellular carcinoma in patients with nonalcoholic fatty liver disease in Italy

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is projected to become the leading cause of hepatocellular carcinoma (HCC) in Western countries within 2025.The Italian Cancer Liver (ITA.LI.CA) database, that has collected over the last 20 years data of a huge western population of HCC patients, offers the ideal possibility to depict the epidemiological trends of NAFLD-associated HCC in the last years.

Method: We analysed 6,485 consecutive HCC patients diagnosed and enrolled from 2002 to 2017 in this multicenter Italian database. To describe epidemiological trends, the study period was divided in eight consecutive biennials (2002-2003 to 2016-2017). We analysed trends in liver disease severity, HCC stage and treatment strategies according to the HCC aetiologies.

Results: The proportion of NAFLD-HCC patients significantly increased in the study period from 7.19% in the first biennium, to 15.53% in the last ($p < 0.001$). Conversely, the proportion of hepatitis C related-HCC patients significantly decreased from 62.83% to 45.96% ($p < 0.001$). The proportion of hepatitis B related–HCC similarly decreased from 18.94% to 12.20% ($p < 0.001$), with a sharp decrease the overall of viral aetiology ($p < 0.001$). The proportion of HCC related to alcohol abuse remained stable around 16% ($p = 0.183$). Cirrhosis was present in about 75% of NAFLD-HCC patients, in contrast to the near totality of other HCC patients ($p < 0.001$). In addition, the proportion of cirrhosis in NAFLD-HCC patients slightly decreased from 86.67% in the first biennium to 74.7% in the last ($p = 0.03$). NAFLD-HCC patients showed less often a clinically significant portal hypertension and an early tumor stage, but these differences did not impact in their potential for radical therapies and overall survival (median survival 42 vs. 44 months in NAFLD vs other HCC patients, $p = 0.77$). Moreover, considering the different treatments and the ITA.LI.CA staging subgroups, no differences in overall survival were observed between NAFLD and other HCC patients.

Conclusions: The proportion of NAFLD-HCC in Italy has significantly increased from 2002 to 2017, with a progressive reduction of the association with cirrhosis (absent in about 1 out of 4 NAFLD-HCC patients). The outcome of NAFLD-HCC patients does not differ from that of the other HCC cases.

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F-08

Comparison of prognostic models in predicting survival of patients with advanced hepatocellular carcinoma undergoing sorafenib treatment: a multicenter cohort study

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Background Currently Sorafenib treatment is the gold standard therapy for patients with advanced hepatocellular carcinoma (HCC). To date, no widely validated scores are available to predict the overall survival of these patients.

Aim The aim of our study is to evaluate the accuracy of the currently available prognostic scores for HCC to predict the overall survival of patients with advanced HCC treated with Sorafenib.

Methods We included all patients undergone Sorafenib treatment that belonged to the prospective multicenter cohort of the Italian Liver Cancer (ITA.LI.CA.) database. We selected clinical data from the visit before treatment administration. Patients lost at follow-up were excluded. We assessed the performance of several prognostic scores [Barcelona Clinic Liver Cancer- BCLC, Italian Liver Association (AISF)-BCLC, TNM, Hong-Kong Liver Cancer- HKLC, Italian Liver Cancer score- CLIP, ITA.LI.CA. Prognostic score, Okuda score, Albumin-Bilirubin (ALBI) score, GRETCH score] through a univariate Cox regression model evaluating the C-index (Harrell's C) and the Akaike Information Criterion (AIC) of each prognostic score. A high C-index and a low AIC were indicators of good accuracy of the score.

Results One-thousand and one-hundred and twenty-nine (1129) patients were included. The mean age of the patients was 61.6 years. A total of 80.8 % of the patients enrolled were male. Seven-hundred and eighty-nine patients died during a median follow-up period of 15 months. The median period of Sorafenib administration was 4 months. During the follow-up 63.1 % of the patients experienced an HCC progression. All the prognostic scores were able to independently predict the overall survival ($p < 0.001$) at univariate analysis, except for ALBI score ($p = 0.152$). The CLIP score yielded higher accuracy (C-index: 0.608, AIC: 6565) followed by the ITA.LI.CA. prognostic score (C-index:0.594, AIC:8569) and the Okuda score (C-index 0.579, AIC 7257) among the scores evaluated.

Conclusion The overall survival of patients included in ITA.LI.CA. database undergoing Sorafenib treatment is slightly higher than that reported in the current literature. To date, the CLIP score and the ITA.LI.CA. Prognostic score showed the highest accuracy in predicting the overall survival of these patients, although it remains poor. Further studies are needed to investigate the prognostic role of other clinical variables.

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F-09

Fatty acids regulate the biology of cholangiocarcinoma cells

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Introduction: The incidence of cholangiocarcinoma (CCA) is increasing worldwide and is associated with poor patient outcomes. Identification molecular features of CCA could be helpful in designing new therapeutic approaches. Cancer cells are often exposed to a metabolically challenging environment with scarce availability of nutrients. This metabolic stress leads to changes in the balance between endogenous synthesis and exogenous uptake of fatty acids (FAs), which are needed by cells to support their own growth. Moreover, alterations in lipid metabolism may affect the response of tumor cells to different drugs. Yet, little is known about the lipid profile of CCA.

Methods: CCA cells lines (CCLP1, HUCCT) were treated with increasing concentration of different fatty acids for 48 h, and cell viability was evaluated. Proliferation and survival were evaluated with Western Blot analysis. Responsiveness of CCA cells to Oxalyplatin, Cisplatin and 5-FU was tested with crystal violet staining. The epithelial-mesenchymal transition program and stem-like markers were tested with real-time PCR.

Results: Exposure of both CCA lines to fatty acids led to a marked increase in cell proliferation, especially with oleic and palmitoleic acid. Western blot analysis demonstrated a robust activation of growth and survival pathways, including AKT and ERK1/2. In addition, exposure to fatty acids before treatment with and chemotherapeutic agents made CCA cells less sensitive to the toxic action of these drugs. Finally. Fatty acid treatment resulted in a marked upregulation of genes controlling epithelial-mesenchymal transition and key gene controlling stemness.

Conclusion: Our results indicate that CCA cells exploit lipid metabolism to gain growth, invasiveness and survival advantages. When exposed to fatty acids, cancer cells are more resistant to the toxic effects of antineoplastic drugs, show a modulation of stem-like features, indicating that lipid metabolism could be a new potential target to affect CCA progression.

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F-10

Spleen stiffness measurement predicts the development of primary hepatocellular carcinoma better than hepatic venous pressure gradient

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Introduction: Hepatocellular carcinoma (HCC) is one of the main complications of chronic liver diseases. Recently, the degree

of portal hypertension (PH) has been associated with HCC development. The gold standard method to evaluate PH is the measurement of the hepatic venous pressure gradient (HVPG), which is an invasive and risky method. In addition, several authors reported that liver and spleen stiffness measurement (LSM and SSM) are good surrogate non-invasive tests (NIT) of PH and its complications. To date, no data are available on the role of SSM in predicting HCC. **Aim** The aim of this study is to evaluate the predictive role of LSM, SSM and HVPG for HCC development in patients with compensated advanced chronic liver diseases (cACLD).

Methods: We retrospectively collected data from patients with cACLD undergone LSM, SSM and HVPG examination within 6 months form transient elastography referred to our center between 2008 and 2018. Patients without at least one-year follow-up, with incomplete records or a previous HCC were excluded. A Spearman's test to evaluate collinearity between SSM and HVPG was performed. We performed univariate analysis to evaluate the predictive role of HVPG, LSM, SSM and other NITs for PH evaluation for the development of HCC. We performed two different multivariate analysis alternatively using SSM or HVPG as markers of PH.

Results: Data of 200 patients which fulfilled inclusion criteria were retrospectively collected, of whom 21 developed CE. One-hundred and thirty (130) patients were males (67%). The median age of patients was 57 years. The main etiology of cACLD was hepatitis C virus (84.4% in patients without HCC and 95% in patients with). SSM and HVPG were confirmed to be collinear (Spearman's Rho= 0.594, p<0.001). At univariate analysis, the platelet count, LSM, SSM, HVPG, and other NITs (Fib-4, LSPS and PSR) were independently associated with HCC development. At multivariate analysis only the SSM [subdistribution hazard ratio(SHR) 1.112, 95% confidence interval (CI) 1.067-1.160, p<0.001] was an independent predictor of HCC development (Wald chi^2 24.8). In the second multivariate replacing SSM with HVPG, the platelet count (SHR 0.979, CI 0.965-0.994, p=0.007) and the LSM (SHR 1.032, CI 1.005-1.061, p=0.019) were independent predictors of HCC development (Wald chi^2 12.8).

Conclusions: SSM is able to predict the development of HCC in cACLD patients, better than HVPG and of the combination of LSM and platelet count.

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F-11

Regulation of the biology of cholangiocarcinoma (CCA) cells by Extracellular-signal-regulated kinase 5 (ERK5)

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Introduction: Cholangiocarcinoma (CCA) is characterized by high resistance to chemotherapy and poor prognosis. Epidermal growth factor (EGF) is involved in CCA development, and overexpression of the EGF receptor (EGFR) has been linked to tumor progression. The EGF signaling pathway may be associated with activation of extracellular signal-regulated kinase 5 (ERK5), a protein belonging to the MAPK family involved in the pathogenesis of different types of cancer. Additionally, ERK5 is implicated in cytoskeletal remodeling and cell motility. The purpose of this study was to investigate the role of ERK5 in the biology of CCA cells.

Methods: Two intrahepatic human cholangiocarcinoma cell lines (HuCCT-1 and CCLP-1) and two primary human iCCA cells were used in this study. Cell growth was determined by cell counting and BrdU incorporation assay. Cell motility and invasion were assessed using modified Boyden chambers. ERK5, p-ERK5, EGFR, VEGF and Angiopoietin 1 were investigated by Western blotting. Silencing of cells was performed by gene silencing with shRNA. XMD8-92 and AX15836 were used to inhibit ERK5 activity.

Results: ERK5 was upregulated in all CCA cells examined and phosphorylation of ERK5 was increased in cells exposed to EGF. Growth of CCA cells in serum-containing medium was decreased after exposure to 10 μM XMD8-92. In addition, migration and invasion induced by EGF were significantly reduced by both XMD8-92 and AX15836 (2 μM). Similar results were obtained in ERK5-silenced cells exposed to EGF, when compared to treated with non-targeting (NT) shRNAs. In addition, in ERK5 silenced cells, expression of VEGF and angiopoietin 1 was reduced compared to NT cells. Of note, conditioned medium (CM) obtained from HuCCT-1 cells induced an increase in migration of both human hepatic stellate cells (HSC) and THP-1 monocytes, an effect reduced when conditioned medium from ERK5-silenced cells was used. Furthermore, the inhibitory effects of metformin on cell growth were more evident in ERK5-silenced cells.

Conclusions: In cholangiocarcinoma cells, ERK5 activity regulates cell growth and motility, release of angiogenic factors and drug resistance.

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F-12

The volume of enhancement of disease (VED) predicts the early response to treatment and overall survival in patients with advanced hepatocellular carcinoma treated with sorafenib

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Introduction: The response of patients with advanced HCC treated with sorafenib is still unpredictable. We analysed the predictive value of the Volume of Enhancement of Disease (VED), a new radiologic parameter based on the arterial enhancement coefficient (ΔArt%) in computed tomography, in the early evaluation of the response to sorafenib in patients with advanced HCC.

Methods: We included patients with advanced hepatocellular carcinoma (HCC) who underwent a multiphase enhanced CT (multidetector Somatom Sensation 64 CT scan) before (T0) and after 60–70 days of therapy with sorafenib (T1), enrolled between 2012–2016. The same target lesions utilised for the assessment of response were used for the calculation of size and for the calculation of VED (volume lesion x â^†art% / volume lesion). We compared these values at T0 and T1 in patients with a clinical benefit (CB, the composite of complete response, partial response and stable disease) from therapy or with progressive disease (PD). Survival probability was evaluated in the study population and in the different subgroups of patients, based on tumor size and VED, but also on ancillary imaging findings and blood chemistries.

Results: Thirty-two patients with advanced HCC treated with sorafenib (25 men, 7 women, mean age 65.8 years) were selected. At T1 8 patients had CB (1 partial response, 7 stable disease) and 24 had PD. VED_{T0} was > 70 % in 8/8 CB patients compared to only 12/24 patients in the PD group ($P = 0.011$). In CB patients, but not in PD, VED_{T1} values were significantly lower than those at T0 ($p = 0.018$).

No significant differences in the ancillary imaging findings were found between the two time points. Patients with $VED_{T0} > 70\%$ showed a significantly higher median survival than those with lower VED_{T0} (506 vs. 266 days, $p = 0.032$). Patients with $VED_{T0} > 70\%$ and alpha-fetoprotein$_{T0} \leq 400$ ng/ml had a significantly longer survival than all other combinations of the two biomarkers (median survival: 582 days vs. 208–213 days for the other combinations of the two biomarkers).

Conclusion: In patients with advanced HCC treated with sorafenib, VED is a novel and simple radiologic parameter obtained by contrast-enhanced CT, which could be helpful in selecting patients who are more likely to respond to sorafenib therapy, and with a longer survival. Patients with baseline VED value > 70% and alpha-fetoprotein ≤ 400 ng/ml showed longer survival.

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F-13

An immunohistochemical study on lymphoid T-cell subsets and activation state in hepatocellular carcinoma

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Introduction: The role of immunotherapy in hepatocellular carcinoma (HCC) is still controversial, and very few is known on the role and the activation state of the CD8+ lymphoid infiltrate in HCC and the tumor aggressiveness.

Aim: To evaluate the activation state of peritumoral lymphocytes in HCC, in relation to the activation of the extratumoral lymphocytes in cirrhosis and the histopathological and biological tumor characteristics.

Materials and Methods: In this preliminary phase, 13 patients transplanted for cirrhosis complicated by HCC were evaluated. Histopathological analysis included tumor dimensions, grade, margins, microvascular invasion (MVI), architecture. Biologically aggressive HCCs were defined by at least two of the following features: Edmondson's grade 3 or 4, MVI, macrotrabecular or solid pattern.

Immunohistochemistry (IHC) was performed for CD8 (cytotoxic T-lymphocytes), T-cell antigen-1 (TIA-1, activated CD8+ lymphocytes), and programmed death-1 (PD1, T-follicular helper marker), on both peritumoral (periHCC) and extratumoral (extraHCC) tissue (from a liver segment distant from HCC). The positivity for the three markers was quantitatively assessed.

Results: We found no correlations between periHCC and extraHCC tissues concerning the global expression of CD8 ($p = 0.125$), TIA-1 ($p = 0.623$) and PD1 ($p = 0.519$). The mean positivity for CD8 was higher in periHCC (68.8 ± 18.6) than extraHCC (58.1 ± 27.1), similarly to PD1 (37.1 ± 10.4 and 33.6 ± 22.9). Conversely, TIA-1 expression was lower in periHCC (1.6 ± 0.8) than extraHCC (1.7 ± 1.0). Moreover, in extraHCC TIA-1 and CD8 positively correlated ($p = 0.034$), but the same correlation wasn't found in periHCC ($p = 0.688$). Biologically aggressive HCCs showed a lower PD1/CD8 ratio compared to the others ($p = 0.05$), and a higher TIA-1/CD8 ratio in extraHCC areas ($p = 0.02$).

Conclusions: HCCs showed more CD8+ lymphocytes and higher PD1 expression compared to the extratumoral tissue, but with a lower amount of activated TIA-1+ cells. In biologically aggressive HCCs both PD1 and TIA-1 are underexpressed in peritumoral tissue, suggesting a more advanced cancer immunoediting.

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F-14

Frequency of TP53, CTNNB1, and TERT promoter mutations in patients with hepatocellular carcinoma

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Mutations in TP53 and CTNNB1 genes as well as in TERT promoter are considered drivers for hepatocellular carcinoma (HCC) development. They show variable frequencies in different geographic areas, possibly depending on liver disease etiology and environmental factors.

Methods: We investigated TP53, CTNNB1, and TERT genetic mutations using direct Sanger sequencing technique in tumor and non-tumor liver tissues from 67 patients with HCC (40 HCV-, 3 HBV-, 2 alcohol-related, and 22 related to cryptogenic liver disease) and in liver tissue specimens from 41 control subjects with non-alcoholic fatty liver. All studied subjects were from Southern Italy. TERT expression was assessed by quantitative RT–PCR in duplicate using TaqMan (Applied Biosystems) gene expression assay.

Results: No CTNNB1 mutation or TP53 R249S substitution were detected in any case. The homo- or heterozygous TP53 R72P polymorphism was found in 10/67 (14.9%) tumors, in 0/67 (0%) non-tumor tissues ($P = 0.001$), and in 0/30 controls ($P = 0.009$) analyzed. Two TERT gene promoter mutations were found in 29/67 (43.3%) tumor tissues examined. None of the non-tumor tissues ($P < 0.0001$) and of the liver specimens from control subjects ($P < 0.0001$) carried these mutations. The most frequent mutation was the known hot spot located at -124 bp from the ATG start site of TERT (-124G> A, 28 cases, 41.8%; $P < 0.0001$). A new previously never reported TERT promoter mutation (at -297 bp from the ATG, -297C >T) was found in 5/67 (7.5%) tumors, in 0/67 (0%) non-tumor ($P < 0.0001$), and in 0/41 (0%) controls ($P = 0.07$). This mutation creates an AP2 consensus sequence, and was found alone (1 case) or in combination (4 cases) with the -124 bp mutation. The mutations at -124 bp and -297 bp induced a 33-fold ($P < 0.0001$) and 40-fold increase of TERT expression levels, respectively. When both mutations were present, TERT expression levels were increased more than 300-fold ($P = 0.001$)..

Real-time PCR experiments showed that mutations at -124 bp and -297 bp induced a 30-fold ($P < 0.0001$) and 40-fold increase of TERT expression, respectively. When both mutations were present

in the promoter, expression of TERT was increased more than 300-fold (P< 0.0001).

Conclusions CTNNB1 mutations are uncommon in patients with HCC in our geographic area, whereas the TP53 R72P substitution and TERT promoter mutations at -124 bp and -297 bp are significantly associated with HCC. A new *TERT* promoter mutation was identified, which generates a de novo binding motif for AP2 transcription factors.The combination of mutations at -124 bp and at -297 bp strongly induces TERT promoter activity.

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F-15

Prognostic and diagnostic role of VEGF-A and HIF-1α in hepatocellular carcinoma treated with chemoembolization

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INTRODUCTION: Hepatocellular carcinoma (HCC), the most common primary liver cancer, is characterized by almost equal incidence and mortality, due to late diagnosis, inadequate therapies and complex mechanisms of carcinogenesis. In hepatocarcinogenesis neo-angiogenesis plays an important role, to such an extent that it is considered as a possible therapy-target.

AIMS: We aimed to analyze prognostic role of circulating VEGF-A and HIF-1αin patients treated by chemoembolization (TACE), an ischemia-inducing treatment, the most used for HCC.

MATERIALS AND METHODS: We selected 163 consecutive patients classified as BCLC A/B and measured the 2 angiogenic biomarkers concentration on a blood sample by using ELISA tests before chemoembolization (t0) and after 4 weeks (t1) from the treatment. The patients' response to treatment was assessed by CT scanning and mRECIST criteria.

RESULTS: Significant correlations between VEGF-A levels, tumoral and clinical features were documented [BCLC (p = 0.009), number of lesions (p = 0.0001) and complications (p < 0.0001)]. VEGF-A predicted treatment response because by mRECIST criteria (p = 0.014). Patients with progressive disease (mRECIST PD) had significantly higher VEGF levels at t0 than those with complete response (mRECIST CR) or disease control (mRECIST PR or SD). On the other hand HIF-1αt0 correlated with lesion size (p = 0.04) and complications (p = 0.002). The prognostic role of the two biomarkers was analyzed with a cut-off obtained by ROC-curves. We found a significant correlation (p- = 0.01) between HIF-1αt0 and survival and, at the Cox multivariate regression, HIF-1αwas confirmed as an independent predictor of survival, together with Child-Pugh (p- < 0.0001), etiology (p-value = 0.0028), lesion size (p- = 0.004) and mRECIST (p = 0.0016).

CONCLUSIONS: Our findings support the use of VEGF-A and HIF-1α as prognostic criteria, possibly to be included in new staging systems, and support the everlasting search of molecules targeting angiogenesis in patients with HCC.

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F-16

The Piedmont-Aosta Valley Oncology Network experience in locally advanced HCC with intrahepatic neoplastic portal vein thrombosis: Y90-radioembolization versus Sorafenib

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Background/Aim SARAH and SIRveNIB trials recently failed to demonstrate superiority of radioembolization (TARE) versus Sorafenib on survival in patients with advanced hepatocellular carcinoma (HCC). To investigate this topic, we have retrospectively analyzed a carefully selected cohort of patients treated with TARE or Sorafenib in five centers of the Piedmont-Aosta Valley Oncology Network.

Methods All patients who received TARE or Sorafenib as first-line treatment from 2012 to 2018 were considered. Inclusion criteria were: well preserved liver function, absence of extrahepatic localizations and presence of neoplastic portal vein thrombosis confined to the liver; thrombosis of the main portal trunk was an exclusion criterion. Kaplan-Meyer and Log-rank estimators were used.

Results 67 out of 286 patients fit the inclusion criteria. 43 were treated with TARE and 24 with Sorafenib. 11 patients (10 treated with TARE and 1 with Sorafenib) were rescued to surgery; 3 underwent OLT and 8 hepatectomy, 8 patients are still alive (mean survival was 54 ± 12 months, median survival not reached). TARE was significantly superior than Sorafenib in downstaging patients to surgery (23 % vs 4 % p = 0.05). In the remaining 56 patients, 33 treated with TARE and 23 with Sorafenib, median survival was 27 months (95 % CI 12-40) and 11 months (95 % CI 6-18) respectively (p = 0.0008). At multivariate analysis tumor progression (HR 3.1, 95 % CI 1.5-6.4, p = 0.002) and TARE (HR 0.38, 95% CI 0.2-0.71, p = 0.003) were the only significant and independent variables associated with survival (p < 0.0001).

Conclusion Our retrospective analysis of patients with locally advanced HCC and neoplastic vascular invasion confined to the liver showed a significant superiority of radioembolization in downstaging patients to curative surgery, providing long survivals. Even in patients who were not rescued to surgery, survival rates resulted significantly better with TARE. Prospective trials are warranted in order to confirm TARE as first-line treatment in such carefully selected patients.

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F-17

Application of BCLC-B subclassification and Hong Kong Liver Cancer Systems to intermediate stage hepatocellular carcinoma

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Introduction and Aim: According to Barcelona Clinic Liver Cancer (BCLC), trans-arterial chemoembolization (TACE) is the recommended treatment for intermediate stage hepatocellular carcinoma (HCC) that is a heterogenous group in terms of tumor characteristics and liver disease stage. Since the single treatment option is limiting the adherence to CPG, several sub-classifications were proposed to increase the yield of intermediate stage HCC treatment. We applied two validated BCLC-B subclassifications and HKLC system to two Mediterranean HCC cohorts from Istanbul and Pisa to estimate the number of intermediate stage cases who could receive curative rather than palliative treatment options.

Material and Methods: We retrospectively reviewed the database of 1091 patients with HCC followed-up in a 10-year period (December 2008-June 2018). Patient, liver disease, tumor and treatment choice associated parameters were recorded. The Bolondi's and Kinki's sub-classification systems were calculated in each patient on the basis of the up-to-seven criteria, Child-Pugh score (CPS), and performance status. HKLC was classified according to the size and number of nodules, CPS, presence or absence of extrahepatic vascular invasion, and metastases. Survivals were calculated using Kaplan-Meier method, and the curves were compared using Log-rank test.

Results: One hundred and eighty-five (21.8 %) patients had an intermediate stage HCC, 57 (30.7 %), 58 (31.3 %) and 124 (67%) of whom were candidates for curative treatments when using the Bolondi's (B1 and B4-up to 7), Kinki's (B1 and B3A) and HKLC (Stage I, IIA and IIB) systems respectively. Overall median survival was 28.7 months (95 % Confidence Interval, 21.7-35.6). Both the Bolondi's and Kinki's sub-staging were able to discriminate survival probabilities for each category, besides the B3A vs B3B in the Kinki's system. Regarding the HKLC classification, a significantly lower median survival was observed for HKLC-IIIA in relation to the categories HKLC-I ($p = 0.000$), HKLC-IIA ($p = 0.019$), HKLC-IIB ($p = 0.000$), HKLC-IIIB ($p = 0.004$).

Conclusions: If HKLC was applied to intermediate stage HCC (BCLC-B) patients, approximately two-third of patients could be candidates for curative treatment. The Bolondi's BCLC sub-classification system showed the best performance in distinguishing survivals.

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F-18

Risk of developing hepatocellular carcinoma (HCC) in patients with cirrhosis of viral etiology evaluated by the association of alpha-fetoprotein (AFP), protein induced by vitamin K absence or antagonist-II (PIVKA-II) and glypican-3 (GPC-3)

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Background and Aims: To date, the role of serum biomarkers is still a matter of debate for HCC detection. We investigated AFP, PIVKA-II and GPC–3 diagnostic accuracy for HCC detection and prediction in patients with cirrhosis of viral etiology under ultrasound surveillance.

Methods: A total of 244 patients with either cirrhosis ($n = 120$,74 M/47F, median age = 57[33–82]years) or HCC ($n = 124$,103 M/21F, median age = 66[31–89]years) were retrospectively enrolled. We also analyzed data from a group of 27 patients with HCC (21 M/6F, median age 67[53–78]years) with available serum samples collected at 9 and 18 months before HCC diagnosis. AFP and PIVKA-II serum values were measured by chemiluminescent immunoassays on Lumipulse® G600 System (Fujirebio Inc, Tokyo, Japan) while GPC-3 by enzyme immunoassay (Fujirebio Diagnostic AB, Gothenburg, Sweden).

Results: AFP, PIVKA-II and GPC–3 serum levels were lower in patients with cirrhosis than in those with HCC (AFP:7.4[95 %CI 6.0–9.0] vs 20.2[95 %CI 14.7–31.5] ng/mL, $p < 0.001$; PIVKA-II:43[95 %CI 41–47] vs 126[95 %CI 96–176] mAU/mL, $p < 0.001$; GPC–3:0.07[95 %CI 0.06–0.10] vs 0.14[95 %CI 0.11–0.18] ng/mL, $p < 0.001$). The higher performance for HCC detection was observed for PIVKA–II (area under the curve [AUC] = 0.804), followed by AFP (AUC = 0.734) and GPC–3 (AUC = 0.626); the combination of AFP + PIVKA–II + GPC–3 furtherly improved the diagnostic accuracy to AUC = 0.833, with sensitivity of 69 % and specificity of 88 % at a cut-off of 0.51 (Youden Index). Serum AFP, PIVKA–II and GPC–3 values distinctly increased from 18 to 9 months prior HCC detection and additionally to HCC diagnosis (Friedman test, $p < 0.05$). The combination of AFP + PIVKA–II + GPC–3 enabled to discriminate between patients who developed HCC (n = 27) from those who did not ($n = 120$) as early as 18 months before tumor diagnosis (Log-rank test, $p = 0.002$) and to predict HCC development (HZ = 3.13, 95 %CI 1.47–6.65, $p = 0.003$).

Conclusions: The combination of AFP + PIVKA–II + GPC–3 showed a good accuracy for HCC detection and may allow the identification of cirrhotic patients under surveillance at higher risk of HCC development.

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F-19

Sarcopenia is common in patients with cirrhosis and unresectable HCC treated by transarterial embolization but is not associated with increased rates of complications

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Sarcopenia has been associated with higher rate of complications in patients with cirrhosis and hepatocellular carcinoma (HCC) undergoing resection or radiofrequency ablation. Little is known about its role in patients affected by unresectable HCC undergoing transarterial embolization (TAE). Patients who underwent the 1st TAE between March 2011 and July 2019 in our Unit were analyzed. Data about age, sex, stage of disease, hospitalization days, onset of complications and readmission during the 1st month were collected. The area of lean muscle mass at the level of the third lumbar vertebra, was segmented using regions of interest in the latest abdominal CT scan prior to TAE. To evaluate sarcopenia, the skeletal muscle index (SMI) was calculated by normalizing cross-sectional muscle area by height. SMI cut-off values were considered $\leq$39 cm^2/m^2 for women and $\leq$55 cm^2/m^2 for men. During the study period, 150 patients affected by unresectable HCC underwent TAE. Most of the patients were males (76.7%) and the mean age at diagnosis was 73.1 $\pm$ 9.3 years (40-88). Main etiology of cirrhosis was HCV (45%), followed by alcohol (23%); CPT class A was present in 81.8% of patients. The average SMI was 41 $\pm$ 8.8 cm^2/m^2 with 128/150 patients (85.3%) classified as sarcopenic. Mean days of hospitalization after TAE were 2 $\pm$ 1.67. Eleven patients (7.3%) had early complications (6 had bleeding, 3 sepsis and 2 liver decompensation) and 9 (6%) had unplanned readmission. At univariate analysis, no statistically significant differences were found between sarcopenic and non-sarcopenic patients: length of hospitalization (2 vs 1.6 days; p-value = 0.26), early complications rate (7.8% vs 4.5%; $p = 0.58$) and rate of readmission (6.3% vs 4.5%; $p = 0.74$). Sarcopenia is common in patients affected by unresectable HCC undergoing TAE. In this group, TAE can be considered a safe treatment option as it wasn't associated with higher rates of early complications or readmission.

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F-20

Circulating microRNA-21 and microRNA-122: prognosis prediction and correlation with HIF-1alpha in hepatocellular carcinoma patients treated with transarterial chemoembolization

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Background and aims: MiR–21 and miR–122 have been identified as promising biomarkers in hepatocellular carcinoma (HCC). We aimed to evaluate their prognostic role in HCC patients treated with transarterial chemoembolization (TACE), a methodology inducing liver ischemia, and the link, if present, with an angiogenesis biomarker (HIF-1alpha).

Methods: Whole blood levels of miR–21 and miR–122 were evaluated in 40 HCC patients, 18 cirrhotics and 10 healthy volunteers, with a second determination in HCC 4 weeks after treatment (at the control CT scanning). The miRNA level before TACE and the miRNA ratio (miRNA after/before TACE) were evaluated as potential progression-free survival (PFS) predictors. MiRNA levels were evaluated with qRT-PCR and expressed as 2^{-DDCt}; an ELISA method was used to measure HIF-1alpha levels.

Results: Both miR–21 and miR–122 were detectable in the blood of HCC patients at significantly higher levels as compared to healthy controls, with no significant difference with cirrhosis. A trend towards a decline in miR-21 after TACE ($p = 0.056$) was observed; miR–122 levels, despite being higher after TACE, were not significantly different. MiR–122 was higher in HCC patients with underlying viral liver disease ($p = 0.03$). MiR–21 ratio and miR–122 before TACE proved to be prognostic predictors: patients with levels of miR–21 ratio and miR–122 below the respective cut-off had a longer PFS ($p = 0.0001$ and $p = 0.009$, respectively). MiR–21 ratio, miR–122 and radiological response (mRECIST), were independent prognostic predictors at Cox multivariate analysis. MiR–21, but not miR–122, positively correlated with HIF-1alpha both before ($r = 0.34$, $p = 0.049$) and after TACE ($r = 0.42$, $p = 0.01$).

Conclusions: MiR–21 and miR–122 are independent predictors of PFS in TACE-treated HCC patients. This is the first report of a link between circulating miR–21 and HIF-1alpha in HCC, indicating a potential role of this miRNA in angiogenesis.

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F-21

Circulating microRNAs as promising non-invasive molecular biomarkers of HCC

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Introduction: Human hepatocellular carcinoma (HCC) is the most frequent primary tumor of the liver and is the third cause of cancer-related deaths. The prognosis of HCC is poor and thus the identification of novel molecular biomarkers for the early diagnosis in at-high risk patients is needed. Circulating microRNAs (miRs) have been detected in different human body fluids, including serum, plasma and urine.

The main aim: of our study was the identification of given miRs as circulating molecular biomarkers of HCC. To accomplish this task we measured the levels of microRNA–23b and –126–3p in the plasma from HCC patients.

Materials and methods, results and conclusions: We studied the circulating expression levels of these miRs by Real-Time PCR and digital drop PCR (ddPCR), because we had previously found their downregulation in HCC tissues respect to their matched peri-tumoral (PT) counterparts. Here, we found that the levels of circulating miR–23b–3p measured by ddPCR were significantly lower in HCC patients ($n = 25$) respect to healthy subjects ($n = 37$) and the ROC analysis displayed a discrete capability of miR–23b–3p to discriminate HCC from controls individuals (AUC = 0.67; $p = 0.019$). The same trend of dysregulation was observed for plasma circulating miR-126–3p. The ROC curve analysis performed on 25 controls and 25 HCC patients supported the diagnostic potential of circulating miR–126–3p (AUC = 0.78; *P*–value = 0.0007). In the same cohort, the expression levels of the tumor suppressor lncRNA GAS5 were significantly lower in HCC patients compared to healthy subjects. The ROC curve analysis evidenced a good diagnostic potential of GAS5 (AUC = 0.72; *P*–value = 0.007). In conclusion, our results contribute to identify potential novel non-invasive biomarkers of diagnosis of HCC and prone us to study the dynamic changes of these non-coding transcripts in the liquid biopsy of HCC patients in response to therapy.

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F-22

SCCA-IgM in hepatocellular carcinoma patients treated with transarterial chemoembolization: gender-related differences

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Background: Squamous Cell Carcinoma Antigen (SCCA)-IgM proved to be useful in defining hepatocellular carcinoma (HCC) patients' prognosis. Gender has an impact on SCCA-modulated p53 and mTOR activity, but no studies evaluated its predictive capacity according to sex.

Aims: Aim of our study was to investigate gender-related differences in SCCA-IgM determination, in particular regarding its prognostic role, in hepatocellular carcinoma (HCC) patients treated with transarterial chemoembolization (TACE).

Materials and methods: SCCA-IgM levels where determined in a group of 208 consecutive patients treated with TACE. In a subgroup of 149 a second determination was obtained 4 weeks after the treatment, when the control CT was performed. Associations with clinical and tumor characteristics, response to treatment and survival were evaluated.

Results: The male and female subgroups differed in sample size (80 % males and 20 % females), age, etiology, MELD, MELD-Na, number of nodules, presence of metastases and AFP levels. There was no difference in SCCA-IgM levels according to gender. Higher SCCA-IgM levels were detected in males with advanced ITALICA prognostic score (> 3) and in females with earlier stage tumors ($\leq$ 3). SCCA-IgM levels and their variation after TACE were not associated with radiological response. At the established cut-off (130 AU/mL), in the overall population SCCA-IgM was not efficient in predicting the prognosis. However, when males and females were separately considered, an opposite behavior was observed: males with SCCA-IgM levels below the cut-off had a longer overall survival (35.7 vs. 20.8 months; $p = 0.007$); in contrast, females with marker levels below it had a worse prognosis (15.7 months vs. 36.4 months; $p = 0.01$).

Conclusion: SCCA-IgM predicts survival differently according to gender. More studies are needed to confirm our data, clarify the prognostic role of SCCA-IgM according to gender and identify the mechanisms underlying this different, gender-specific, behavior.

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F-23

Personalized platelets/liver stiffness ratio improves and secures the screening of esophageal varices needing treatment

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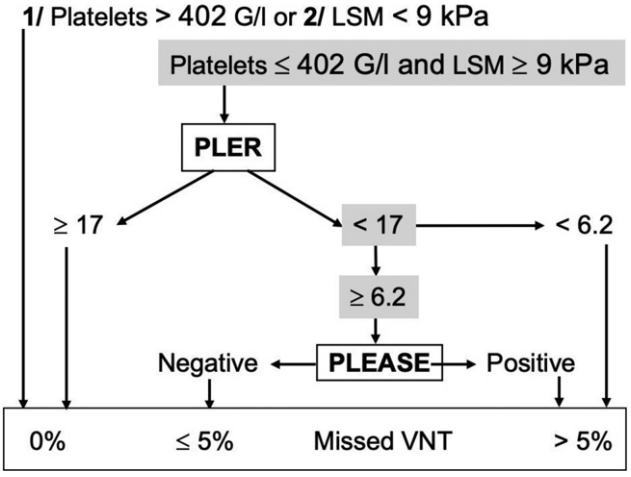
Introduction: Based on platelets and liver stiffness measurement (LSM by vibration-controlled transient elastometry), the Baveno VI criteria (B6C), the expanded B6C (EB6C) or the ANTICIPATE score can be used to rule out varices needing treatment (VNT).

Aim: We aimed to evaluate and improve these published tests in order to safely spare unnecessary endoscopy.

Material and Methods: 2368 patients were randomized in derivation (2/3, $n=1579$) and validation (1/3, $n=789$) populations with chronic liver diseases (CLD) of various etiologies and severities in a multicenter retro-prospective study. Published tests were compared to two new tests: PLER (platelets/LSM ratio) and PLEASE (PLER adjusted on etiology/sex/INR). In the derivation population, patient characteristics were: VNT: 15.1%, etiologies: viral: 50.2%, NAFLD: 28.9%, alcoholic: 20.8%, MELD score: 9.5 ± 3.0, LSM≥10 kPa: 93.0%. Patient characteristics were not significantly different in the validation population.

Results: 1/ Tests to diagnose VNT. AUROC for VNT were significantly different between scores: PLER: 0.761, ANTICIPATE: 0.770, PLEASE: 0.798. PLEASE score was better calibrated than other scores (Spearman's r: 0.37, $p<0.001$). 2/ Tests to spare endoscopy. Performances for spared endoscopy rate and safety for missed VNT rates (respectively, in parentheses) were, in increasing order: B6C: 23.9% (2.9%), ANTICIPATE: 24.3% (4.6%), PLER: 26.6% (4.6%), PLEASE: 34.8% (3.3%) and EB6C: 41.9% (10.9%). Differences in spared endoscopy rates were significant between tests ($p=0.001$) except for B6C vs ANTICIPATE. Differences in missed VNT rates were significant only between EB6C vs other tests (0.009). PLEASE was the only safe test (missed VNT < 5%) whatever the sex or etiology. A VariScreen algorithm (Figure), based successively on platelets or LSM then PLER (in 94.2% of patients) then PLEASE (in only 35% of patients), secured screening with no missed VNT in poor liver function (MELD≥10). The rates of VariScreen for spared endoscopy and missed VNT were 35.7v% and 2.9%, respectively. Test performance and safety were not significantly different between populations. Tests and Variscreen algorithm can be calculated at http://forge.info.univ-angers.fr/~gh/wstat/pler-please-variscreen.php

Conclusion: B6C are safe for missed VNT rate regardless of CLD etiology and severity, and regardless of sex; EB6C are unsafe and no longer recommended. To improve current VNT screening, we propose the sequential VariScreen algorithm applicable to any main-aetiology CLD and secured for liver severity.



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F-24

Long-term albumin therapy is not futile in patients with cirrhosis and uncomplicated ascites not normalizing on-treatment serum albumin concentration

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Introduction/Aims: The benefits of long-term human albumin (HA) administration to patients with cirrhosis and ascites seen in the ANSWER trial[1] were associated to a significant increase of serum albumin concentration (SA). A post-hoc analysis[2] showed that survival paralleled with on-treatment SA at month 1 and optimal results follow the achievement of normal SA. This study aimed to determine whether patients randomized to the standard medical treatment plus HA arm (SMT + HA) in the ANSWER trial who failed to normalize on-treatment SA ($\geq$ 3.5 g/dL) at month 1 have any advantage as compared to those receiving SMT alone.

Methods: Patients not normalizing on-treatment SA at month 1 were matched with those enrolled in the SMT arm alive at 1 month by using propensity score (built from the baseline variables found by multivariable logistic regression: SA, MELD and Child-Pugh). Kaplan-Meier method and Cox regression assessed survival. The incidence rates of complications were computed using Poisson distribution.

Results: In SMT + HA arm, 40 patients (21 %) failed to normalize SA at month 1, and were compared with 40 patients receiving SMT alone selected by propensity score. The 40 patients who received HA had a significantly higher 18-month overall survival (K-M estimates: 61.3 % SMT + HA vs 36.7 % SMT; $p = 0.0315$), corresponding to a 57 % reduction in mortality HR (0.43 [95 %CI 0.19–0.95], $p = 0.036$). These patients also showed a significant reduction in the incidence rate ratio of paracentesis (0.62 [95 %CI 0.47–0.82], $p < 0.001$) and some complications of cirrhosis, namely spontaneous bacterial peritonitis (0.33 [95 %CI 0.14–0.64], $p < 0.001$), hepatic encephalopathy grade III/IV (0.41 [95 %CI 0.22–0.73], $p = 0.001$), and hyponatremia (0.43 [95 %CI 0.25–0.72], $p < 0.001$).

Conclusion: Patients who failed to normalize SA during long-term HA therapy had a clear benefit in survival and occurrence of complications as compared to those only receiving SMT. HA treatment cannot be considered futile in this patient subset. [1]TheLancet 2018;391:2417–29 [2]JHepatol 2019;70:e53

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F-25

Myeloid cell-specific deficiency of ERK5 regulates the response to liver regeneration after partial hepatectomy (PH) in mice

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Introduction: The extracellular signal-regulated kinase 5 (ERK5) is a member of the Mitogen-Activated Protein Kinases family, and is involved in the modulation of proinflammatory mediators in endothelial cells and monocytes, and in the differentiation of monocytes to macrophages. In addition, signals derived from macrophages regulate liver regeneration after PH. We recently generated mice deletion of the ERK5 gene in cells of myeloid lineage(*LysMCRE/ERK5KO*).This study was designed to investigate the phenotypic response of LysMCRE ERK5 KO mice subjected to PH.

Methods: *LysMCRE/ERK5KO* mice were generated crossing *ERK5 floxed* mice (control mice) with mice expressing Cre-recombinase under the control of M-lysozyme promoter. Mice were subjected to a 65% partial hepatectomy (PH). Mice were sacrificed at 8, 24, 48 and 168 hours. Serum ALT and AST were measured using standard biochemical assays. Intrahepatic gene expression was assayed by quantitative real-time PCR.

Results: Measurement of liver-to body weight ratio showed that recovery of liver mass was slightly lower at 24 and 48 hours after PH in *LysMCRE/ERK5KO* mice, while no differences between the two experimental groups were observed at late time point (168 hours). Expression of the proliferation marker PCNA was decreased in*LysMCRE/ERK5KO* 48 hours after PH. Interestingly, although we did not observe a significant impairment of liver mass recovery in *LysMCRE/ERK5KO* mice, in these animals severe liver damage was evident at 24 and 48 hours after PH, as indicated by higher ALT and AST levels compared to the control group. Histological analysis confimed this result showing a higher degree of hepatic tissue damage in *LysMCRE/ERK5KO* mice subjected to PH. Analysis of M1/M2 markers in liver tissue showed a reduced expression of M2 markers (ARG1, MRC2), together with a parallel increase in M1 markers (CCL2, IL1β) in the *LysMCRE/ERK5KO* group 48 h after PH) + , compared to control mice.

Conclusion: This study suggests that ERK5 modulates the liver regeneration process regulating macrophage plasticity. Genetic loss of ERK5 in myeloid cells is associated with severe liver damage and reduced cell proliferation, a phenotype associated with enhanced M1 polarization of hepatic macrophage.

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F-26

Efficacy of transjugular intrahepatic porto-systemic shunt in cirrhotic patients with hepatorenal syndrome – chronic kidney disease

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Background and aims: transjugular intrahepatic porto-systemic shunt (TIPS) has proved to ameliorate renal function in patients with type 2 hepatorenal syndrome (HRS). However, available evidence is based on: 1- 'old' diagnostic criteria for type 2 HRS and not on the current definition of HRS–chronic kidney disease (CKD) and 2- studies of relatively small sample size. Among patients who underwent TIPS for refractory ascites over the last 11 years, we aimed to investigate the renal function of those with HRS-CKD.

Methods: 38 out of 199 patients fulfilled the current diagnostic criteria for HRS-CKD and were included in the analysis. Renal function (serum creatinine - sCr and Glomerular Filtration Rate – GFR using *Modification* of *Diet* in Renal Disease 4 – MDRD4 and Chronic Kidney Disease Epidemiology Collaboration– CKD-EPI formulas) was evaluated 1 week and 1 – 3 – 6 and 12 months after TIPS.

Results: Renal function significantly improved since 1 week after TIPS (sCr: 1.94 ± 0.56 vs 1.40 ± 0.32 mg/dl; p < 0.001; GFR-MDRD4: 36.29 ± 9.65 vs 53.72 ± 14.4 ml/min/1.73 m^2; p < 0.001), and the improvement was maintained during the follow up. Considering the baseline CKD stages, the amelioration in renal function was observed in stage G3a (GFR-MDRD4 49.81 ± 3.65 vs 59.31 ± 11.0 ml/min/1.73 m^2; p = 0.025) as well as in stage G3b (GFR-MDRD4 38.29 ± 4.97 vs 53.75 ± 16.83 ml/min/1.73 m^2; p < 0.001) and stages G4-G5 (GFR-MDRD4 25.25 ± 3.15 vs 50.43 ± 11.67 ml/min/1.73 m^2; p < 0.001). Since one week after TIPS and during the whole follow up, sCr and GFR became comparable between stages G3a vs G3b vs G4-G5 (p = ns), whilst significantly different (p < 0.05) at baseline.

Conclusions: TIPS led to an early and persistent improvement in renal function in patients with HRS-CKD, irrespective of the baseline CKD stage. After TIPS, renal function parameters became rapidly comparable between patients with slightly reduced GFR and patients with severe HRS-CKD.

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F-27

Subtle changes of c-reactive protein and serum creatinine during the index hospitalization predict early readmission in patients with decompensated cirrhosis

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Background/Aims: Patients with decompensated cirrhosis had a high risk of early re-hospitalization. This study aims at identifying new predictive factors and the prognostic impact of readmission within 30 days (early readmission) after discharge from an index hospitalization for acute decompensation (AD).

Methods: Three hundred twenty-nine patients discharged after hospitalization due to AD were included in this prospective observational study. Laboratory and clinical data at admission, during hospital stay and at discharge of the index hospitalization were collected. Readmissions and its causes and mortality were recorded up to 1 year.

Results: Cumulative incidence of readmission was 18% at 30 days (early readmission), 39% at 90 days and 63% at 1 year. Early readmission was associated with a higher 1-year mortality (54% vs 33%, p=0.001). The most frequent causes of early readmission were bacterial infection (21%), hepatic encephalopathy (19%) and ascites (19%). Data collected both at admission (Child-Pugh, MELD-Na, diabetes), during hospital stay (acute-on-chronic liver failure) and at discharge (MELD-Na, platelet count, days spent in hospital) were significantly associated with early readmission. We then investigated if subtle changes of routinely laboratory parameters between admission and discharge were associated with early readmission. Multivariable competing risk regression showed that increases as small as 0.2 mg/dl of serum creatinine (SCr) and C-reactive protein (CRP) were associated with an increased hazard ratio (HR) of early readmission (SCr: HR=1.9 [95%CI 1.1-3.2], p=0.034; CRP: HR=1.8 [95%CI 1.1-3.2], p=0.031). Such increase in SCr was also associated with a higher 1-year probability of death (59% vs 31%, p<0.001).

Conclusion: Besides already established parameters related to the severity of disease, even subtle increases in SCr and CRP (0.2 mg/dl) between admission and discharge emerged as new risk factors for early readmission and worse prognosis, thus identifying patients who need for closer surveillance after discharge.

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F-28

Terlipressin vs noradrenaline for the treatment of hepatorenal syndrome in patients with acute-on-chronic liver failure: a 5-year retrospective analysis

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Background and aims: Hepatorenal syndrome (HRS) is a type of acute kidney injury (AKI) that develops in cirrhotic patients. Most patients with HRS-AKI have acute on chronic liver failure (ACLF). Response to vasopressor treatment and predictive factors of mortality in HRS-AKI patients with ACLF are still unclear.

Methods: A retrospective analysis of cirrhotic patients admitted in our intensive care unit from January 2014 to July 2019 was performed. Patients with ACLF and HRS-AKI were treated with albumin

plus terlipressin (T) or plus noradrenaline (NA). Patients were censored at the time of death, liver transplantation or end of follow-up.

Results: Among 128 consecutive ACLF patients, 37 were diagnosed as HRS-AKI. No significant differences were observed in demographic, clinical and laboratory parameters. Response to treatment was observed in 19/37 (51%) patients, 16/24 (67%) in group T vs 3/13 (23%) in group NA (p=0.019). Response was achieved in 15/24 (63%) patients with grade 1, 4/9 (44%) with grade 2, 0/4 with grade 3 ACLF (p=0.02). Non responders had higher MELD-Na than responders (34 ± 5.2 vs 30 ± 5.4; p = 0.03). The type of vasoconstrictor [OR 5.88 (1.09-31.64); p=0.03] was the only independent predictive factor of response to treatment. With respect to 28-day mortality, 18/19 (95%) responders to treatment were alive vs 7/18 (39%) of non-responders (p<0.01). Leukocytes (p=0.01), MELD-Na (p<0.01) and ACLF grade 3 (p<0.01) were also associated with 28-day mortality. Non response to treatment with vasoconstrictor and albumin was, together with MELD-Na [HR 1.17 (1.04-1.33; p=0.01), the only independent predictive factor of 28-day mortality [HR 11.15 (1.35-92.12; p=0.025)].

Conclusions: Terlipressin was far superior to noradrenaline in treating HRS-AKI in patients with ACLF and non response to treatment was the strongest independent predictor of 28-day mortality.

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F-29

The prevalence of esophageal varices needing treatment depends on gender, etiology and BMI

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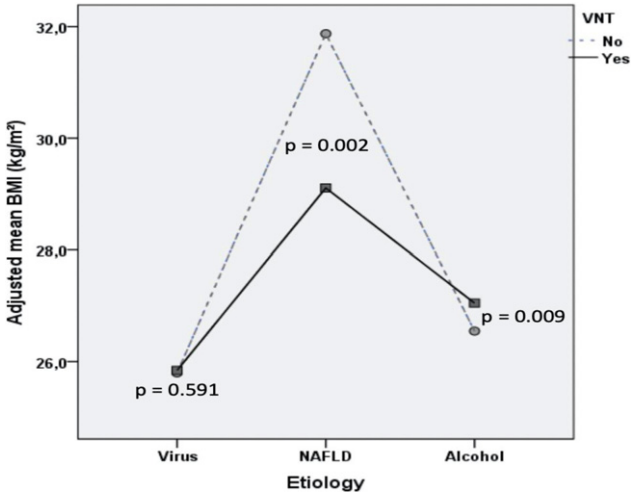
Introduction: The epidemiology of esophageal varices has so far been evaluated under conditions restricted by the size and etiology of the population. It is essential to know the epidemiological predictors to improve predictive scores.

Aims: The main objective was to evaluate the epidemiology of varices needing treatment (VNT) in a vast population of multiple etiologies.

Method and Methods: 2,290 patients with chronic liver disease were included in 8 countries in a retro-prospective study. Their characteristics were, age: 59±11 years, men: 63.5%, etiologies: virus: 50.0%, NAFLD: 29.5%, alcohol: 20.5%, BMI: 28.4±5.8 kg / m^2, MELD score: 9.5±3.0, liver stiffness ≥10 kPa: 93%. The VNT prevalence was 14.9%.

Results: The main significant differences between patients with VNT vs no VNT were: increased prevalence in men, high MELD, alcohol etiology and decreased in NAFLD vs virus etiology, lower BMI and creatinine. Thus, the odds ratio of VNT for men was 1.55 (1.19-2.03) after adjusting for covariates. In multivariate analysis, the independent predictors of VNT were: etiology, sex, platelets, prothrombin index, liver stiffness, albumin and ALT without role for age, BMI, AST, creatinine, and MELD score. This model provided the first score of usual tests (SCOUT 1). A second model taking into account the multiple interactions called SCOUT 2 made it possible to increase the AUROC for VNT to 0.819 vs 0.806 for SCOUT 1 (p=0.019). SCOUT scores were compared to published VNT scores ANTICIPATE and PLER (ratio platelets/liver stiffness). SCOUT 2 was very well calibrated according to gender, etiology and MELD, unlike other scores. The sensitivity ≥95% for VNTs (condition of Baveno VI criteria for missed VNT £5%) was for VNT scores or tests: Baveno VI: 24.1% (of patients), PLR: 29.2%, ANTICIPATE: 31.5%, SCOUT 1: 34.8%, SCOUT 2: 37.8% (p<0.001 between each test). This analysis also showed a significant interaction between BMI and etiology or prothrombin index. Thus, BMI of VNTs adjusted on covariates (by ANCOVA) was significantly decreased in NAFLD (p=0.002) but significantly increased in alcohol (p= 0.009) vs no VNT (Figure 1).

Conclusion: The prevalence of VNTs varies according to etiology, liver function and fibrosis and sex. The role of BMI is unmasked owing to a real interaction with etiology: negative influence in NAFLD and positive in alcoholic etiology. These new findings allow improving the performance and calibration of VNT predictive scores and finally test to rule out VNT. Figure 1:



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[1] All authors and centers, merged in the VEB6 group for the present study, are listed at the end of the main text.

F-30

Adipopenia, among the nutritional parameters, is the one that best correlates with mortality in decompensated cirrhotic patients: results of a prospective study

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Introduction and Aims: patients with liver cirrhosis (LC) often have malnutrition (MN) which is associated with decompensation, infection and death. Nevertheless, nutritional status (NS) is rarely evaluated in clinical practice and there is no general agreement on definition and methods, especially in decompensated cirrhosis. Aims of this study were: 1) to investigate MN prevalence in cirrhotics with ascites; 2) its impact on mortality and 3) its relationship with infectious ascites (SBP).

Methods: NS was assessed in addition to routine clinical procedures in all cirrhotics with ascites consecutively admitted in two Liver Centres between November 2014-October 2016. The end of study was September 2019. NS was evaluated using anthropometric parameters (weight, height, mid-arm-circumference, triceps-skinfold-thickness) and their derivate measurements: BMI according to Campillo, Upper-Muscle-Area (UMA), Upper-Fat-Area (UFA). All patients underwent diagnostic paracentesis and were followed-up till the end of study. An independent Ethical Committee approved the study.

Results: 110 patients were enrolled: male 69.1%, median age 61; aetiology: HCV 52.7%, Alcohol 33.6%, HBV 33.6%; Child-Turcotte-Pugh Class-A 10.9%, B 64.5%, C 24.5%; MELD<14: 43.6%, 14-20: 33.6%, >20: 22.7%; SBP 27.3%. Prevalence of MN was: 30.9% according to corrected BMI, 67.3% according to UMA, and 40% to UFA. During follow-up, 4 patients underwent OLT. Nineteen patients were lost to follow-up. Patients alive at 3-6-12 months and at the end of the study were: 68.1%, 59.3%, 45.1%, 24.2%, respectively. At univariate analysis SBP, MELD, UFA, UMA and age were significantly associated with mortality. At multivariable analysis SBP, MELD>20, MELD>14 and UFA were independently associated with mortality (OR=3.09, 2.89, 2.35 and 2.22, respectively). There was a strong correlation between adipopenia and SBP (p=0.008); but not with sarcopenia.

Conclusions: UFA, that measures the adipopenia, was abnormal in 40% of the cirrhotic population investigated and, among the parameters of malnutrition, was the only test independently associated with mortality.

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F-31

Long-term prospective study of development of hepatocellular carcinoma in compensated cirrhosis

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Background and Aims: Hepatocellular carcinoma (HCC) is the 5th incident solid tumor in males and the 2nd for mortality. With the aim of identifying clinical/biologic risk factors for HCC development, we started in 2013 a prospective study in patients with liver cirrhosis undergoing hepatic venous pressure gradient (HVPG) measurement (ClinicalTrials.gov:NCT03083002).

Method: 445 consecutive patients with liver cirrhosis prospectively enrolled from July 2013 (66.5% CP-A, 23.2% CP-B, 10.3% CP-C) when undergoing HVPG/transjugular liver biopsy, were followed-up every 6 months with US and blood tests. Etiology, portal vein thrombosis, HVPG,esophageal varices, Child-Pugh,MELD Score, time to HCC development were recorded. Incident cases of HCC were biopsied for pathological and transcriptomic characterization. Independent risk factors for HCC were evaluated by Cox regression analysis.

Results: Median follow-up was 40 months. 61 patients died during follow-up, 34 developed HCC (incidence 4-5% per year). Preliminary results of analysis of hepatic and circulating biomarkers of angiogenesis, portal hypertension and fibrosis as predictive factors for HCC development indicate marked activation of angiogenesis as related with HCC risk. At univariate analysis HVPG>15 (but not HVPG>10 or >20 mmHg), F2/F3 esophageal varices, viral vs. non-viral etiology,and albumin were statistically associated with HCC development (HVPG/F2-F3 varices collinear). In HVPG>15 multivariate model, none of these factors was significantly associated with HCC development while in F2/F3 esophageal varices model,the latter were independently linked with it (HR 2.258,95% CI:1.135-4.494). Albumin only had borderline significance (.586, CI% .337-1.018).

Conclusion: Neither HVPG>10,>15 or >20 was independently associated with HCC development. Previous data indicating HVPG>10 as a significant risk factor for HCC were influenced by the cohort studied, which was free of varices at enrollment. In a cohort of compensated patients with liver cirrhosis not selected for absence of varices, more severe portal hypertension as indicated by F2/F3 varices was the only independent risk factor for HCC development.

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F-32

Spleen Stiffness/Platelets-Based Models Can Predict Presence of Esophageal Varices in Patients With Compensated Liver Cirrhosis

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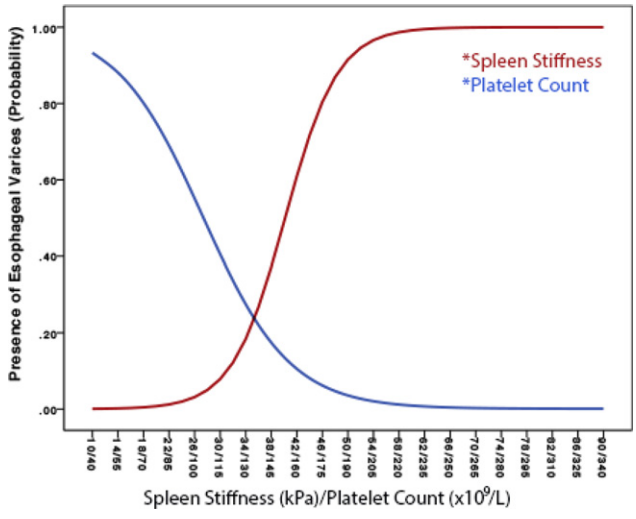
Background and Aims: Recent findings showed that patients with small-size esophageal varices (EVs) are more prone to hepatic decompensation. We want to evaluate the predictive capability of spleen stiffness (SS) and platelet count as non-invasive surrogates to appropriate EVs screening.

Method: We measured spleen stiffness (SS) using point-Shear-Wave Elastography (pSWE) with Philips Affiniti 70 system in 216 patients with compensated liver cirrhosis. Seventy-three patients had EVs. The association between varices (discrete; 0 = no, 1 = yes) and SS and platelet count was evaluated using logistic regression. According to statistical results we created SS and platelet count-based models in which the linear predictor (LP) was employed to calculate the probability of EVs using the following formula: {1-[1/(1+e(LP))]}.

Results: The LP according to SS was equal to -9.686 + 0.241*SS(kPa). SS-based model had the following discriminative and calibration metrics: AIC=121, BIC=129, AUROC=0.95, Pseudo-R2 (Nagelkerke)=0.70, Hosmer-Lemeshow (p-value)=0.146. Whereas, the LP according to platelet counts was +4.087 – 0.039*platelet count(x10*9/L). Platelet count-based model had the following discriminative and calibration metrics: AIC=292, BIC=295, AUROC=0.84, Pseudo-R2 (Nagelkerke)=0.411, Hosmer-Lemeshow (p-value)=0.4. According to the figure, the probability of EVs is < 7% with SS values < 30 kPa. The slope of the curve rapidly increases between 30 and 50 kPa. After 50 kPa the probability steadily increases and reaches a plateau at 70 kPa, where the probability is > 97%. Conversely, the probability of EVs according to platelet count increase drastically for values < 140(x10*9/L).

Conclusion: the two probability models showed similar but excellent discriminative and calibration metrics. It was possible to create a probability model according to SS-values that could decide to spare endoscopic screening in low-risk patients (for any grade of EVs). Having a given probability instead of a single number to rule-in or rule-out a specific event is indeed more helpful and could support the clinician in the decision of performing an invasive test if the probability is high. Cut-off values, even if they are chosen to be the most sensitive or specific, are always subjects to false-positives and false negatives; and, sometimes, even with low SS and high platelet count, the clinical presentation may require more invasive tests, making cut-offs pointless. In conclusion, the results of this study further emphasize the potential clinical relevance of SS measurement by pSWE elastography in the clinical workup of cirrhotic patients. Figure:



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F-33

Sarcopenia correlates with mortality in cirrhotic patients who undergo transjugular intrahepatic portosystemic shunt creation for refractory ascites

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Introduction: Sarcopenia correlates with clinical outcome in cirrhotic patients but it's not very clear its role in patients with refractory ascites. Muscle area quantification at the level of third lumbar vertebra using abdominal computed tomography (CT) images is a novel technique for the evaluation of sarcopenia.

Aim: With the present study we aimed to evaluate the possible association of sarcopenia and correlates it with mortality after TIPS placement in a subgroup of patients with refractory ascites.

Materials and Methods: Retrospectively clinical charts of all cirrhotic patients with diagnosis of refractory ascites who underwent TIPS creation in our Hospital in the period of 3 years (between January 2015 and November 2018) were reviewed. Evaluation of sarcopenia was made by measuring the psoas muscle (PMA) and total abdominal muscles areas (TAMA). Data were obtained in a semi-automated way by using a specific software.

Results: 115 pts had a TIPS and 90 were included in the study (mean age 60.6 years). Most frequent cause of cirrhosis was alcohol consumption/NASH. Mean pre TIPS MELD score was 12. All patients had an upper abdominal CT scan before TIPS (average time of 56.35 days before the procedure). Technical success of TIPS was 100%. Mean porto-caval gradient pre-TIPS and post-TIPS were 15.9 (±4.38) mmHg and 6.46 (±2.61) mmHg respectively. 16 patients died 6 months after TIPS. At univariate analysis hemoglobin level, white blood cell count, serum albumin, serum bilirubin, MELD score pre-TIPS as well as sarcopenia were risk factors associated with 6-months mortality after TIPS. Multivariate Cox regression analysis confirmed that sarcopenia, leucopenia, MELD score and PPG were independent predictors of post-TIPS 6-months mortality.

Conclusion: Sarcopenia correlates with 6 months mortality in patients with cirrhosis who undergo TIPS placement for refractory ascites

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F-34

RECK- and TIMP-mediated downregulation of matrix metalloproteinase activity by obeticholic acid in hepatic ischemia/reperfusion

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Introduction: We have shown a reduction in matrix metalloproteinases (MMPs) activity and iNOS content by the farnesoid X receptor (FXR) agonist obeticholic acid (OCA) in liver submitted to ischemia/reperfusion (I/R). Of note, iNOS is known to regulate the MMP activity in I/R injury. The reversion-inducing-cysteine-rich protein with kazal motifs (RECK), an MMP modulator, was found to be a transcriptional target of FXR.

Aim: This study evaluated the effects of OCA on RECK, tissue inhibitors of metalloproteinases (TIMPs) and iNOS content in liver after I/R.

Materials and Methods: Male Wistar rats (n=20) were orally administered 10 mg/kg/day of OCA (5 days) or vehicle and subjected to a 60-min partial-hepatic ischemia or sham-operated. After a 60-min reperfusion tissue samples were collected for RECK, TIMP-1, TIMP-2 and iNOS expression by Western blot analysis and MMP-2 and MMP-9 analysis by zymography. Serum levels of AST, ALT and total and direct bilirubin were quantified.

Results: I/R induced a decrease in liver RECK and TIMPs expression and a concomitant increase in MMP-2 and MMP-9 activity. OCA administration increased RECK, TIMP-1 and TIMP-2 and reduced MMP-2 and MMP-9 activity. An inverse correlation between RECK versus MMP-2 and MMP-9 was found. A positive correlation between MMP-2 and MMP-9 versus iNOS was observed. An inverse correlation between MMP-2 and MMP-9 versus TIMPs was found. Although not significantly, OCA administration reduced hepatic serum enzyme levels in the I/R group and a significantly lower level of direct bilirubin was detected in the I/R group treated with OCA.

Conclusions: Our results demonstrate the ability of OCA to limit the activation of MMP-2 and MMP-9 induced by hepatic I/R damage, probably via timely recovery of the RECK and TIMPs. While further studies will clarify the sequence of alterations and cause-effect patterns, these results suggest that changes in RECK protein may have therapeutic potential in MMP modulation during hepatic I/R damage.

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F-35

Transjugular intrahepatic portosystemic shunt is an effective and safe treatment of cirrhotic patients with portal vein thrombosis or cavernoma

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TIPS is a well established treatment in selected patients with refractory ascites and/or gastrointestinal bleeding (GIB). Whether TIPS may also be a safe and effective therapeutic option for cirrhotic patients with chronic portal vein thrombosis (PVT) or cavernoma is still not clear. We Investigated the feasibility, safety and efficacy of TIPS in cirrhotic patients with PVT. All consecutive patients with PVT or cavernoma undergoing TIPS placement from April 2014 to April 2019 in GOM Niguarda are here considered. All patients completed at least 6 months of follow-up after TIPS. Of 153 patients undergoing TIPS insertion, 50(32%) had cirrhosis complicated by PVT or cavernoma. In 11 cases(22%) PVT was associated with GIB, in 16 (32%) with ascites. 32(64%) patients had failed recanalization while on anticoagulation, 18 could not be anticoagulated for contraindications. Majority of patients was male (72%), leading etiologies were post-viral and post-alcohol cirrhosis. Median age was 57 years. Median MELD was 14 (range 8–18). TIPS placement was technically feasible in 96%(48/50)of patients. PVT extension is described in table 1. Trans-splenic approach was necessary in 8/50(16%). Early post-TIPS complications were: hemoperitoneum (3 cases,6%), sovra-hepatic vein occlusion (1 case,2%) and systemic infection (6 cases, 12%). During follow-up 94%(15/16) recovered ascites and 15 patients(30%) had at least 1 portosystemic-encephalopathy episode; 33/48 (68%) patients had a complete recanalization and 11/48 (22%) had a partial recanalization. Liver related mortality was 6%. 18 patients were listed to transplantation after achieving portal patency, 6 have been already transplanted, 8 are on waiting list and 4 could be delisted for clinical improvement. TIPS in cirrhotic patients with PVT with or w/o cavernoma is effective and well tolerated. Complete recanalization was achieved in 2 patients out of three, obtaining a clinical beneficial effect on symptomatic PH. Recanalization allowed patients to be listed for LT when needed

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F-36

Infection in cirrhosis: a changing epidemiologic setting

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Background: Bacterial and fungal infections represent a leading cause of decompensation and death in patients with cirrhosis. Even if a great proportion of infections are culture-negative, the analysis of microbiological findings is of utmost importance to assess local epidemiology, prevalence of multidrug resistant (MDR) strains and address early empirical therapy.

Aim: To retrospectively analyse epidemiology of bacterial and fungal culture-positive infections (CP-I) in a cohort of hospitalized patients with cirrhosis.

Material and Methods: All patients with cirrhosis consecutively admitted at Multivisceral Transplant Unit, Padua University Hospital, over 2 years period, were collected. After exclusion of colonisations, all cases of CP-I were retrospectively analysed. Type and source of infection, empirical or guided antibiotic/antifungal agent(s) used and eventual resistance were evaluated.

Results: One-hundred ninety-five patients during 319 hospitalizations were considered in the study period. Seventy-two (37%) patients (M/F 47/25, 55.7 [10] years) developed at least one CP-I. 137 CP-I occurred (fungal/bacterial 121/16), 62% of them hospital-acquired. Urinary tract and bloodstream infections were the commonest (41% and 29%). Amongst bacterial CP-I, gram positive (G+) strains occurred more frequently than gram negative (G-) ones (54.5% vs 45.5%), being Enterococci and Enterobacteriaceae the prevalent rods. Prevalence of MDR CP-I was 34%. Antibiotic empiric therapy was administered in 55% of patients but it was not adherent to guidelines EASL in most cases of nosocomial infections, with a minor resolution of infection. A total of 16 (12%) fungal infections occurred in the study period, mostly caused by Candida *spp* and involving the urinary and respiratory tract. Caspofungine and anidulafungina were the most common fungal agents used.

Conclusions: In our cohort, bacterial/fungal infection occurred in more than one third of hospitalized cirrhotic patients. Of them, 40% were CP-I. The increasing prevalence of G+ and MDR bacterial strains, should be taken into account for antibiotic stewardship and empiric therapy.

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F-37

Risk of contrast-induced acute kidney injury in cirrhotic patients undergoing computed tomography: myth or reality?

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Background and Aims: Cirrhotic patients have been considered at increased risk for iodinated contrast-induced acute kidney injury (CI-AKI), but evidence is scant and conflicting. Our study aimed at clarifying this issue.

Methods: An observational retrospective and a subsequent prospective study were undertaken in consecutive patients hospitalized from January 2018 to October 2019. Three cohorts were compared: cirrhotics (A) and non-cirrhotics (C) undergoing contrast-enhanced CT scan (CECT) and cirrhotics not exposed (B) to iodinated contrast media (ICM). Kidney function was evaluated at T0 (24–48 h before CECT for cohorts A/C; at enrollment for B) and after 2-5-7 days (T1). CI-AKI was defined according to KDIGO criteria. Patients with any potential cause of clinical impairment and of serum creatinine (sCr) increase between T0 and T1 were excluded.

Results: Overall, 294 patients were enrolled: 83, 95 and 116 in cohort A, B and C, respectively. CI-AKI incidence in cohort A did not differ from C (2.4 vs 2.6%, $p = 0.48$) or B (2.4 vs 1%, $p = 0.94$). All cases were stage 1a, except one case stage 1b, and all regressed spontaneously in few days. Mean sCr and eGFR (MDRD-4) did not change significantly after CECT in any cohort. In a subgroup of 69 consecutive cirrhotic patients urinary NGAL was measured, showing no significant changes from T0 to T1 in any patient neither in cohort A (26 ± 20 vs 24 ± 23 ng/ml, $p = 0.48$) nor B (30 ± 34 vs 31 ± 30 ng/ml, $p = 0.86$).

Conclusion: Cirrhosis per se does not increase the risk of CI-AKI after CECT compared to the general population. AKI episodes were mild, rapidly reversible, with comparable incidence between CECT and non-CECT patients, hence likely attributable to spontaneous sCr fluctuations rather than to ICM. Even the assessment of NGAL, a sensitive marker of tubular damage, could not detect any sign of CI-AKI.

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The impact of age in mortality and complications development in cirrhotic outpatients

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Background and aims: The observation of differences in prognostic terms between compensated and decompensated cirrhosis led to the development of prognostic stages of cirrhosis based on the development of complications. However, the role of age in determining survival and the development of complications in patients with cirrhosis has never been considered. The aim of the study was therefore to evaluate the role of age in clinical outcomes of cirrhotic outpatients. Patients and methods: From March 2012 to March 2019 650 outpatients with cirrhosis were enrolled in the study and were follwed until death, liver transplant or the end of follow up. Patients were subdivided in 4 classes according to their age: 196 were younger than 50 years old at inclusion, 232 were 51–60 years old, 144 were 61–70 years old and 78 were older than 70 at inclusion.

Results: There was no significant difference in 12 and 60 months transplant free survival in the comparison between the 4 groups. On the contrary, in every group transplant-free survival was significantly lower comparing patients who developed complications during follow up and patients who didn't. Moreover, there was no difference in complications' development (SBP, HRS, ascites, refractory ascites, ACLF, hepatic encephalopaty, variceal bleeding) comparing the 4 groups. According Cox' regression, MELD score (HR 1.17, $p < 0.001$), mean arterial pressure (HR 0.98, $p < 0.001$) and the development of at least a complication (HR 3.30, $p < 0.001$) were found to be independent predictors of mortality at multivariate analysis.

Conclusions: Age doesn't seem to affect transplant-free survival and complications development in patients with cirrhosis. Thus, for patients at any age preventing and treating effectively any possible complication seem to be the key to reduce mortality.

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F-39

Inhibiting NOXs with extra-virgin olive oil polyphenols as a strategy to prevent hepatic fibrogenesis

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Introduction: An exaggerated activation of NADPH oxidases (NOXs), key enzymes in the production of reactive oxygen species (ROS), is implicated in inflammatory and fibrotic disorders. Although polyphenols display antioxidant activity, only few *in vitro* results have been obtained about their effect on the inhibition of specific NOX isoforms (e.g. NOX1 and 4) and nothing is known about the consequences of NOX inhibition on immune cell activation and/or recruitment in the liver, a process playing a pivotal role in fibrogenesis. Aim: to describe the *in vivo* role of NOXs in fibrogenesis and evaluate the antifibrotic and antioxidant effects of 4 polyphenols (oleacein, oleocanthal, tyrosol and hydroxytyrosol) extracted from extra-virgin olive oil.

Materials and Methods: liver fibrosis was induced by CCl_4 to 6 BALB/C mice; 6 untreated mice were used as controls. After sacrifice, liver fibrosis was assessed by Sirius red. mRNA levels of hepatic NOX1/4, alpha-SMA, COL1A1, IL-6, IL-10, IL-17 and IL-23 were assessed by qPCR; CD68 hepatic expression was evaluated by IHC. Hepatic ROS production was measured by DCFDA. LX2 and HepG2 cells were used as *in vitro* models for testing oleacein, oleocanthal, tyrosol and hydroxytyrosol with preliminary *in vitro* assays.

Results: A significant increase of hepatic ROS ($p < 0.0001$), NOX1/4, IL-6, IL-10, IL-17 and IL-23 mRNA levels ($p < 0.05$), aSMA and CD68 positive cells were observed in fibrotic mice compared to controls. Furthermore, we demonstrated that oleacein, oleocanthal and tyrosol significantly decreased the *in vitro* ROS production in HepG2 cells, and the mRNA levels of NOX1/4, alpha-SMA and COL1A1 and in TGFbeta1-activated LX2 cells, displaying an activity comparable to the NOX1/4 inhibitor GKT136901.

Conclusions: Inhibiting NOXs with polyphenols extracted from olive-oil should be considered as a strategy to prevent hepatic fibrogenesis by reducing oxidative stress and immune cell activation in the liver. Further *in vivo*studies will address this hypothesis.

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F-40

Hepatic ischemia induces a time-dependent increase in SerpinB3 gene expression

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Introduction and Aim Understanding the mechanisms of liver ischemia injury and developing strategies to counteract this injury will reduce acute complications in liver transplantation thus expanding the potential pool of usable donor grafts. The inflammatory response to hepatic ischemia is associated with an increase in cytokine production, leading to liver injury. Recently, SerpinB3, that is undetectable in normal liver, has been reported to be induced by oxidative stress in hypoxic conditions and to determine cell death resistance by the inhibition of apoptosis and increase of cell proliferation. The aim of the present study was to investigate whether acute liver ischemia might affect the molecular expression of SerpinB3 in relation to inflammatory cytokines profile in the liver.

Materials and Methods Male Wistar rats ($n = 15$) were subjected to partial-hepatic ischemia (60, 120, 180 min) by clamping the hepatic artery and the portal vein; sham-operated rats ($n = 12$) were used as control group. At the end of the procedure, liver and blood samples were collected. Hepatic enzymes were analyzed in serum, while gene expression of SerpinB3 and inflammatory cytokines were assessed in the liver

Results Liver ischemia injury was confirmed by increased hepatic enzymes (ALP, ALT, gGT) in the ischemia treated group, compared to the sham group. Hepatic ischemia induced a progressive and significant increase of SerpinB3 expression, reaching a peak (18 fold increase) at 180 min, while the increase of inflammatory cytokines occurred earlier. In detail, for IL1B the peak expression was observed at 60 min, while IL6 and TNFα peaks occurred at 120 min. No significant modifications were observed in the liver of sham-operated rats.

Conclusions The present data demonstrate that SerpinB3 is increased in ischemic liver, but its late induction, compared to inflammatory cytokines, might explain the inefficient protection in hepatic ischemia. Early administration of SerpinB3-based compounds might be considered as new potential strategies to counteract this injury.

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F-41

Sarcopenia in liver transplant candidates

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Sarcopenia has recently emerged as an independent factor associated with elevated mortality in cirrhotic patients waiting for liver transplantation (LT). We aimed to investigate the association between sarcopenia and peri-transplant and post-transplant outcomes in LT candidates. 410 cirrhotic patients, who received a LT at Niguarda Hospital, from January 2012 to December 2016 were enrolled. Skeletal muscle index at the third lumbar vertebra was measured by CT scan, and sarcopenia was defined using previously published gender and BMI –specific cutoffs. 365 patients (69%) were male, with a median age at LT of 54 years. The most common etiologies of cirrhosis were HCV (52%), alcohol (16%) and autoimmune diseases (6%). Sarcopenia was diagnosed in 69 patients (16%) and was more frequent in those with refractory ascites ($p = 0.000$), and a higher MELD score at LT ($p = 0.000$). While on waiting-list, sarcopenic patients were more frequently admitted to the hospital for episodes of acute decompensation ($p = 0.05$), bacterial infections ($p = 0.000$) and to ICU to manage major cirrhosis complications ($p = 0.000$). Sarcopenic patients had longer ICU ($p = 0.001$) and hospital stays ($p = 0.002$), after LT, and a higher rate of bacterial and fungal infections (0.001) in the early post-LT period. Interestingly, MDR infections, especially caused by KPC bacteria, were more represented in sarcopenic patients ($p = 0.014$). Instead, we haven't observed any correlation between sarcopenia and post-LT complications. The median survival after LT was 1282 days for sarcopenic and 1411 for non-sarcopenic patients ($P = 0.016$). At multivariate analysis, older age at LT and pre-LT sarcopenia, as well as post-LT MDR infections, use of CRRT and prolonged ventilation in ICU were all independently associated with mortality. Sarcopenia, in our cohort, has been associated with a higher risk of waiting-list complications and post-LT infections, longer hospital and ICU stays and increased mortality after LT.

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Cold ischemic injury is reduced by the mGluR5 negative allosteric modulator MPEP in rat livers from cardiac death donors

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Background: we previously demonstrated that the blockade of mGluR5 reduces inflammation and necrosis in both cold and warm ischemia/reperfusion injury models; in fact, the administration of 2-methyl-6(phenylethylnyl) pyridine (MPEP) reduced Bax/Bcl-2, TNF-α and iNOS protein levels after the normothermic reperfusion of rat and mouse livers. In this study, we evaluated whether MPEP reduces the hepatic preservation injury in rat livers from cardiac death donors (DCD).

Methods: livers from DCD rats were isolated after an in situ, 30-min, warm ischemia and preserved for 22 hours at 4 °C with UW solution, then washed out with Ringer-Lactate. 10 mg/Kg MPEP or vehicle were administered 30-min before the portal clamping and added to the UW solution (3 μM). LDH release during washout was quantified. Liver samples were collected for WB analysis of iNOS, eNOS, NFkB, ICAM-1, caspase-3, caspase-9 and BAX.

Results: comparable levels of LDH release were detected during washout when comparing vehicle-treated DCD and MPEP-treated DCD. An increase in eNOS content occurred after MPEP treatment; iNOS expression was unchanged. NFkB and ICAM-1 expression were reduced in the MPEP-treated liver. MPEP treatment was associated with a reduced activation of the apoptosis markers caspase-3, caspase-9 and BAX.

Conclusion: these results suggest that MPEP can be used to recover cold-stored DCD livers for transplantation. In fact, MPEP donor pretreatment and organ treatment during cold storage protects against apoptosis and significantly increases eNOS, whose overexpression has been previously demonstrated to be protective in hepatic ischemia/reperfusion. Moreover, NFkB, one of the nuclear factors involved in injury progression, and ICAM-1, an NFkB target protein, are reduced after MPEP treatment. Since the current work investigated the effect of mGluR5 blockade after cold preservation only, future studies need to evaluate MPEP-induced protection after warm reperfusion as well as in rat orthotopic liver transplantation models.

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F-43

ESBLE and MRSA carriage in cirrhotic patients: a retrospective study on clinical outcomes before and after liver transplantation

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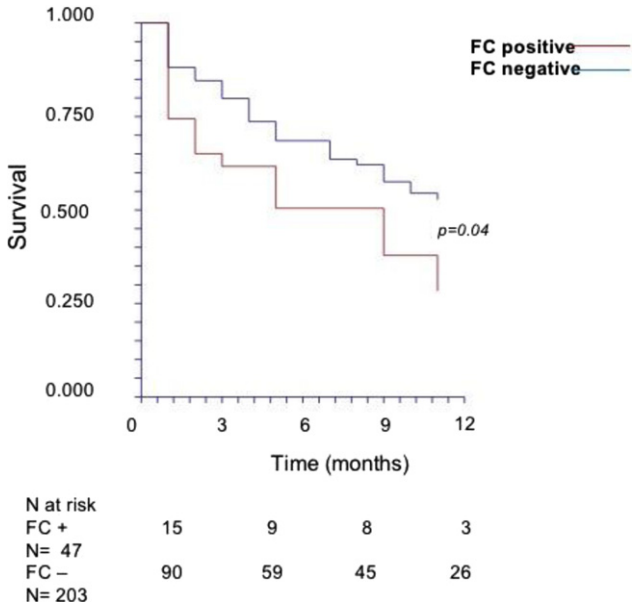
Introduction: Infections are very common in cirrhosis and they are associated with an increased risk of liver failure and liver-related complications (LRC), especially, in patients waiting for liver transplantation (LT). It is known that pre-LT colonization with Methicillin-Resistant-Staphylococcus-Aureus (MRSA) or Extended-Spectrum-Beta-Lactamase (ESBL) bacteria is an independent risk factor for infections after LT. Aim: The aim of this study was to evaluate the impact of MRSA and ESBLE colonization at 6 and 12 months on LRC and infections on waitlist and after LT.

Materials and Methods: We retrospectively included 250 of 483 cirrhotic patients that underwent LT from December 2015 to January 2018, screened for MRSA or ESBLE colonization at the time of waitlist inscription and after LT

Results: 76% of patients ($n = 109$) were male with mean age of 57.5 ± 10, the most frequent cause of liver disease was alcoholic (39%, $n = 99$), median MELD score was 19 (12-28). Only 1 patient was positive for MRSA. 19% of patients ($n = 47$) were fecal carriers (FC) at the moment of inscription on waitlist and 15% (n = 37) after LT. Infection free-survival on waitlist and after LT, according to FC was not statistically different between two groups [HR: 1.5, 95%; $p = 0.28$); [HR 0.99; $p = 0.9$]. LRC-free-survival at 6 and 12 months was significantly lower in FC vs. No FC [HR 1; $p < 0.04$)]. MELD score > 19 [HR 3; ($p = 0.01$)] and occurrence of infection < 3 months on waitlist [HR 4.13; ($p < 0.001$)] were independent risk factors for LRC occurrence at multivariate analysis

Conclusion: Our study is the first showing, in a cohort of cirrhotic patients waiting for LT, that LRC-free survival is lower in FC, but infection free survival is not different in the two groups.



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The role of postoperative ascites In determining long term survival after curative surgery for hepatocarcinoma: a national multicentric study

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Background: postoperative ascites (POA) is the most common complication after liver surgery for hepatocarcinoma (HCC), but its impact on survival is not reported. The aim of the study is to investigate its impact on overall survival (OS) and disease-free-survival (DFS), and secondarily to identify the factors that may predict the occurrence.

Method: Data were collected from 23 centers participating to the Italian Surgical HCC Register (HE.RC.O.LE.S. Group) between 2008 and 2017. POA was defined as $\geq$ 500 ml of ascites in the drainage after surgery for at least 3 consecutive days. Patients were then divided between no POA and POA, and risk adjustment analysis was conducted by Cox Regression to Investigate the risk factors for mortality.

Results: Among 1849 patients resected for HCC, 1,656(89.5%) patients did not experienced POA while 193(10.4%) had the complication. Presence of cirrhosis (OR = 1.995; 95%CI = 1.12–3.43; $p = 0.006$) and varices (OR = 2.323; 95%CI = 1.32-4.07; p:0.002) were predictors of ascites, while laparoscopic surgery was protective (OR = 0.230; 95%CI = 0.12–041; $p < 0.001$). Ninety-day mortality was higher in the POA group (8.8% vs 1.7% in no-POA group, $p < 0.001$). Median OS for no POA group was not reached, while it was 46 months(95%CI = 35.66–56.33)for those with POA($p < 0.001$). After risk-adjustment for confounders, POA independently increased the risk of mortality (HR = 1.465; 95%CI = 1.01-2.10;p:0.040)together with presence of microvascular invasion (HR = 1.867; 95%CI = 1.30-2.67;p:0.001). Relapse risk after surgery was not predicted by the occurrence of POA.

Conclusion: the occurrence of POA is strongly correlated with long term mortality, and its occurrence is relatively frequent. More efforts in surgical planification should be made to limit its presentation.

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F-45

Therapy with DAA increases post-OLT survival but not the risk of recurrence in patients undergoing liver transplantation for HCV-related HCC

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Introduction: The role of direct acting antivirals (DAAs) for hepatitis C virus (HCV) in hepatocellular carcinoma (HCC) recurrence is a source of great debate. Current evidence is unable to determine whether DAAs increases or decreases risk of recurrence. However, it has not been investigated the role of DAAs in patients undergoing orthotopic liver transplantation (OLT) for HCC. As a post-OLT recurrence is a deadly event, we compared the risk of recurrence and the overall survival (OS) of patients treated with DAA and obtaining SVR before OLT with an historical cohort of patients transplanted for HCC before the arrival of DAAs.

Matherials and Methods: We enrolled retrospectively 48 patients from the Bologna Liver Transplant Unit who underwent OLT in the DAA era for HCV-related HCC, from 2015 to 2019, comparing to an historic cohort of 128 patients transplanted for the same indication from 2003 to 2013. We performed multivariable regression analysis to identify factors associated with time to recurrence and overall survival.

Results: Recurrence rate was 12.5% for the first group (mean time to recurrence 16.8 mo) and 20.3% for the second (mean time to recurrence 24.5 mo). OS was significantly different: 91.7% vs 60.6%. In the Cox analysis, active HCC at transplant, number of nodules and diameter of the biggest nodule and alpha-fetoprotein were significantly associated with time-to-progression, whilst OS was associated with DAA treatment, microvascular invasion, diameter of the largest nodule at transplant and LN_{10}AFP at transplant. Analysing the competing causes of death, most of the effects on the increased survival in the DAA cohort derived for the reduction of the risk of liver decompensation.

Conclusions: Post-OLT recurrence did not vary significantly between the two groups. However, overall survival is increased in the DAA group. Therefore probably their efficacy is due to other effects, in particular the prevention of liver decompensation.

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F-46

Early liver transplantation in active drinkers with and without alcoholic hepatitis: a monocentric case series

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Introduction: Early liver transplant (eLT) is an effective therapeutic option for patients with severe alcoholic hepatitis (SAH).

Whether eLT should be offered to active drinkers (AC) with rapidly progressive acute liver failure (ALF) without a definite diagnosis of SAH, is unknown.

Aim: we report the outcome of eleven AC with ALF and diagnosis of probable SAH who received eLT.

Methods: all AC admitted to our unit from April 2016 to June 2019 with clinically diagnosed 'probable SAH' according to NIAAA criteria and with a Maddrey Score (MS) > 32, were enrolled. Patients not improving after medical therapy, irrespective of the use of steroids (CS), were evaluated for eLT. The definite diagnosis of SAH was based on the histology of the explanted liver. Psycho-social selection by a dedicated team and tailored support pre- and post-LT were the cornerstone of the program.

Results: Forty patients with alcoholic cirrhosis and ALF due to probable SAH were enrolled. The majority (33/40, 82%) did not receive CS mainly for active infection (24/40, 60%). Sixteen (40%) patients, with median baseline MS 64 and MELD-Na 24, improved with medical treatment (MT). None died after a median follow up of 14 months (5–23); two received liver transplant beyond six months. Eleven (27.5%) patients had psychiatric or medical contraindication for eLT. Median FU was 4 months (0–7). Thirteen (32.5%) patients, with a median baseline MD 94 and MELD-NA 36, underwent eLT. All eLT patients are alive, after a median follow up of 18 months (12–33); one patients relapsed in heavy alcohol use about 25 months after eLT. On explant, all LT recipients had cirrhosis with only 6 also having SAH confirmed.

Conclusion: eLT should be considered in AC with ALF irrespective of definite diagnosis of SAH. Stringent psycho-logical support pre and post LT is crucial to avoid alcohol relapse.

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F-47

Impact of direct-acting antivirals in the management of post-liver transplant recipients compared with the interferon-era

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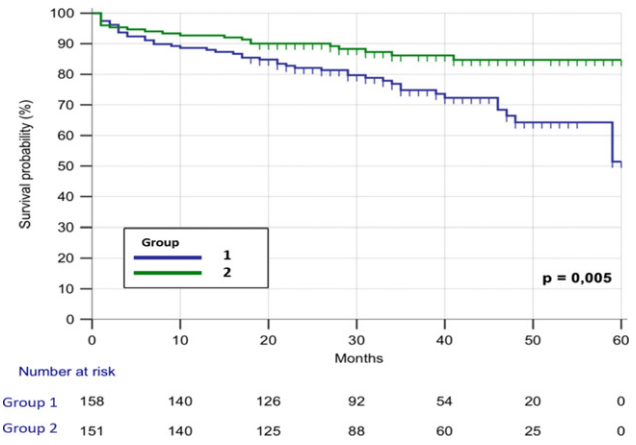
Introduction and Aims: Direct-acting antivirals (DAA) revolutionized HCV therapy, especially in liver transplant (LT) setting. We aimed to investigate the post-LT management during DAA-era compared with the interferon-one.

Methods: We enrolled 309 HCV patients who underwent LT in our Center: Group-1 (G1) included 158 patients consecutively transplanted since 06/2009 to 12/2012, follow-up until 06/2014; group-2 (G2) included 151 patients consecutively transplanted since 06/2014 to 12/2017, follow-up until 06/2019. We evaluated: donor/recipient characteristics, graft survival, complication rates (rejection, biliary and vascular complications, cytomegalovirus infections, HCC and tumor incidence).

Results: G1 vs G2 at LT: MELD 16 vs 12 ($p < 0.001$); 58% vs 76% with HCC ($p = 0.001$); 91% vs 36% ($p < 0.001$) with active HCV infection. G1 and G2 did not differ for recipient age and sex, donor age (median 65 years), ischemia-riperfusion injury and graft macrovesicular steatosis. G1 vs G2 immunosuppression: cyclosporine 68% vs 2% and tacrolimus 25% vs 97%, ($p < 0.001$). Post-LT: 15/143 HCV viremic patients in G1 achieved viral eradication with IFN-therapy; the 54 patients in G2 who were viremic at LT underwent pre-emptive successful DAA therapy. G1 vs G2 graft survival at 1, 2 and 3 years were: 87% vs 92% ($p = 0.004$); 82% vs 90% ($p = 0.03$); 75% vs 86% ($p = 0.02$), respectively; re-transplant rate 9% vs 5% ($p = 0.27$). Rejections occurred in 30% vs 13% ($p < 0.001$); 91% of G1 vs 32% of G2 underwent liver biopsy ($p < 0.001$); cytomegalovirus infections 29% vs 47% ($p = 0.003$); vascular complications 13% vs 7% ($p = 0.09$); biliary complications 24% vs 19% ($p = 0.27$); recurrent HCC 5% vs 2% ($p = 0.22$); de novo tumor 7% vs 10% ($p = 0.41$).

Conclusions: Despite a median donor age of 65 years, with 25% of the donor older than 75 years in G2, in DAA-era compared with interferon-one the post-LT management was simplified: graft survival significantly improved, rejection rate significantly decreased with a reduction trend in biliary complications.



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F-48

Early recurrence of hepatocellular carcinoma after liver transplantation can be predicted by fdg-pet and microvascular invasion at explant pathology

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Background and aims: Hepatocellular carcinoma (HCC) may recur early after liver transplantation (LT), and one of the main driver for recurrence is microvascular invasion (mVI), which is not

always detectable by pre-operative imaging examination. The role of F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) is poorly investigated in this setting, therefore we aimed to identify predictors of the recurrence of HCC after LT, including FDG-PET, with particular attention to early-recurrence (≤ 12 months) risk.

Methods: This is a single center, retrospective study including all consecutive patients who underwent LT for HCC. Epidemiological, clinical, radiological and histological data were collected and analysed. Results: Between 01/2010 and 07/2019, 449 LTs were performed, 182 (41 %) with HCC: 158 (84%) males, median age 58 (36-71) years, 60% HCV-positive, 25 % MELD ≥ 15, 54 % Child-Pugh A, median AFP 9 (1–60,500) ng/mL, 29% FDG-PET positive. At explant pathology: 86% with at least one active HCC nodule [median number *per* liver 2 (1–22)], median size 32 (3–239) mm; 16% micro-satellitosis and 27% mVI. During a median follow-up of 42 (2–118) months, HCC recurred in 29 (16%) patients (probability of recurrence at 1- 3- 5-years: 5%, 11%, 15%, respectively): 13 recurred ≤ 12 months after LT and 16 recurred > 12 months. By univariate analysis, the risk-factors for early-recurrence were micro-satellitosis, mVI, G3/4, FDG-PET positive, "Milan criteria"-out. By multivariate analysis, only mVI and FDG-PET positivity were confirmed as independent predictors of early-recurrence (HR 0.22, $p = 0.019$ and HR 0.11, $p = 0.09$). The over-all survival in our cohort was 96 months (95%CI:20–89), being 49 months (95%CI:20-78) in the 13 early-recurrent patients, 64 (95%CI:39–89) in the 16 late-recurrent ones and 104 (95%CI:21–85) in non-recurrent.

Conclusions: The FDG-PET in the pre-LT setting and mVI at explant pathology may help to identify those patients at high risk of early HCC recurrence, deserving of aggressive surveillance or pre-emptive treatment after LT.

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F-49

Epidemiology, features and outcomes of patients transplanted for hepatocellular carcinoma in the last decade: a single center experience

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Background and aim: Hepatocellular carcinoma (HCC) represents an increasing indication for liver transplantation (LT), however the implications of HCC-recurrence after LT is still debated. We aimed to identify the recurrence rate and its predictors and the impact on overall survival (OS) after LT in the last decade.

Methods: This is a retrospective, single center study including all consecutive LT patients with HCC (01/2010-07/2019). Epidemiological, clinical, radiological and histological data were collected and analysed. Immunosuppression was CNI-based.

Results: In our Center, 449 LTs were performed, 182 (41%) with HCC: 84% males, median age 58-yrs, 60% HCV, 25 % MELD ≥ 15, median AFP = 9 ng/ml, median time-lag between HCC diagnosis and LT 17 months, 74% pre-LT bridging/down-staging therapy. At explant pathology: 16% micro-satellitosis, 27% microvascular invasion (mVI), 50% Edmonson score = G3/4; 76% "Milan"-in. During a median follow-up of 42 months, HCC recurred in 29 (16%) patients after a median time of 9 (2–46) months. The probability of recurrence at 1-, 3-, 5-years was 5%, 11% and 15%, respectively. By multivariate analysis, independent risk-factors for HCC recurrence were: micro-satellitosis (HR = 0.31, $p = 0.023$) and mVI (HR = 0.38, $p = 0.04$): 1-, 3- and 5-years probability of OS was 94%, 87% and 77%, respectively; being 95%, 89% and 85% in the recurrence-free patients *vs* 89%, 76% and 43% in the recurrence-group ($p < 0.005$). The patients transplanted after 2015 ($n = 108$) were older (p = 0.04), more frequently males ($p = 0.02$), with lower MELD ($p = 0.0001$), more frequently treated by locoregional therapies ($p = 0.002$) and with higher rates of G3/4-HCC ($p = 0.001$) at explant pathology compared to those transplanted before 2015 ($n = 74$), still with comparable OS [100.9 (95%CI 90.16–111.8) *vs* 91.4 (95%CI 81.7-101.1) months ($p = 0,15$)].

Conclusions: Tumor-related features at explant pathology predict HCC-recurrence. Moreover, in the last few years, we have transplanted older patients with less severe disease but with more advanced tumors, with similar OS figures, still fitting with transplant benefit.

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F-50

Role of a dedicated referral system for patients with liver disease and potential indication for liver transplantation: prospective data from a single centre experience

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Introduction: An adequate referral system for patients with liver cirrhosis, acute liver injury (ALI) or acute liver failure (ALF) and potential indication to liver transplantation (LT) is crucial to guarantee a rapid diagnostic and therapeutic management. Aim: to develop a referral system for patients with potential indication to LT and to assess clinical characteristics and outcomes of referred patients.

Materials and Methods: A referral system was implemented in October 2017 at Multivisceral Transplant Unit, Padua University

Hospital, based on a 24/7 telephone availability and a dedicated email. All adult patients referred for the first time were prospectively collected, and stratified according to liver disease, timing, and type of evaluation.

Results: 163 patients were referred between October 2017 and October 2019 (M/F 100/63, mean age 54 ± 10 years; inpatients/outpatients 77/86). Overall, referral was urgent in 44 cases (27%), cirrhosis was the most common indication (78%), and the main reason for referral was evaluation for LT (80%). Considering inpatient referrals (n = 77), 54 (70%) had cirrhosis (mean ± SD MELD score at admission: 25.4 ± 9.5), whereas 22 (28.5%) were referred for ALI/ALF. Amongst patients with cirrhosis, ALD was the most frequent etiology (65%), whereas DILI was the most frequent indication amongst patients with ALI/ALF (47%). After a follow-up of 172 ± 190 days, 50.7% were alive, 35% died without LT, 10% underwent LT and 3.9% were lost at follow-up. 22 (28%) patients required ICU admission, and amongst these 73% died. After stratification according to liver disease, the proportion of patients who died without LT was 44% and 50% for patients referred for cirrhosis and ALF respectively.

Conclusions: Due to the high mortality rate and the frequent need of ICU admission amongst referred patients the development of a structured referral system is mandatory and the timing of referral should be properly defined as it can significantly impact on patient outcome.

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A.I.S.F. 2020

Abstracts Evaluation Procedure

Thanks to experts evaluating all the abstracts according to predetermined Clinical and Experimental categories.

The experts for the 2020 Annual Meeting are listed below:

Category A. **"EXPERIMENTAL VIRAL HEPATITIS"**
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Category B. **"HEPATITIS B & DELTA CLINICAL"**
B. Coco, Pisa - V. Di Marco, Palermo - A. Marzano, Turin - G. Taliani, Rome

Category C. **"HEPATITIS C CLINICAL"**
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Category F. **"AUTOIMMUNE HEPATITIS & BILIARY DISEASE"**
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Category H. **"EXPERIMENTAL LIVER DAMAGE, FIBROSIS, CIRRHOSIS & PORTAL HYPERTENSION"**
M. Fraquelli, Milan - F. Marra, Florence – M. Parola, Turin - G. Svegliati-Baroni, Ancona

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Category L. **"HEPATOCELLULAR CARCINOMA EXPERIMENTAL"**
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Category M. **"HEPATOCELLULAR CARCINOMA CLINICAL"**
G. Cabibbo, Palermo – A. Cucchetti, Bologna - E. Giannini, Genoa - M. Iavarone, Milan - F. Piscaglia, Bologna - G.L. Rapaccini, Rome – F. Trevisani, Bologna

Category N. **"LIVER FAILURE, HEPATOBILIARY SURGERY & TRANSPLANTATION"**
M. Angelico, Rome - L. Baiocchi, Rome - P. Burra, Padua - M.F. Donato, Milan - E. Gringeri, Padua – L. Pasulo, Bergamo - Q. Lai, Rome

Category O. **"MISCELLANEOUS: GENETIC, PEDIATRIC, NUTRACEUTICALS, DILI, OTHER"**
A. Gasbarrini, Rome – G. Germani, Padua – A. Lleo, Rozzano (MI) – L. Valenti, Milan

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1590-8658/