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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Alcohol and Cannabis Consumption Does Not Diminish Cure Rates in a Real-World Cohort of Chronic **Hepatitis C** Virus Infected Patients on Opioid Substitution Therapy-Data From the German**Hepatitis C**-Registry (DHC-R).

BACKGROUND:
The importance of alcohol and cannabis consumption for the effectiveness of treatment of chronic hepatitis C virus (HCV) infection with direct acting antivirals (DAAs) in people on opioid substitution therapy (OST) has not been investigated in detail.
METHODS:
We investigated sustained virological response (SVR) rates and proportion of lost to follow-up (LTFU) between OST (n = 739) and non-OST patients (n = 7008) in the German Hepatitis C-Registry (Deutsches Hepatitis C-Register, DHC-R), which is a national multicenter prospective non-interventional real-world registry. Non-OST patients comprised patients with former/current drug use (non-OST/DU; n = 1500) and patients never consuming drugs (non-OST/NDU; n = 5508).
FINDINGS:
SVR 12/24 rates (intention to treat [ITT]) in patients consuming no or less than 30 g/day (women) or 40 g/day (men) were significantly higher in non-OST/NDU (range 91%-92%) vs OST patients (range 83%-86%), mainly due to significantly higher LTFU rates in OST (range 11%-12%) compared with non-OST/NDU (range 2%-3%). In non-OST/NDU with high alcohol consumption of more than 30/40 g/day, SVR 12/24 rates (ITT) were lower (85%) but did not differ to OST (85%) with high alcohol consumption. No significant differences could be seen for SVR 12/24 in per-protocol (PP) analysis independent of alcohol consumption or amount of alcohol intake. Cannabis use did not significantly influence SVR 12/24 in ITT or PP or LTFU.
CONCLUSIONS:
High SVR rates could be achieved in both OST and non-OST patients irrespective of alcohol or cannabis consumption. However, LTFU is more likely in patients with current or former drug use than in patients without drug history and in patients with high alcohol consumption but occurred mainly after end of antiviral treatment (EOT), leaving a high chance for HCV elimination in these patients.

New patterns emerge after a sustained increase in the incidence of **hepatitis C** virus infection from 2004 to 2017: a joinpoint regression analysis.

OBJECTIVES:

Hepatitis C virus (HCV) infection continues to be a major public health concern in China. There is little information available in the literature about age- and sex-specific HCV incidence trends. The goal of this study was to examine recent trends in HCV incidence rates in Hunan, China, according to age and gender.

STUDY DESIGN:
A descriptive study was implemented with a joinpoint analysis.

METHODS:
Based on the annual reported incidence data of hepatitis C in Hunan, China, from 2004 to 2017, we performed a joinpoint regression analysis to examine trends in the annual percentage change (APC) and the average annual percentage change (AAPC) in the incidence of HCV infection throughout the study period; we stratified the analysis by gender and age. The software calculates the APC, AAPC and the 95% confidence intervals for each trend segment and tests whether the slope for each segment has a significant difference from the prior segment using a Z test.

RESULTS:
From 2004 to 2017, the overall incidence rate of HCV infection rose from 0.93 per 100,000 to 20.88 per 100,000 (AAPC, 25.2%). In particular, women aged ≥65 years had the fastest increasing rate (AAPC, 29.9%). The incidence of different demographic groups showed no significant difference in increasing trends before 2013. However, new patterns emerged after 2013: the incidence of people aged 0-14 years was no longer significantly elevated; a significant yearly decline occurred in the incidence of HCV in people aged 15-29 years; the incidence of HCV in people aged ≥30 years continued to increase, with significantly slower increasing rates than before; and women aged ≥65 years showed a significantly higher yearly increase in incidence than that in men in the same age group (APC, 11.1% in women versus 5.3% in men).

CONCLUSION:
The overall increasing rate of HCV infection significantly slowed after 2007 and 2013. The differences in incidence trends among demographic groups have obviously increased in the last 5 years, and the reasons underlying these different trends urgently require further study. People in older age groups, especially women aged ≥65 years, still experienced increases in incidence rates in the last 5 years. This finding indicates that programmes for the prevention and control of HCV infection in older people require continued strengthening.

IgG1 and IgG4 antibodies against Core and NS3 antigens of **hepatitis C** virus.
INTRODUCTION:
IgG subclasses involved in the immune response to hepatitis C virus (HCV) antigens have been rarely studied. We investigated the immune response mediated by IgG1 and IgG4 antibodies against the recombinant core and NS3 antigens in patients with chronic hepatitis C.

METHODS:
Sixty patients infected with HCV genotype 1 without antiviral treatment and 60 healthy subjects participated in the study. Serum levels of alanine aminotransferase, HCV viremia, and the presence of cryoglobulinemia and liver fibrosis were determined. We investigated the serum

IgG1 and IgG4 antibodies against recombinant HCV core and NS3 non-structural protein antigens using amplified indirect ELISA.

RESULTS:
Anti-core and anti-NS3 IgG1 antibodies were detected in 33/60 (55%) and 46/60 (77%) patients, respectively, whereas only two healthy control samples reacted with an antigen (NS3). Anti-core IgG4 antibodies were not detected in either group, while 30/60 (50%) patients had anti-NS3 IgG4 antibodies. Even though there were higher levels of anti-NS3 IgG4 antibodies in patients with low viremia (< 8 × 105 IU/mL), IgG1 and IgG4 antibody levels did not correlate with ALT levels, the presence of cryoglobulinemia, or degree of hepatic fibrosis. High production of anti-core and anti-NS3 IgG1 antibodies was observed in chronic hepatitis C patients. In contrast, IgG4 antibodies seemed to only be produced against the NS3 non-structural antigen and appeared to be involved in viremia control.

CONCLUSIONS:
IgG1 antibodies against structural and non-structural antigens can be detected in chronic hepatitis C, while IgG4 antibodies seem to be selectively stimulated by non-structural HCV proteins, such as the NS3 antigen.

Effectiveness and safety of daclatasvir/sofosbuvir with or without ribavirin in genotype 3 **hepatitis C**virus infected patients. Results in real clinical practice.
OBJECTIVE:
Direct-acting antivirals have shown high efficacy in all hepatitis C virus (HCV) genotypes, but genotype 3 (G3) treatments continue to be a challenge, mainly in cirrhotic patients. The aim of this study is to analyse effectiveness and safety of daclatasvir associated with sofosbuvir with or without ribavirin in G3-HCV infected patients in real clinical practice.

METHODS:
An observational, prospective, cohort study over 2.5 years, in G3-HCV infected adult patients, in all fibrosis stages including patients with decompensated cirrhosis. Treatment was a combination of sofosbuvir 400 mg/day + daclatasvir 60 mg/day, with or without a weight-adjusted dosing of ribavirin for 12 or 24 weeks. The primary efficacy endpoint was sustained virologic response rates 12 weeks after therapy (SVR12). The primary safety endpoint was treatment withdrawal rates secondary to severe adverse events.

RESULTS:
A total of 111 patients were enrolled, 32.4% cirrhotics and 29.9% treatment-experienced. The global SVR12 rate was 94.6%, while the SVR12 rate in F3-4 fibrosis stage patients was 90.8% versus 100% in patients with F0-2 fibrosis (p=0.03). In cirrhotic patients, SVR12 was 100% versus 40% depending on whether ribavirin was added or not to daclatasvir/sofosbuvir (p=0.001). No other patient or treatment basal variables influenced the treatment effectiveness. No patient treatment withdrawal secondary to severe adverse events was observed.

CONCLUSIONS:
Daclatasvir/sofosbuvir ± ribavirin is highly effective in G3-HCV infected patients. Advanced degrees of fibrosis significantly decrease the effectiveness of this treatment, which motivates the need for the addition of ribavirin in cirrhotic patients. The regimen was safe and well tolerated.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Phosphorylated tyrosine 93 of **hepatitis C** virus nonstructural protein 5A is essential for interaction with host c-Src and efficient viral replication.

The hepatitis C virus (HCV) nonstructural protein 5A (NS5A) plays a key role in viral replication and virion assembly, and regulation of the assembly process critically depends on phosphorylation of both serine and threonine residues in NS5A. We previously identified SRC proto-oncogene, non-receptor tyrosine kinase (c-Src) as an essential host component of the HCV replication complex consisting of NS5A, the RNA-dependent RNA polymerase NS5B, and c-Src. Pull-down assays revealed an interaction between NS5A and the Src-homology 2 (SH2) domain of c-Src; however, the precise binding mode remains undefined. In this study, using a variety of biochemical and biophysical techniques, along with molecular dynamics simulations, we demonstrate that the interaction between NS5A and the c-Src SH2 domain strictly depends on an intact, phosphotyrosine binding-competent SH2 domain and on tyrosine phosphorylation within NS5A. Detailed analysis of c-Src SH2 domain binding to a panel of phosphorylation-deficient NS5A variants revealed that phosphorylation of Y93 located within domain 1 of NS5A, but not of any other tyrosine residue, is crucial for complex formation. In line with these findings, effective replication of subgenomic HCV replicons as well as production of infectious virus particles in mammalian cell culture models were clearly dependent on the presence of tyrosine at position 93 of NS5A. These findings indicate that phosphorylated Y93 in NS5A plays an important role during viral replication by facilitating NS5A's interaction with the SH2 domain of c-Src.

Hepatitis C and kidney transplant: The eradication time of the virus has arrived.

Hepatitis C virus (HCV) infection is a factor that reduces the survival of the patient and the graft in renal transplant (RT). The availability of directly acting antivirals agents (DAAs), very effective and with an excellent safety profile, it allows eradicate HCV from patients with kidney disease, and this is a revolutionary radical change in the natural evolution of this infection, until now without effective and safe treatment for the contraindication use of interferon in kidney transplant patients. The efficiency of some DAAs for all genotypes, even in patients with renal insufficiency constitutes a huge contribution to eradicate HCV in the RT population independently the genotype, severity of kidney failure, progression of liver disease and previous anti HCV therapy. All this is raising, although with controversies, the possibility of use kidneys from infected HCV+ donors for transplant in uninfected receptors and can be treated successfully in the early post-TR, thus increasing the total "pool" of kidneys for RT.

Blistering Disease During the Treatment of **Chronic Hepatitis C** With Ledipasvir/Sofosbuvir.

Abstract

Hepatitis C virus-associated porphyria cutanea tarda can result from viral-induced inhibition of uroporphyrinogen decarboxylase and the subsequent accumulation of uroporphyrins and associated metabolites in urine.

Glutathione peroxidase and malondialdehyde in children with **chronic hepatitis C**.

Abstract

AIM OF THE STUDY:

We aimed to assess oxidative stress factors, glutathione peroxidase (GPX) and malondialdehyde (MDA) in children with chronic hepatitis C (CHC) and their relation to treatment response.

MATERIAL AND METHODS:
The study included 50 children with chronic hepatitis C virus (HCV) before treatment (naïve HCV), 25 children responders to HCV treatment, 25 children non-responders to HCV treatment and 25 healthy controls. All patients and controls were subjected to GPX and MDA measurement by enzyme-linked immunosorbent assay.

RESULTS:
The average GPX activity in erythrocytes of naïve CHC patients was 29.2 ±10.3 mU/ml. It was statistically significantly lower than the average activity of GPX in erythrocytes of the healthy control group (47.3 ±5.2 mU/ml) ($p < 0.05$). The average GPX activity in erythrocytes of the responder group was 34.93 ±3.17 mU/ml. It was statistically significantly higher than the average activity of GPX in erythrocytes of the non-responder group (11.7 ±4.2 mU/ml) ($p < 0.05$). Plasma MDA was significantly higher in naïve CHC patients than in healthy controls (9.7 ±3.7 nmol/ml vs. 3 ±1.1 nmol/ml, $p < 0.0001$). Furthermore, plasma MDA concentration was significantly decreased in the responder group (5.36 ±0.7 nmol/ml) and elevated in the non-responder group (16.05 ±2.9 nmol/ml).

CONCLUSIONS:
Lower pretreatment levels of GPX and higher MDA level might be markers of oxidative stress occurring in HCV patients. Reversal of changes of these levels with completion of the treatment may indicate a correlation between oxidative stress and the viral pathogenesis.

[Ledipasvir/sofosbuvir combination for **chronic hepatitis C** infection in children and adolescents]
INTRODUCTION:
Hepatitis C virus infection is world health problem. The aim of this study was to assess the safety and efficacy of ledipasvir/sofosbuvir combination in chronic Hepatitis C Virus (HCV) genotype 1 and 4 infection in paediatric patients.

METHODS:
Eligible patients to be treated with ledipasvir/sofosbuvir were patients from 6 to 18 years old with a chronic HCV genotype 1 or 4 infection. The duration and doses of antiviral drugs were changed depending on patient age, fibrosis stage, and PEGylated interferon+ribavirin experience status. The primary efficacy endpoint was the percentage of patients with a sustained virological response 12 weeks post-treatment.

RESULTS:
A total of nine patients (7 males) with a median age of 14.8 years (8.48-17.91) were treated with ledipasvir/sofosbuvir combination. Five patients received previous treatment with PEGylated interferon+ribavirin during a median of 8.5 months (3-12 months). Eight patients had some degree of fibrosis (1 patient presented with F1, three patients F2, 2 patients F3, and 2 patients F4). The median pre-treatment viral load was 6.2 Log [5.9-6.8] with the HCV RNA becoming negative six weeks after starting the treatment in 100% of the patients. All patients maintained a sustained viral response at 12 weeks. Three patients (33.3%) had some type of adverse effect (2 headache and one oral thrush). The median post-treatment follow-up was 24 weeks (12-104).

CONCLUSIONS:
Treatment with ledipasvir/sofosbuvir in paediatric patients with chronic HCV infection genotype 1 and 4 is safe and effective with SVR12 and similar to those reported in adults.

HIV/HCV Coinfection

Trends in **hepatitis C** treatment initiation among HIV/**hepatitis C** virus-coinfected men engaged in primary care in a multisite community health centre in Maryland: a retrospective cohort study.

OBJECTIVES:
Little is known about the cascade of hepatitis C care among HIV/hepatitis C virus (HCV)-coinfected patients in community-based clinics. Thus, we analysed our data from the interferon era to understand the barriers to HCV treatment, which may help improve getting patients into treatment in the direct-acting antivirals era.

DESIGN:
Retrospective cohort study.

SETTING:
Four HIV clinics of a multisite community health centre in the USA.

PARTICIPANTS:
1935 HIV-infected men with >1 medical visit to the clinic between 2011 and 2013. Of them, 371 had chronic HCV and were included in the analysis for HCV care continuum during 2003-2014.

OUTCOME MEASURES:
HCV treatment initiation was designated as the primary outcome for analysis. Multivariate logistic regression was performed to identify factors associated with HCV treatment initiation.

RESULTS:
Among the 371 coinfected men, 57 (15%) initiated HCV treatment. Entering care before 2008 (adjusted OR [aOR, 3.89; 95% CI, 1.95 to 7.78), higher educational attainment (aOR, 3.20; 95% CI, 1.59 to 6.44), HCV genotype 1 versus non-1 (aOR, 0.21; 95% CI, 0.07 to 0.65) and HIV suppression (aOR, 2.13; 95% CI, 1.12 to 4.06) independently predicted treatment initiation. Stratification by entering care before or after 2008 demonstrated that higher educational attainment was the only factor independently associated with treatment uptake in both periods (aOR, 2.79; 95% CI, 1.13 to 6.88 and aOR, 4.10; 95% CI, 1.34 to 12.50, pre- and post-2008, respectively). Additional associated factors in those entering before 2008 included HCV genotype 1 versus non-1 (aOR, 0.09; 95% CI, 0.01 to 0.54) and HIV suppression (aOR, 2.35; 95% CI, 1.04 to 5.33).

CONCLUSIONS:
Some traditional barriers predicted HCV treatment initiation in those in care before 2008; however, the patients' level of educational attainment remained an important factor even towards the end of the interferon era. Further studies will need to determine whether educational attainment persists as an important determinant for initiating direct-acting antiviral therapies.

Steatosis Rates by Liver Biopsy and Transient Elastography With Controlled Attenuation Parameter in Clinical Experience of **Hepatitis C** Virus (HCV) and Human Immunodeficiency Virus/HCV Coinfection in a Large US Hepatitis Clinic.

BACKGROUND:
Steatosis contributes to liver fibrosis in hepatitis C virus (HCV) and human immunodeficiency virus (HIV)/HCV coinfection. Liver biopsy (LB) is the reference standard for grading steatosis and staging fibrosis, yet recent advances in noninvasive modalities have largely supplanted LB, which may limit recognition of steatosis. We evaluated steatosis rates by LB and transient elastography (TE) with controlled attenuation parameter (CAP) among HCV-infected and HIV/HCV-coinfected patients in a US clinic.

METHODS:
Patients with chronic HCV infection during pretreatment evaluation by LB (n = 421; December 2001 through May 2014) and TE with CAP (n = 1157; May 2016 through May 2017) were included. Fibrosis and steatosis rates by LB and TE with CAP were stratified by HCV versus HIV/HCV coinfection status.

RESULTS:
Steatosis was not reported in 26.1% of LBs. Moderate to severe steatosis (grade ≥S2) was detected more often with CAP than with LB (in 24.0% vs 11.4% of patients, respectively). Median CAP values were higher in patients with HCV monoinfection than in those with coinfection (230 vs 215.5 dB/m, respectively; P < .001). With TE, the rate of advanced fibrosis (values F3-F4) was higher in HCV monoinfection than in coinfection (25.9% vs 14.8%, respectively; P <.001). With both LB and TE, advanced fibrosis (F3-F4) was significantly associated with moderate to severe steatosis (S2-S3) in HCV monoinfection compared with HIV/HCV coinfection (33.3% vs 4.4%, respectively for LB [P = 0.003] and 36.0% vs 29.0% for TE [P = 0.008]).

CONCLUSIONS:
In patients with chronic HCV undergoing liver fibrosis staging, steatosis was detected more often with CAP than LB, with median CAP values higher in HCV monoinfection than HIV/HCV coinfection. Steatosis severity may be increasing in the modern HCV treatment era.

Public Health Considerations among People who Inject Drugs with HIV/HCV Co-Infection: A Review.

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) co-infection among persons who inject drugs (PWID) is a major public health concern. There are limited data in clinical trials on the use of direct-acting antiviral (DAA) therapy for treatment of HCV in co-infected PWID. It is critical for these patients to gain access to treatment in order to decrease progression of liver disease and decrease transmission of both HIV and HCV. Additional harm reduction interventions, including needle and syringe programs and opioid substitution treatment, should be made available to this vulnerable population. Despite the importance of DAA treatment, the cost of DAA therapy and access to medical care is still a barrier to appropriate therapy. The purpose of this review is to present available data on the use of DAAs in co-infected PWID, review guideline recommendations for treatment and retreatment of HCV in co-infected PWID, provide cost considerations for DAA therapy, and provide recommendations about caring for patients who continue to inject drugs.

Hepatitis C Direct Acting Antivirals and Ribavirin Modify Lipid but not Glucose Parameters.

Chronic hepatitis C (HCV) infection perturbs lipid and glucose metabolism. The influence of direct acting antiviral (DAA) treatment and ribavirin on these measures was evaluated.Furthermore, the effect of HCV cure on these parameters was assessed. Participants were allocatedto one of three 12-week treatment groups: non-cirrhotic genotype 1aparitaprevir/ritonavir/ombitasvir/dasabuvir (PrOD) plus ribavirin; non-cirrhotic 1b-PrOD;compensated cirrhotic 1a or 1b-PrOD plus ribavirin. Fasting insulin, glucose, lipid andapolipoprotein measures were assessed at baseline, Treatment Weeks 4 and 12, and 12 and 24 weekspost-dosing. Twenty-three of 24 participants achieved SVR (PP= 23/24, 96% SVR). Overall, totalcholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels all increased intreatment and post-dosing. However, LDL-C levels decreased during treatment in ribavirinrecipients. Fasting glucose, insulin, and HOMA-IR were unchanged during treatment and 12 weekspost-treatment. By 12 weeks post-treatment, controlled attenuation parameter (CAP) scores, ameasure of steatosis, increased from baseline (mean 30.3 ± 63.5, p = 0.05). This regimen was safe andhighly effective and did not influence glucose metabolism. Ribavirin exposure may mitigate someon-treatment lipid changes. Further mechanistic studies are needed to understand how ribavirinimpacts lipid pathways, as there could be therapeutic implications. The metabolic pathophysiologyof increased CAP score with HCV treatment requires explanation.

Ombitasvir/paritaprevir/ritonavir plus ribavirin for 24 weeks in patients with HCV GT4 and compensated cirrhosis (AGATE-I Part II).

BACKGROUND AND AIMS:
AGATE-I Part I previously reported high sustained virologic response rates in hepatitis C genotype 4 patients with cirrhosis, with 12 and 16 weeks' treatment with a combination of two direct-acting antivirals, ombitasvir and paritaprevir (codosed with ritonavir), plus ribavirin. Part II, reported here, extended the trial to include a 24-week treatment arm to fully assess treatment duration in patients with chronic hepatitis C genotype 4 infection and compensated cirrhosis.

METHODS:
Enrollment took place between June and November of 2015. Treatment-naive and interferon-experienced patients with chronic hepatitis C genotype 4 infection and compensated cirrhosis were enrolled into Arm C; patients previously treated with a sofosbuvir-based regimen were enrolled into Arm D. All patients received a 24-week treatment with ombitasvir, paritaprevir, and ritonavir plus ribavirin. The primary outcome was the proportion of patients with a sustained virologic response (hepatitis C virus RNA < 25 IU/mL) at posttreatment week 12 in the intention-to-treat population. The safety population included all patients who received at least one dose of study drug.

RESULTS:
In total, 64 patients were enrolled into AGATE-I Part II. Sustained virologic response at posttreatment week 12 was achieved in 57 of 61 patients (93.4%; 97.5% confidence interval, 92.6-97.7) in Arm C and 3 of 3 patients (100%) in Arm D. Two patients were missing SVR12 data, and two prematurely discontinued treatment. The most common adverse events for Arm C were fatigue (16 [26%]) and asthenia (15 [25%]). Results were comparable with those reported in Part I.

CONCLUSIONS:

AGATE-I Part II indicates that extending treatment beyond 12 weeks in genotype 4-infected patients with compensated cirrhosis does not offer additional benefit.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Identifying Areas with Disproportionate Local Health Department Services Relative to Opioid Overdose, HIV and **Hepatitis C** Diagnosis Rates: A Study of Rural Illinois.

Background: U.S. rural populations have been disproportionately affected by the syndemic of opioid-use disorder (OUD) and the associated increase in overdoses and risk of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) transmission. Local health departments (LHDs) can play a critical role in the response to this syndemic. We utilized two geospatial approaches to identify areas of discordance between LHD service availability and disease burden to inform service prioritization in rural settings. Methods: We surveyed rural Illinois LHDs to assess their OUD-related services, and calculated county-level opioid overdose, HIV, and hepatitis C diagnosis rates. Bivariate choropleth maps were created to display LHD service provision relative to disease burden in rural Illinois counties. Results: Most rural LHDs provided limited OUD-related services, although many LHDs provided HIV and HCV testing. Bivariate mapping showed rural counties with limited OUD treatment and HIV services and with corresponding higher outcome/disease rates to be dispersed throughout Illinois. Additionally, rural counties with limited LHD-offered hepatitis C services and high hepatitis C diagnosis rates were geographically concentrated in southern Illinois. Conclusions: Bivariate mapping can enable geographic targeting of resources to address the opioid crisis and related infectious disease by identifying areas with low LHD services relative to high disease burden.

Epidemiology and management of **hepatitis C** virus infections in immigrant populations.

BACKGROUND:
At present, there is a continuous flow of immigrants from the south of the world to north-western countries. Often immigrants originate from areas of high-prevalence of viral hepatitis and pose a challenge to the healthcare systems of the host nations. Aims of this study is to evaluate the prevalence and virological and clinical characteristics of hepatitis C virus (HCV) infection in immigrants and the strategies to identify and take care of the immigrants infected with HCV.

MAIN BODY:
We conducted an electronic literature search in several biomedical databases, including PubMed, Google Scholar, Scopus, Web of Science, using different combinations of key words: "HCV infection; chronic hepatitis C, immigrants; low-income countries". We included studies written in English indicating the epidemiological data of HCV infection in the immigrant population, studies that assessed the clinical presentation, clinical management and treatment with directly acting antiviral agent in immigrants, HCV infection is unevenly distributed in different countries, with worldwide prevalence in the general population ranging from 0.5 to 6.5%. In Western countries and Australia this rate ranges from 0.5 to 1.5%, and reaches 2.3% in countries of south-east Asia and eastern Mediterranean regions, 3.2% in China, 0.9% in India, 2.2% in Indonesia and 6.5% in Pakistan; in sub-Saharan Africa the prevalence of HCV infection varies from 4 to 9%. Immigrants and refugees from intermediate/high HCV endemic countries to less- or non-endemic areas are more likely to have an increased risk of HCV infection due to HCV exposure

in their countries of origin. Because of the high HCV endemicity in immigrant populations and of the high efficacy of directly acting antiviral agent therapy, a campaign could be undertaken to eradicate the infection in this setting.

CONCLUSIONS:
The healthcare authorities should support screening programs for immigrants, performed with the help of cultural mediators and including educational aspects to break down the barriers limiting access to treatments, which obtain the HCV clearance in 95% of cases and frequently prevent the development of liver cirrhosis and hepatocellular carcinoma.

Transmission of **hepatitis C** virus in the dialysis setting and strategies for its prevention.
Hepatitis C virus (HCV) infection is more common among hemodialysis patients than the general population and transmission of HCV in dialysis clinics has been reported. In the context of the increased morbidity and mortality associated with HCV infection in the end stage renal disease population, it is important that dialysis clinics have processes in place for ensuring recommended infection control practices, including Standard Precautions, through regular audits and training of the staff. This review will summarize the epidemiology of HCV infection and risk factors for HCV transmission among hemodialysis patients. In addition, the proper protocols are required to investigate suspected cases of HCV transmission in dialysis facilities and recommendations for prevention of HCV transmission in will be reviewed.

HEPATOCELLULAR (LIVER) CANCER

Is there a sex difference in postoperative prognosis of hepatocellular carcinoma?
BACKGROUND:
Although men carry a higher risk of hepatocellular carcinoma (HCC) than women, it is still controversial whether men also have a poorer postoperative prognosis. A retrospective study was conducted to evaluate the postoperative prognostic predictors of HCC focusing on sex differences.

METHODS:
We enrolled 516 consecutive adult patients with HCC (118 women, 398 men), who received surgical resection between January 2000 and December 2007, and were followed-up for >10 years. Clinical and laboratory data together with postoperative outcomes were reviewed.

RESULTS:
At baseline, female patients had a higher anti-hepatitis C virus antibody prevalence (P = 0.002); lower hepatitis B virus surface antigen prevalence (P = 0.006); less microvascular invasion (P = 0.019); and lower alpha-fetoprotein (P = 0.023), bilirubin (P = 0.002), and alanine transaminase (P = 0.001) levels. Overall, there were no significant sex differences in terms of intrahepatic recurrence-free survival (RFS), distant metastasis-free survival (MFS), and overall survival (OS). However, subgroup analysis showed that women had favorable RFS (P = 0.019) and MFS (P = 0.034) in patients with alpha-fetoprotein ≤ 35 ng/mL, independent of other clinical variables (adjusted P = 0.008 and 0.043, respectively). Additionally, men had favorable OS in patients with prothrombin time (international normalized ratio [INR]) <1.1 (P = 0.033), independent of other clinical variables (adjusted P = 0.042).

CONCLUSIONS:
Female sex is independently associated with favorable postoperative RFS and MFS in patients with alpha-fetoprotein ≤35 ng/mL, while male sex is independently associated with favorable OS in patients with prothrombin time INR <1.1

Treatment Strategies for **Hepatocellular Carcinoma** ‒ a Multidisciplinary Approach.
Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver and its mortality is third among all solid tumors, behind carcinomas of the lung and the colon. Despite continuous advancements in the management of this disease, the prognosis for HCC remains inferior compared to other tumor entities. While orthotopic liver transplantation (OLT) and surgical resection are the only two curative treatment options, OLT remains the best treatment strategy as it not only removes the tumor but cures the underlying liver disease. As the applicability of OLT is nowadays limited by organ shortage, major liver resections ‒ even in patients with underlying chronic liver disease ‒ are adopted increasingly into clinical practice. Against the background of the oftentimes present chronical liver disease, locoregional therapies have also gained increasing significance. These strategies range from radiofrequency ablation and trans-arterial chemoembolization to selective internal radiation therapy and are employed in both curative and palliative intent, individually, as a bridging to transplant or in combination with liver resection. The choice of the appropriate treatment, or combination of treatments, should consider the tumor stage, the function of the remaining liver parenchyma, the future liver remnant volume and the patient's general condition. This review aims to address the topic of multimodal treatment strategies in HCC, highlighting a multidisciplinary treatment approach to further improve outcome in these patients.

Hepatocellular carcinoma recurrence after liver transplantation: Risk factors, screening and clinical presentation.
Liver transplantation is the best treatment option for cirrhotic patients with early-stage hepatocellular carcinoma, but it faces the problem of scarcity of donors and the risk of tumor recurrence, which affects between 15% and 20% of the cases, despite the use of restrictive criteria. The risk of recurrence depends on a number of factors, related to the tumor, the patient, and the treatment, which are discussed in this review. Some of these factors are already well established, such as the histopathological characteristics of the tumor, Alpha-fetoprotein (AFP) levels, and waiting time. Other factors related to the biological behavior of the tumor and treatment should be recognized because they can be used in the refinement of the selection criteria of transplant candidates and in an attempt to reduce recurrence. This review also discusses the clinical presentation of recurrence and its prognosis, contributing to the identification of a subgroup of patients who may have better survival, if they are timely identified and treated. Development of recurrence after the first year, with AFP levels ≤ 100 ng/mL, and single site capable of locoregional therapy are associated with better survival after recurrence.

Molecular Mechanisms Driving Progression of Liver Cirrhosis towards **Hepatocellular Carcinoma**in Chronic Hepatitis B and C Infections: A Review.
Almost all patients with hepatocellular carcinoma (HCC), a major type of primary liver cancer, also have liver cirrhosis, the severity of which hampers effective treatment for HCC despite recent progress in the efficacy of anticancer drugs for advanced stages of HCC. Here, we review recent knowledge concerning the molecular mechanisms of liver cirrhosis and its progression to

HCC from genetic and epigenomic points of view. Because ~70% of patients with HCC have hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection, we focused on HBV- and HCV-associated HCC. The literature suggests that genetic and epigenetic factors, such as microRNAs, play a role in liver cirrhosis and its progression to HCC, and that HBV- and HCV-encoded proteins appear to be involved in hepatocarcinogenesis. Further studies are needed to elucidate the mechanisms, including immune checkpoints and molecular targets of kinase inhibitors, associated with liver cirrhosis and its progression to HCC.

The 100 most influential manuscripts on **hepatocellular carcinoma**: a bibliometric analysis.

OBJECTIVE:

Citation analysis represents one of the best available methods to identify the most influential articles. This study aimed to identify and characterize the top 100 highly cited articles (T100) that focus on hepatocellular carcinoma and to reveal the trends in accomplishments within this field.

METHODS:

A search of the Thomson Reuters Web of Science citation indexing database was conducted using terms related to hepatocellular carcinoma. The T100 were selected and analyzed further based on the number of citations, authorship, year of publication, journal, country of origin, institution, and article type.

RESULTS:

Hepatology published the highest number of papers (n = 15), and the United States produced the highest number of contributions (n = 31). Barcelona University was the institution with the highest number of articles in the T100 (n = 9). The T100 articles included 35 observational studies, 13 randomized control studies, 25 basic research articles, 18 reviews, seven clinical guidelines, and two meta-analyses.

CONCLUSIONS:

This is the first bibliometric study to identify the most influential papers in hepatocellular carcinoma research. This report presents major advances and changes in research regarding hepatocellular carcinoma and can serve as a guide for writing a citable article.

Hepatocellular carcinoma surveillance in the 21st century: Saving lives or causing harm?

Hepatocellular carcinoma (HCC) is the third most common cause of cancer related death worldwide. Prognosis and treatment options largely depend on tumor stage at diagnosis, with curative treatments only available if detected at an early stage. However, two thirds of patients with HCC are diagnosed at a late stage and not eligible for cure. Therefore several liver professional societies recommend HCC surveillance using abdominal ultrasound with or without alpha fetoprotein in at-risk populations, including patients with cirrhosis and subsets of those with chronic hepatitis B. Available data suggest HCC surveillance can significantly improve early tumor detection, curative treatment eligibility, and overall survival. However, the potential

benefits of HCC surveillance must be considered in light a shifting HCC demographic from a viral-mediated cancer to an increasing proportion of patients having non-alcoholic steatohepatitis, which has been shown to limit ultrasound sensitivity and may mitigate observed benefits. Further, benefits of HCC surveillance must be weighed against potential physical, financial and psychological harms. Continued data for both benefits and harms of HCC surveillance in contemporary populations are necessary. In the interim, providers should continue to strive for high quality HCC surveillance in at-risk patients.

Efficacy and safety of external-beam radiation therapy for **hepatocellular carcinoma**: An overview of current evidence according to the different target population.

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors. During the recent years, external-beam radiation therapy (EBRT) has been safely and effectively employed for the management of HCC. We overviewed the current evidence regarding the efficacy and safety of EBRT for HCC according to the different target population. PubMed database was searched for identifying English-language full-text articles regarding EBRT for the treatment of HCC. Search items were "hepatocellular carcinoma AND radiation therapy". Until now, preliminary evidence has suggested the following role of EBRT for HCC. 1) EBRT, especially stereotactic body radiation therapy, is an emerging choice of therapy for small HCC. 2) EBRT combined with non-surgical treatment can achieve an excellent intrahepatic tumor control and a potential survival benefit for huge HCC. 3)Adjunctive EBRT may improve the efficacy of transarterial chemoembolization for HCC with portal vein tumor thrombosis. 4) EBRT can relieve the pain and improve the quality of life for patients with extrahepatic metastases. 5) EBRT may be a bridge to liver transplantation by minimizing the tumor progression. 6) Adjunctive EBRT may reduce the tumor recurrence and improve the survival after resection. In summary, EBRT is a promising choice of treatment of HCC. However, more high-quality evidence is needed to further establish the status of EBRT for the management of HCC.

Role of SIRT-3, p-mTOR and HIF-1α in **Hepatocellular Carcinoma** Patients Affected by Metabolic Dysfunctions and in Chronic Treatment with Metformin.

Abstract

The incidence of hepatocellular carcinoma deriving from metabolic dysfunctions has increased in the last years. Sirtuin- (SIRT-3), phospho-mammalian target of rapamycin (p-mTOR) and hypoxia-inducible factor- (HIF-1α) are involved in metabolism and cancer. However, their role in hepatocellular carcinoma (HCC) metabolism, drug resistance and progression remains unclear. This study aimed to better clarify the biological and clinical function of these markers in HCC patients, in relation to the presence of metabolic alterations, metformin therapy and clinical outcome. A total of 70 HCC patients were enrolled: 48 and 22 of whom were in early stage and advanced stage, respectively. The expression levels of the three markers were assessed by immunohistochemistry and summarized using descriptive statistics. SIRT-3 expression was higher in diabetic than non-diabetic patients, and in metformin-treated than insulin-treated patients. Interestingly, p-mTOR was higher in patients with metabolic syndrome than those with different etiology, and, similar to SIRT-3, in metformin-treated than insulin-treated patients. Moreover, our results describe a slight, albeit not significant, benefit of high SIRT-3 and a

significant benefit of high nuclear HIF-1α expression in early-stage patients, whereas high levels of p-mTOR correlated with worse prognosis in advanced-stage patients. Our study highlighted the involvement of SIRT-3 and p-mTOR in metabolic dysfunctions that occur in HCC patients, and suggested SIRT-3 and HIF-1α as predictors of prognosis in early-stage HCC patients, and p-mTOR as target for the treatment of advanced-stage HCC.