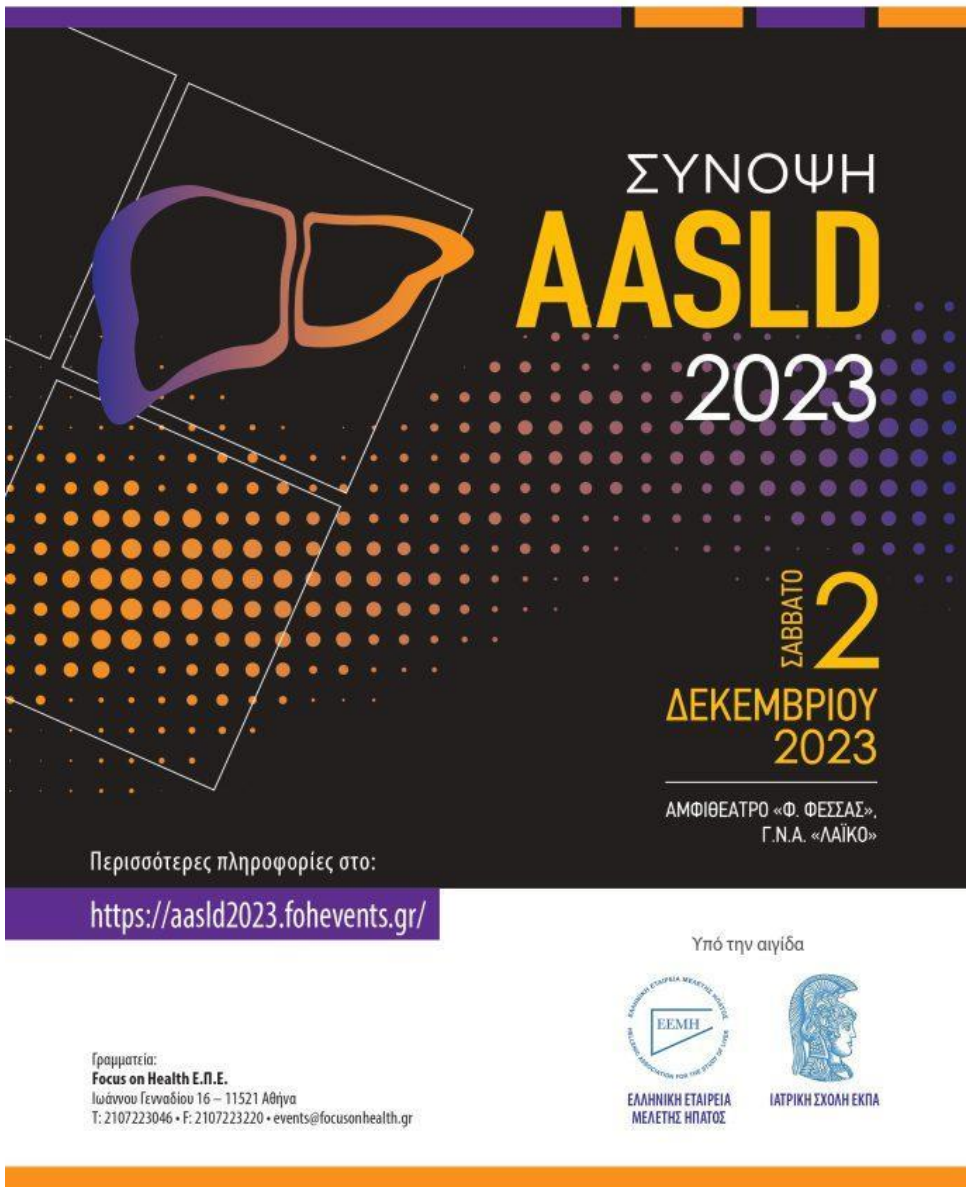


Ηπατίτιδα C

κι άλλες…

Χαρά Κρανιδιώτη
Παθολόγος – Ηπατολόγος, Επιμελήτρια Α’ ΕΣΥ
Β’ Πανεπιστημιακή Παθολογική Κλινική
ΓΝΑ Ιπποκράτειο

Εισαγωγή

Ηπατίτιδα C

- Abstracts: 120
  - Plenary 1
  - Late Breaking 2
  - Oral 7

Others ….

- Absracts: 10
  - Hapatitis A (2)
  - Hepatitis E (3)
  - Acute unknown hepatitis in children (1)
  - Tuberculosis (2)
  - HSV-2 (1)
  - Dengue (1)

Επιδημιολογικά δεδομένα ηπατίτιδας C

8 εργασίες

Total HCV patients treated with direct acting antivirals since 2014

Alexis Voeller, Devin Razavi-Shearer, Ivane Gamkrelidze, Kathryn Razavi-Shearer, Sarah Blach, Homie Razavi

Center for Disease Analysis Foundation, Lafayette, CO, United States

CDA FOUNDATION POLARIS OBSERVATORY

Aim: cumulative HCV treatment in 2014-2022

Methods:

- Prior to 2019, average SVR rate with DAAs in each country
- National registration data

Data was also collected from experts in over 100 countries through Polaris Observatory annual surveys

Results:

2014-2022, 13.2 million HCV patients have been treated, globally with DAAs.

SOF-based 82%

Most HCV treatments took place in lower-middle income countries.

- **The peak percentage of SOF-based regimens in 2019 →Egyptian elimination program**.
- There has been an increase in other DAAs starting in 2019.
- In 2019 there were 1.6 million patients cumulatively treated with other DAAs compared to 2.4 million cumulative patients in 2022.

Conclusions:

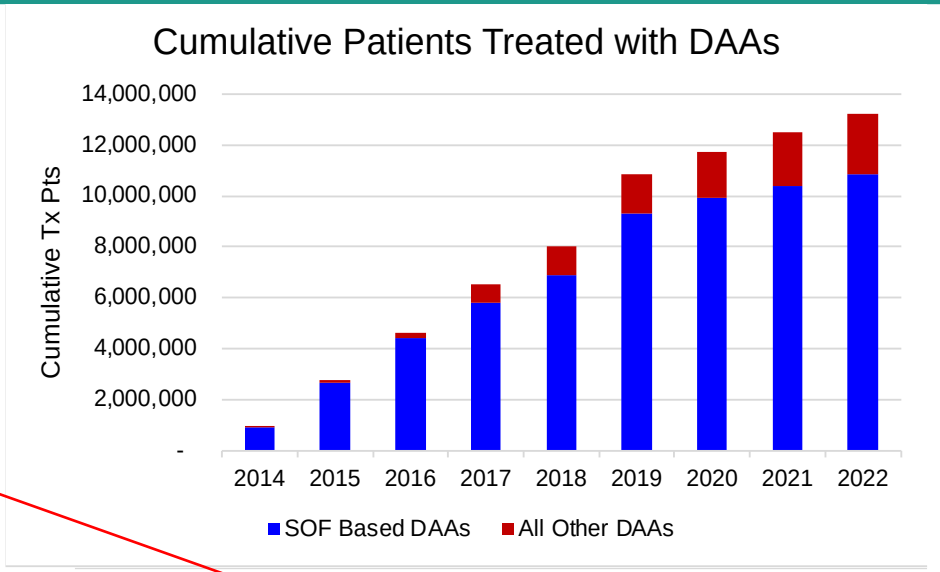
LMIC ↑impact on the total number of HCV patients treated globally.

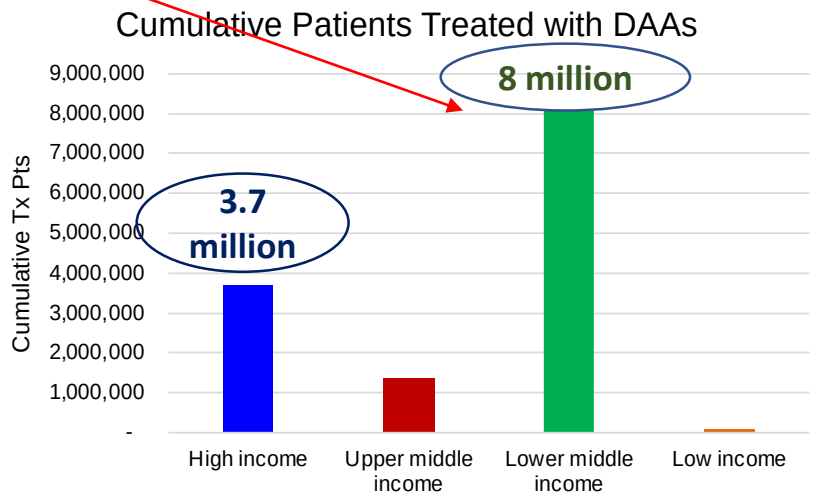
- Generic sofosbuvir + daclatasvir is the dominant DAA treatment.

With 89% → immediate access to generic versions

High income-countries → removing all treatment restrictions

To achieve the global elimination of HCV → continued expansion of generic access to medications and removal of fibrosis restrictions in LMIC





VIRAL ELIMINATION:
ONE COUNTRY IS WORTH A THOUSAND SPEECHES

World Health Organization

In accordance with normative standards established by WHO
and the recommendation of the Viral Hepatitis Subgroup of the Global Validation Advisory Committee

The World Health Organization

certifies the achievement of the Gold Tier on the
Path to Elimination of Hepatitis C Virus
as a Public Health Problem

Arab Republic of Egypt

Dr Tedros Adhanom Ghebreyesus
WHO Director General
October 2023

The Telegraph

'Nothing short of astounding': How Egypt defied the odds to eliminate hepatitis C

Within a decade, the country has gone from having among the worst global rates of the disease to near eradication

By Charlotte Lytton
8 November 2023 · 8:00am

Poster #: 5030-C

Estimating Prevalence of Hepatitis C Virus Infection in the United States, 2017–2020

Late-Breaking abstract

Eric W. Hall[1], Heather Bradley[2], Neil Gupta[3], Laurie K. Barker[3], Karon Lewis[3], Jalissa Shealey[2], Eduardo Valverde[4], Patrick Sullivan[2], Megan G. Hofmeister[3]

[1]School of Public Health, Oregon Health & Science University, Portland, Oregon
[2]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia
[3]Division of Viral Hepatitis, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia
[4]Office of the Director, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia

- **Background: 2013-2016 data: 2.4 million people → HCV RNA positive in US**
- **AIM:** HCV prevalence 2017-2020
- **Methods: prevalence models**
  1. NHANES + literature for estimating non-NHANES population *[National Health and Nutrition Examination Survey (NHANES)]*
  2. Above + accounting for under representation of PWID in NHANES
- **Results:**
  1. **Model 1:** estimated 2.4 million HCV RNA+ (95% CI 1.32-3.63 million)
  2. **Model 2:** estimated 4 million HCV RNA+ (95% CI 2.4-5.61 million)

			HCV RNA (current HCV infection)					
Model	**Years**	**N**	**n**	**Lower**	**Upper**	**%**	**Lower**	**Upper**
Hofmeister et al. 2019	2013-2016	244,869,800	2,386,100	1,983,900	2,807,800	1.0	0.8	1.1
NHANES+ Model	2017-2020	254,207,200	2,463,700	1,321,700	3,629,400	0.97	0.52	1.43
PWID Adjustment Model	2017-2020	254,207,200	4,043,200	2,401,800	5,607,100	1.59	0.94	2.21

- **Conclusions**

Despite years of effective cure, estimate prevalence of HCV in 2017-2020 remains unchanged from2013-2016 when using comparable methodology. It is substantially higher when accounting for increased PWID in the US.

Differences in baseline characteristics of direct acting antiviral (DAA)-treated Greek HCV patients according to source of infection

S. SIAKAVELLAS , H. KRANIDIOTI , A. KOURIKOU , C. KARAGEORGOS , A. GOULAS , S. VASILEIADI , G. KONTOS , N. PAPADOPOULOS [1], M. DEUTSCH and S. MANOLAKOPOULOS

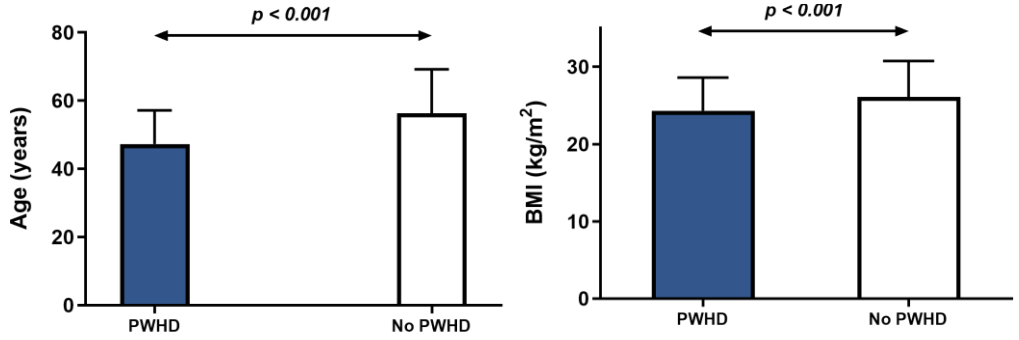
1.Hepatogastroenterology Unit, 2nd Academic Department of Internal Medicine, National and Kapodistrian University of Athens Medical School, HIppocration General Hospital, Athens, Greece

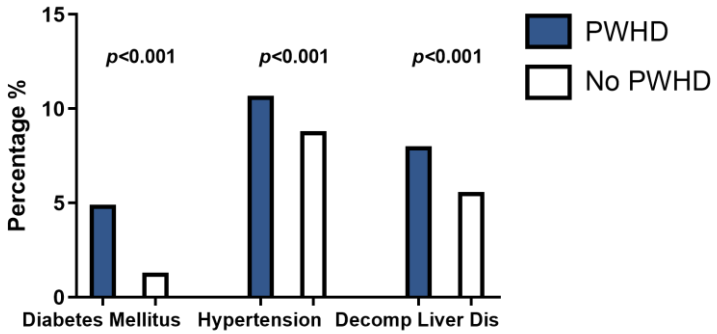
The aim of this study was to identify potential differences in the makeup of the PWHD and non-PWHD HCV patient subgroups.
Patients: The HERACLIS cohort, is the largest national HCV registry of patients treated with DAAs in tertiary liver centers from 2015 until 2022.

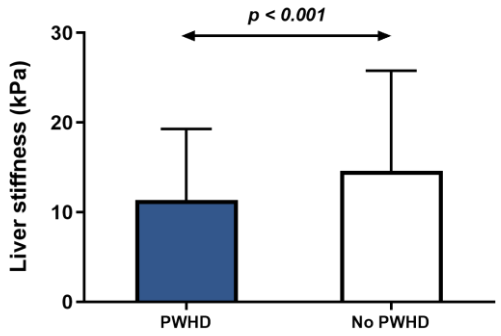
Results: 680 patients were included in the study, men: **70.9%,** median age 50.8 years old, **62% (n=422) PWHD**
13.6% decompensated liver disease at DAA initiation.

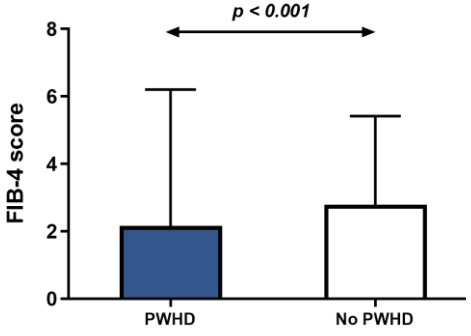
Conclusions

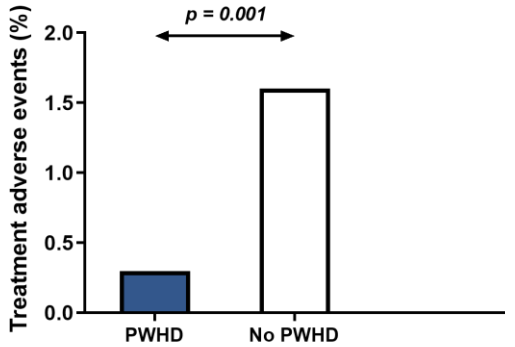
The main differences observed between PWHD and non-PWHD populations of HCV patients imply a concomitant presence of an element of metabolic syndrome in the non-PWHD cohort with a subsequent potential effect on the degree of underlying liver fibrosis











Πρόσβαση στη θεραπεία
(Models of care delivery – Elimination)

41 εργασίες

Early Read-Time Performance of the OraQuick® HCV Rapid Antibody Assay for the Exclusion of HCV Viremia

Jessie Torgersen[1,2], Rebecca Russell[2], Julia Gasior[1], Dena M. Carbonari[1], Nancy Aitcheson[1,2], David Smookler[3,4], Camelia Capraru[3,4], Bettina Hansen[3,4], Jordan J. Feld[3,4], Vincent Lo Re III[1,2]

1. University of Pennsylvania Perelman School of Medicine, PA, USA; 2. University of Pennsylvania Health System, PA, USA; 3. Viral Hepatitis Care Network, ON, Canada; 4. Toronto General Hospital Research Institute, ON, Canada

Background:

- Rapid POC tests for HCV allow for testing and linkage for difficult-to-reach populations
- OraQuick® rapid HCV antibody lateral flow immunoassay (OQ) detects HCV antibodies with results finalized after 20 min.
- Prior work found that OQ-positivity after >5 min identified people without HCV viremia; these observations have not been externally validated.

Objective: To evaluate the performance of OQ early reading time for the exclusion of HCV viremia among patients with reactive HCV antibody

Methods:

- Single-center study June 2021-August 2023
- Adults with HCV Ab positive were enrolled
- Presence of both control and test bands were evaluated at every minute between 5-10 minutes, then at 20 and 40 minutes
- Early reading time of OQ assay was evaluated against standard-of-care reflex HCV RNA test
- Proportion of positive OQ was compared by HCV viremic status

AASLD Nov. 10-14, 2023

OraQuick® Rapid Antibody Test HCV

Results

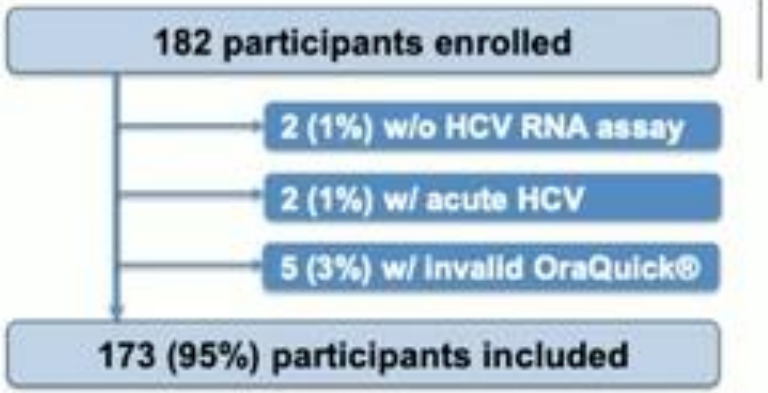


Figure 1: Participants Included in Analysis

- 97% with HCV viremia had positive OQ by 5 minutes; 99% by 7 minutes
- 41% and 49% without HCV viremia had positive OQ by 5 and 7 min

Table 2: Performance of OraQuick® Rapid HCV Antibody Assay for Identification of Chronic HCV Viremia at Different Incubation Times

Time of reading	Positive OraQuick®		Negative OraQuick®		Sensitivity (95% CI)	Specificity (95% CI)
	HCV viremia	No HCV viremia	HCV viremia	No HCV viremia		
5 min	118	21	4	30	96.7% (91.8-99.1%)	58.8% (44.2-72.4%)
6 min	119	23	3	28	97.5%	54.9%
7 min	121	25	1	26	99.2% (99.5-100%)	51.0% (38.6-65.2%)
8 min	121	26	1	25	99.2% (95.5-100%)	49.0% (34.8-63.4%)
9 min	121	27	1	24	99.2% (95.5-100%)	47.1% (32.9-61.5%)
10 min	121	30	1	21	99.2% (95.5-100%)	41.2% (27.6-55.8%)
20 min	122	38	0	13	100% (97.0-100%)	25.5% (14.3-39.6%)
40 min	122	38	0	13	100% (97.0-100%)	25.5% (14.3-39.6%)

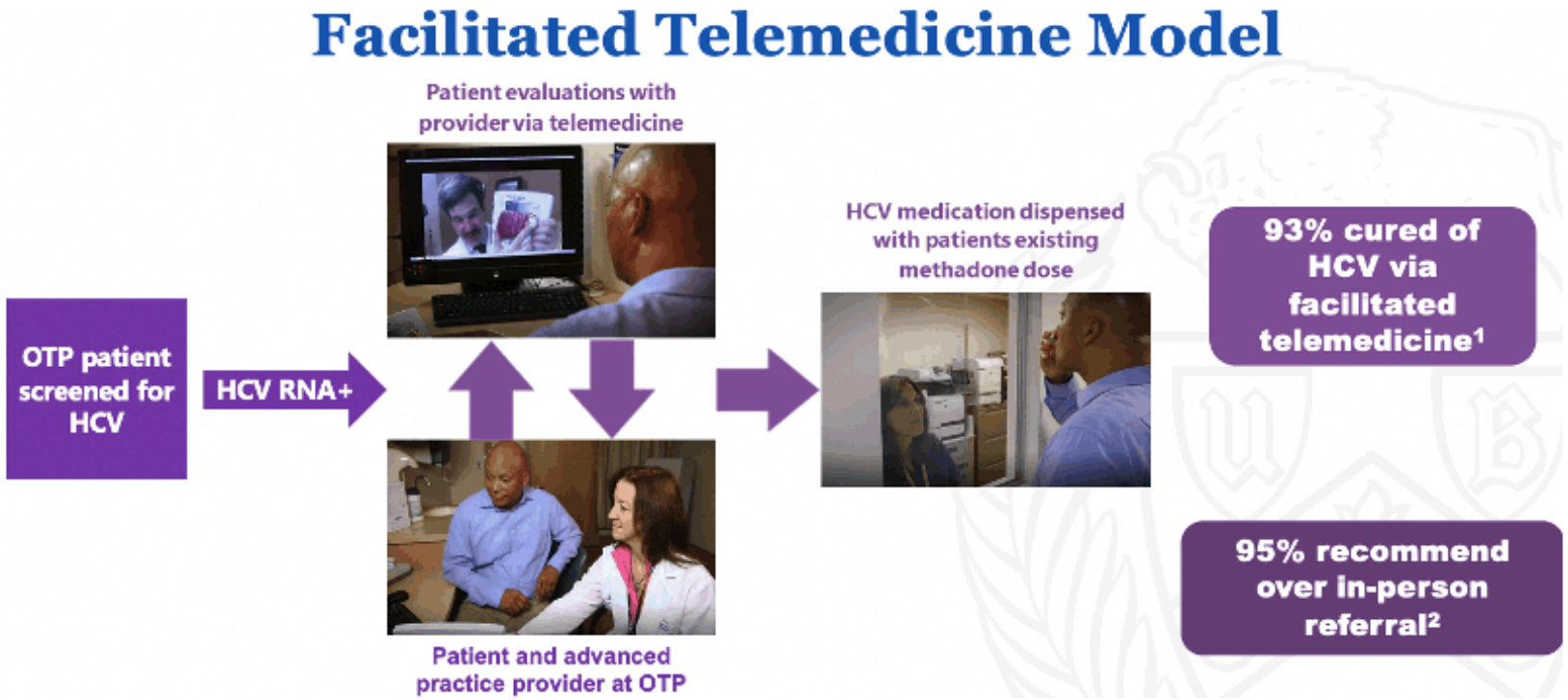
Abbreviations: CI: confidence interval; HCV: hepatitis C virus

Conclusions: Negative OQ by 7 min reliably excludes HCV viremia

- **May reduce need for RNA testing and improve throughput,** where HCV RNA assay may be costly or challenging
- Early read-time results (by 7 minutes) cannot be used to exclusively identify HCV viremia

53: HEALTHCARE ACCESS THROUGH FACILITATED TELEMEDICINE FOR UNDERSERVED POPULATIONS: A STEPPED WEDGE CLUSTER RANDOMIZED CONTROLLED TRIAL OF HEPATITIS C VIRUS TREATMENT AMONG PERSONS WITH OPIOID USE DISORDER

Background: Telemedicine removes geographic and temporal obstacles to healthcare access.
SVR12 rates for HCV infection among persons with opioid use disorder through facilitated telemedicine (FTM) versus offsite liver specialist referral (usual care or UC).
Methods: prospective, cluster randomized trial utilizing the stepped wedge design to compare SVR12 rates between FTM onsite in opioid treatment programs (OTPs) to UC.

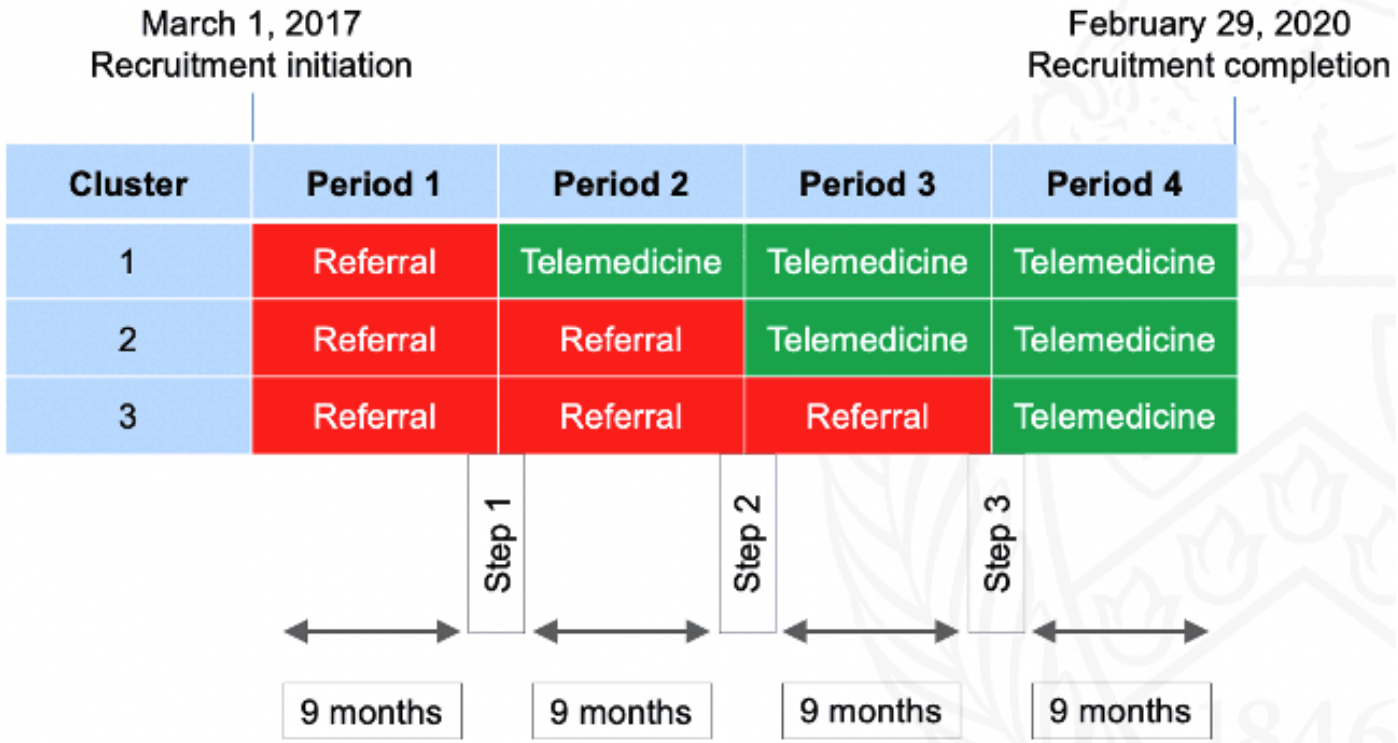


METHODS: Between 3/1/17 and 2/29/20, **602 participants at 12 OTPs throughout New York State** were enrolled. All OTPs began with **UC and every 9 months, 4 sites, randomly selected, transited from UC to FTM during 3 steps. Follow-up for two years to assess for reinfection.**

Multiple imputation was used to handle missing data (5.8% missingness).

To estimate the intervention effect: non-parametric, within-period, cluster-level method. To assess for heterogeneity of treatment effects: generalized linear mixed effects models.

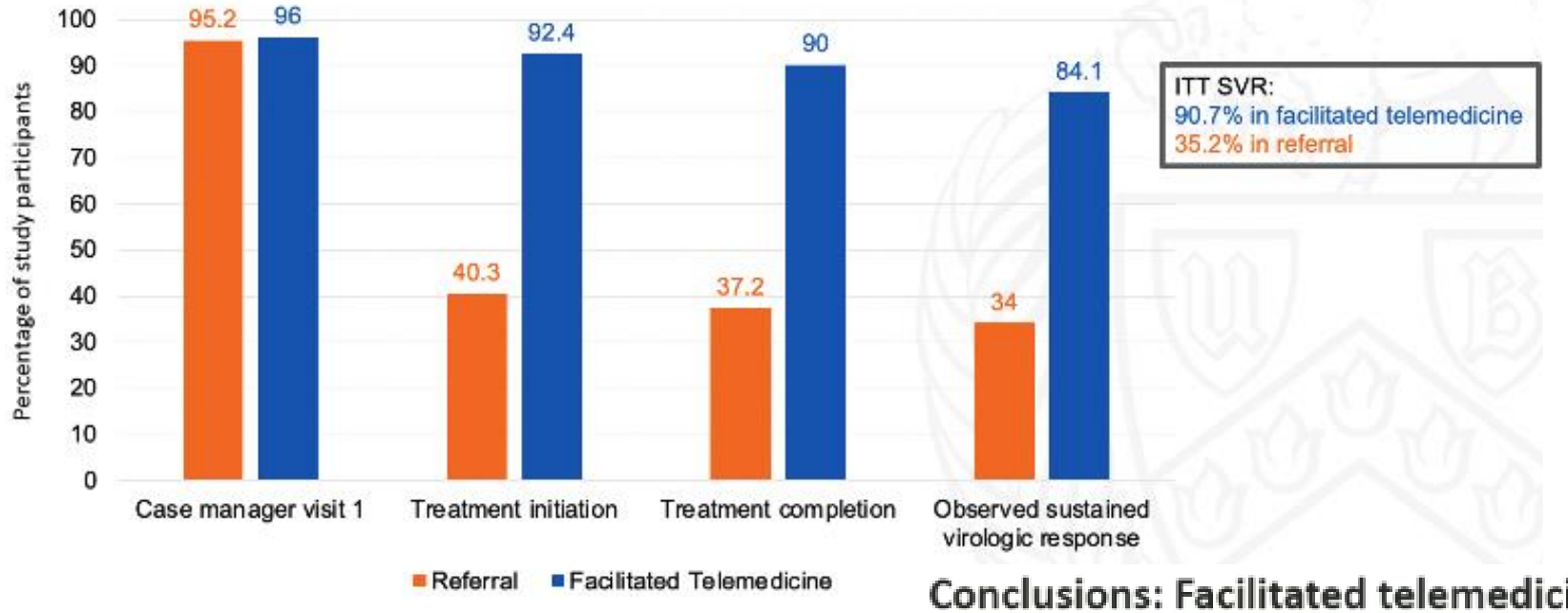
Study Design



Results: 602 participants (FTM [n=290] and UC [n=312]) with mean age of 48.1 ± 13.0 years, 61.3% male.

- In FTM, 268/290 (92.4%) participants initiated treatment vs 126/312 (40.4%) UC participants.
- The overall SVR12 was 90.7% in FTM compared to 35.2% in referral.
- Drug use decreased significantly (p=<.0001) among cured participants, regardless of intervention arm.
- HCV reinfection incidence of 2.42 per 100 person-years of observation.
- Participants reported very high healthcare delivery satisfaction, equivalent between arms.

HCV Care Cascade: SVR results



Conclusions: Facilitated telemedicine can increase access to HCV cure in underserved populations.

Θεραπεία

23 εργασίες

Ongoing experience of implementing "The Toronto Protocol": An ultra-short course of glecapriver/pibrentasavir + ezetimibe for solid organ transplant from HCV+ donors to HCV-uninfected recipients

Wesam Aleyadeh, Marcelo Cypel, Rhonda Allan, June Wang, Dipika Munyal, Atul Humar, Jordan J. Feld

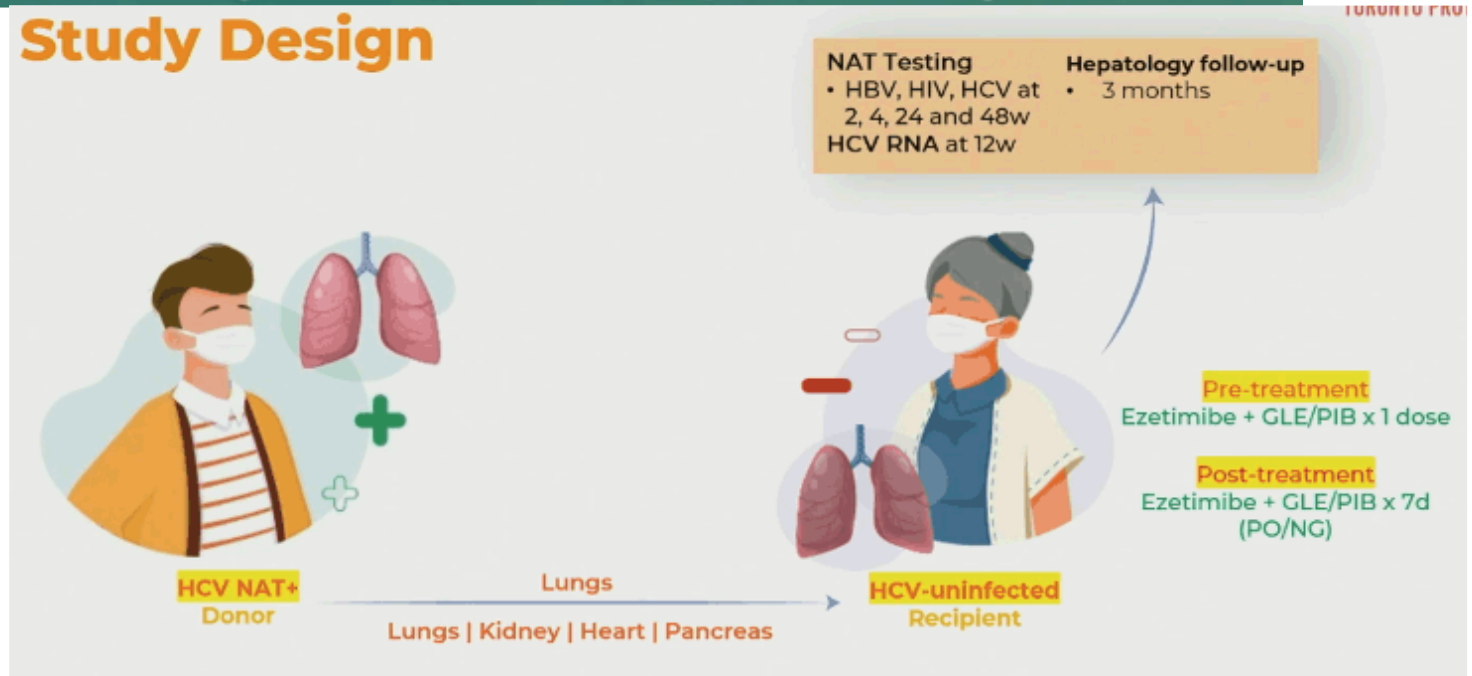
Toronto Centre for Liver Disease & Multi-Organ Transplant Centre, Toronto General Hospital, University Health Network, University of Toronto

Oral presentation

Background: overdose crisis →increase in transplantation of organs from HCV-infected donors (D+) to uninfected recipients (R-).

Ultra-short course of glecaprevir/pibrentasvir (G/P) combined with ezetimibe (E) prevented chronic infection in non-liver solid organ recipients.

2 cohorts: extended follow-up for patients in the **original study (n=30), plus** outcomes since adoption of the Toronto Protocol as standard of care (SOC) (n=58).



The primary endpoint was establishment of chronic HCV infection, defined as positive HCV RNA 12 weeks post-transplant or need for retreatment**. Additional outcomes include graft rejection and patient survival.**

Results

	Initial Trial (n=30)	Standard of care (n=58)
Mean age (range)	61 (27-76)	57 (22-80)
Sex		
Male	23 (77%)	34 (59%)
Female	7 (23%)	24 (41%)
Transplanted organ		
Lung	13 (43%)	14 (24%)
Kidney	10 (33%)	32 (55%)
Heart	6 (20%)	6 (10%)
Kidney/Pancreas	1 (3%)	3 (5%)
Pancreas	0	3 (5%)

Undetectable HCV RNA at 12 weeks		
	30 (100%)	58 (100%)
Episodes of rejection requiring treatment		
	3 (10%)	9 (16%)
Graft survival* at 6-months		
	28 (93%)	57 (98%)
Patient survival at 6-months		
	28 (93%)	57 (98%)
AEs related to treatment		
	1 (3%)	1 (3%)
HCV-related complications		
	0 (0%)	0 (0%)

*Graft loss was only reported in the event of patient death

Conclusion: An ultra-short regimen of G/P+E prevented chronic HCV infection in all D+/R- transplant recipients and was well tolerated, allowing the majority to complete treatment before hospital discharge.

These results support the current AASLD/IDSA guidance recommendation to initiate treatment promptly after transplantation.

Pregnancy

2 εργασίες

CHARACTERIZING LINKAGE TO HEPATITIS C VIRUS CARE DURING AND FOLLOWING PREGNANCY: IDENTIFYING MISSED OPPORTUNITIES FOR TESTING AND TREATMENT

Presenting Author: Andrew B Mendlowitz* [ORAL PRESENTATION]
Author: Jennifer A. Flemming, Tatyana Kushner, William W. L. Wong, Zoe R Greenwald, Jeff Kwong, Camelia Capraru, Jordan J. Feld, Mia Biondi

Background: Pregnancy is an opportune time for HCV screening and linkage to care.

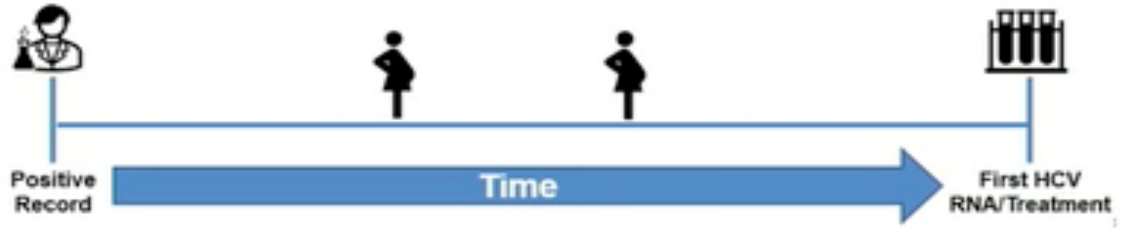
Aim: Characterize linkage to HCV care during and following pregnancy

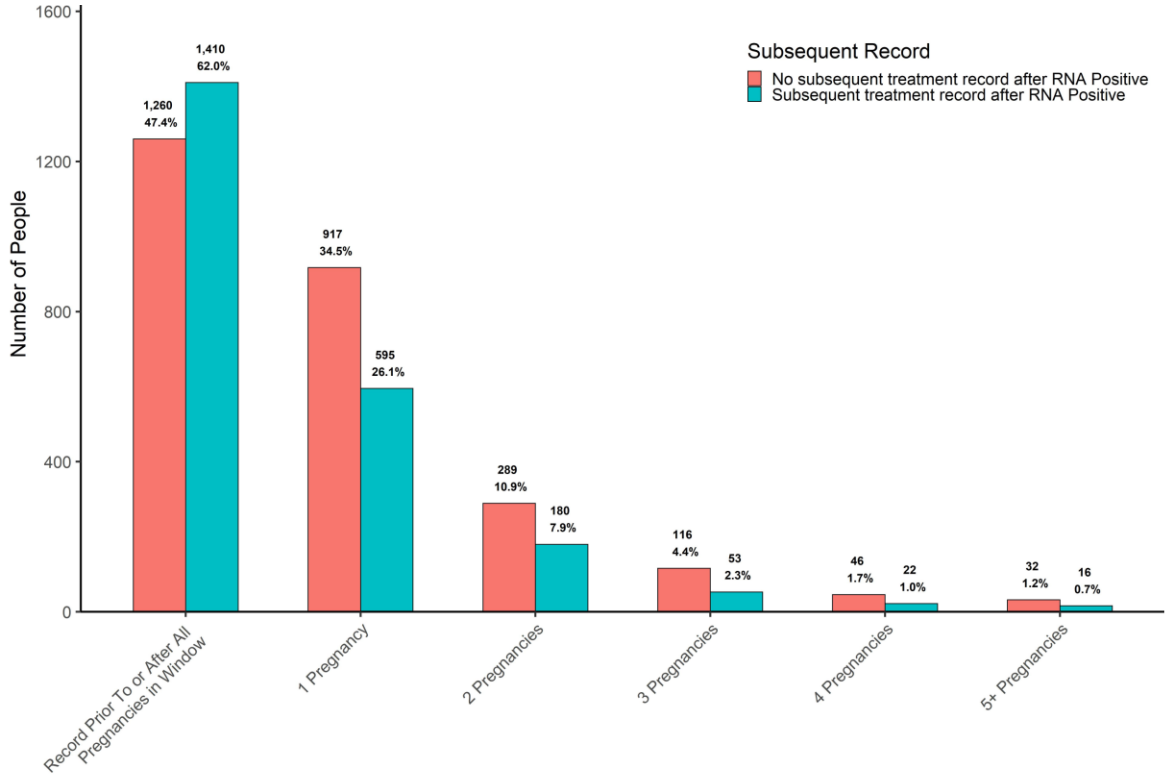
Methods: Retrospective cohort study using health administrative data and HCV testing records in Ontario, Canada 1999-2021

Results: 27,032 HCV Ab+ and 7,669 HCV RNA+

- 47% of HCV Ab+ did not have HCV RNA testing
- 44% of HCV RNA+ were never treated
- Multiple "missed opportunities" for diagnosis and treatment

Conclusions: There are major drop-offs in the HCV care cascade during pregnancy leading to missed opportunities to prevent transmission.





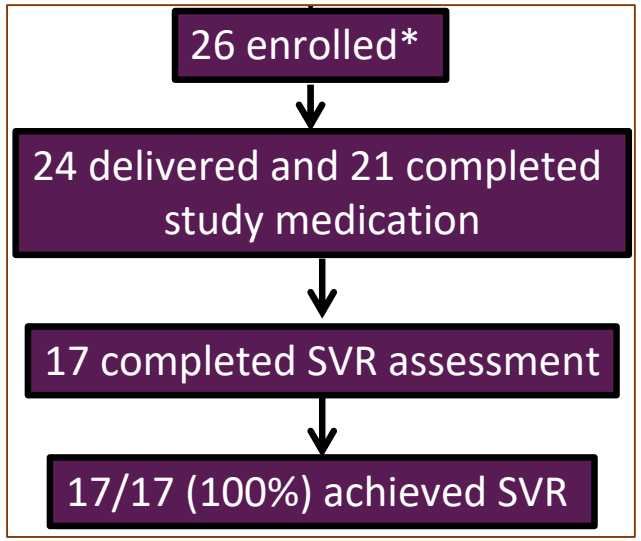
Safety, Tolerability, and Outcomes of Sofosbuvir/Velpatasvir in Treatment of Chronic Hepatitis C Virus during Pregnancy: interim results from the STORC study

Late-Breaking abstract

Catherine Chappell, MD[1]; Jasmin Charles, PA-C[2]; Marcela Smid, MD[2]; Kara Rood, MD[3]; John Cafardi, MD[4]; Tatyana Kushner, MD[5]; Mia Biondi, PhD, NP-PHC[6]; Jordan Feld, MD[6]; Mark Yudin, MD[7]; Genevieve Eastabrook, MD[8]; Cathleen Letterio, MSN[9]; Kyung min Kwon, MD[9]; Bruce Kreter, PharmD[9]; Sharon Hillier, PhD[1]

[1]University of Pittsburgh, [2]University of Utah, [3]Ohio State University, [4]The Christ Hospital, [5]Mount Sinai, [6]University Health Network, [7]University of Toronto, [8]London Health Science Centre, [9]Gilead Sciences

- Aim, is to present interim data from the STORC study, an international, multi-center study evaluating the safety and efficacy of sofosbuvir/velpatasvir (SOF/VEL) for HCV treatment in pregnancy.
- **Methods:** In this phase 4, open-label, single-arm study, pregnant individuals with HCV infection are enrolled (Jul 2022-Sep 2023) between 20+0- and 30+0-weeks of gestation and treated with a 12-week course of SOF/VEL. HCV RNA testing is performed at screening, enrollment, 4, 8 and 12 weeks after SOF/VEL initiation, at delivery and 12 weeks after SOF/VEL completion (SVR12). The primary endpoints are SVR12 and preterm birth (defined as < 37 weeks gestation). Infants are followed for one year with HCV RNA testing.



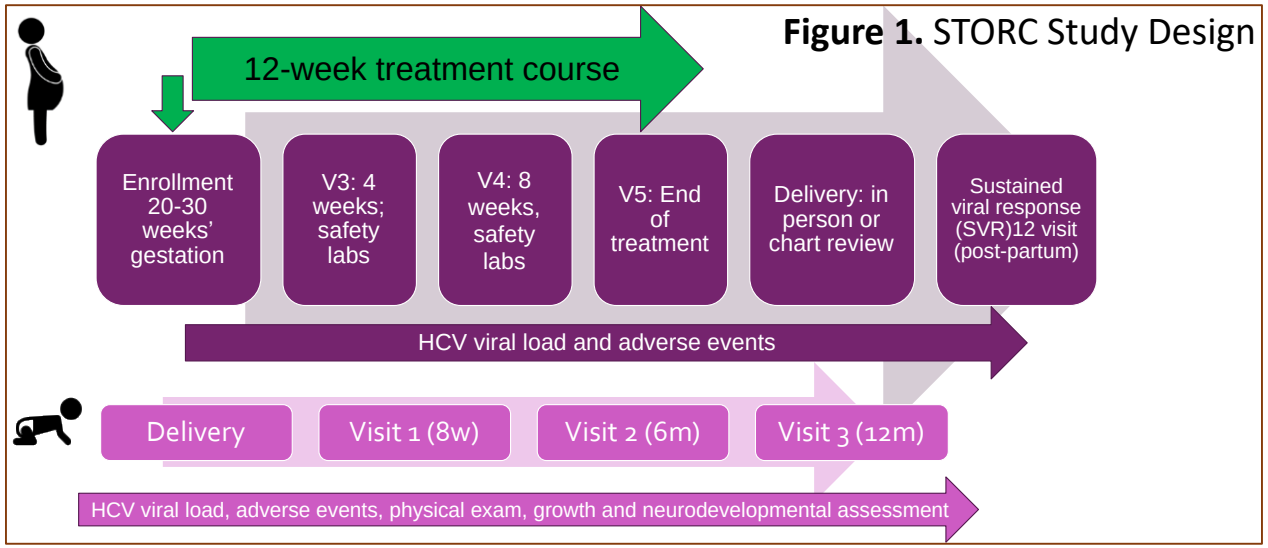


Figure 1. STORC Study Design

Safety, Tolerability, and Outcomes of Sofosbuvir/Velpatasvir in Treatment of Chronic Hepatitis C Virus during Pregnancy: interim results from the STORC study

Catherine Chappell, MD[1]; Jasmin Charles, PA-C[2]; Marcela Smid, MD[2]; Kara Rood, MD[3]; John Cafardi, MD[4]; Tatyana Kushner, MD[5]; Mia Biondi, PhD, NP-PHC[6]; Jordan Feld, MD[6]; Mark Yudin, MD[7]; Genevieve Eastabrook, MD[8]; Cathleen Letterio, MSN[9]; Kyung min Kwon, MD[9]; Bruce Kreter, PharmD[9]; Sharon Hillier, PhD[1]

[1]University of Pittsburgh, [2]University of Utah, [3]Ohio State University, [4]The Christ Hospital, [5]Mount Sinai, [6]University Health Network, [7]University of Toronto, [8]London Health Science Centre,[9]Gilead Sciences

Results

Delivery and Safety Outcomes

Among participants who have delivered (n=24), 3 (12.5%) had a preterm birth. Median gestational age for all births was 38+0 weeks' (range 33+5, 41+1).

Detailed information on the preterm births:

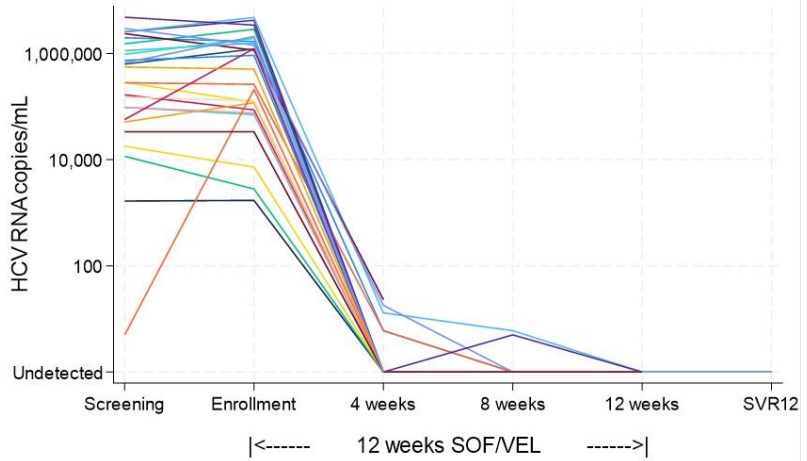
1. 36+4 weeks' preterm premature rupture of membranes
2. 33+4 weeks' spontaneous preterm labor
3. 36+2 weeks' preterm premature rupture of membranes

There have been 177 adverse events reported (117 maternal and 60 infant). 22 were related to SOF/VEL (all maternal and **Grade 3** including: nausea/vomiting (8), fatigue (5), headache (3), gastric reflux (2), numbness in fingers (1), arthralgias (1), insomnia (1), diarrhea (1).

There have been 13 serious adverse events (SAEs) reported. **None were deemed related to SOF/VEL.** 4 maternal SAEs including: COVID (1), pre-eclampsia with severe features (1), opioid withdrawal (2). 7 infant SAEs including: transient tachypnea of newborn (1), hyperbilirubinemia (1), preterm birth (1), neonatal opioid withdrawal syndrome (1), hypoxia (1), hypoglycemia (1), chronic constipation (1), and Hirschsprung Disease (1).

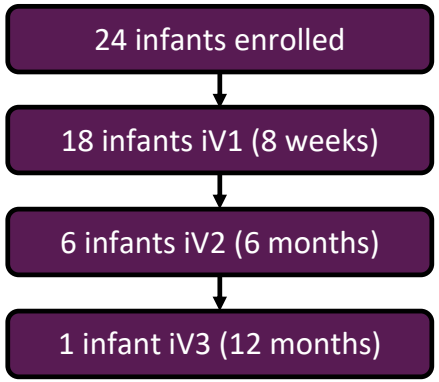
None of the participants have discontinued the study medication.

Figure 3. HCV viral response to SOF/VEL during pregnancy



15 participants had HCV RNAs assessed at delivery and all (100%) were undetectable.

Figure 4. Infant Participant Flow



100% of infants tested are HCV RNA undetectable (N=16)

1 infant did not get blood sampling, 1 had an insufficient sample

Παρακολούθηση μετά το SVR

17 εργασίες

Incidence and associations of HCV reinfection in the era of direct acting antivirals. The RECARE study

S. VASILEIADI , O. ANAGNOSTOU , M. MANOLAKOPOULOU , K. KOUSTENIS , C. KARAGEORGOS , A. GOULAS , C. KRANIDIOTI , S. SIAKAVELLAS , E. HADZIYANNIS , M. DEUTSCH , and S. MANOLAKOPOULOS

Hepatogastroenterology Unit, 2nd Academic Department of Internal Medicine, National and Kapodistrian University of Athens Medical School. Hippocration General Hospital of Athens, Athens, Greece

AIM: HCV Reinfection rate after successful HCV therapy with DAAs in PWUD and associated factors

METHODS: PWUD treated with SVR 2014-2021
All patients were contacted at least one year after the end of treatment via phone call for follow-up.
Detectable HCV RNA after achieving SVR was defined as reinfection.
199 patients were called twice; 85 of them responded

Results: 11 HCV reinfections were identified during 452.2 PY of follow-up, **reinfection rate 2.6/100 PY.**
Reinfection rate was associated with **age**, long total **history of IV drugs**, **HIV**, **cannabis** consumption, **high risk behavior**, **incarceration**

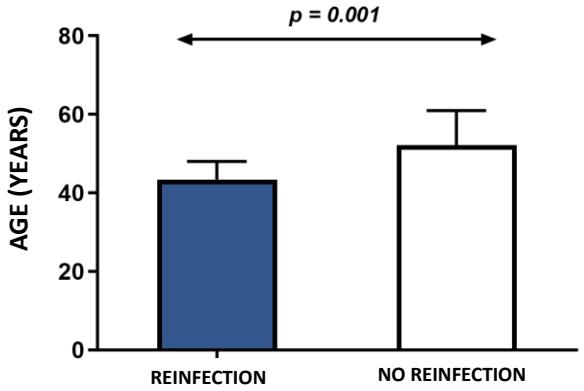


Figure 1: Correlation of reinfection with age

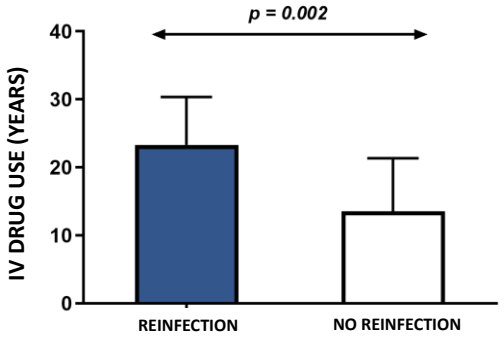


Figure 2: Correlation of reinfection with chronic IV drug use

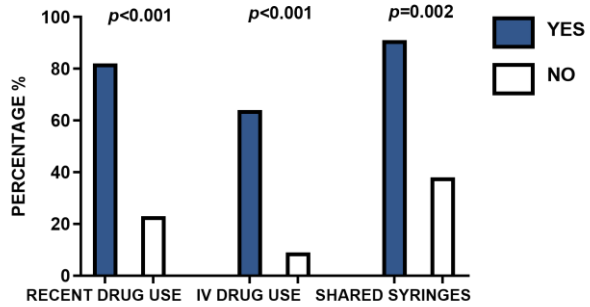


Figure 3: Percentage of reinfection in association with high-risk behaviors.

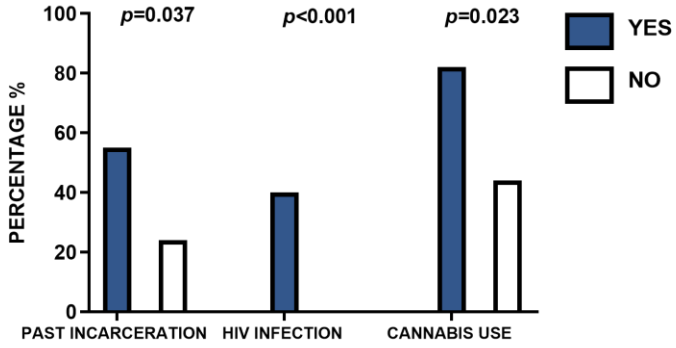


Figure 4: Percentage of reinfection in association with patients' history.

Table 3. Multivariate analysis	
	P-value
Age	0.010
Total history of intravenous drug use	0.021
History of incarceration	0.023
Drug use within last 12 months	0.054
HIV coinfection	0.001

Long-term risk of liver-related and non-liver-related death after direct-acting antiviral-mediated sustained virologic response in hepatitis C virus patients

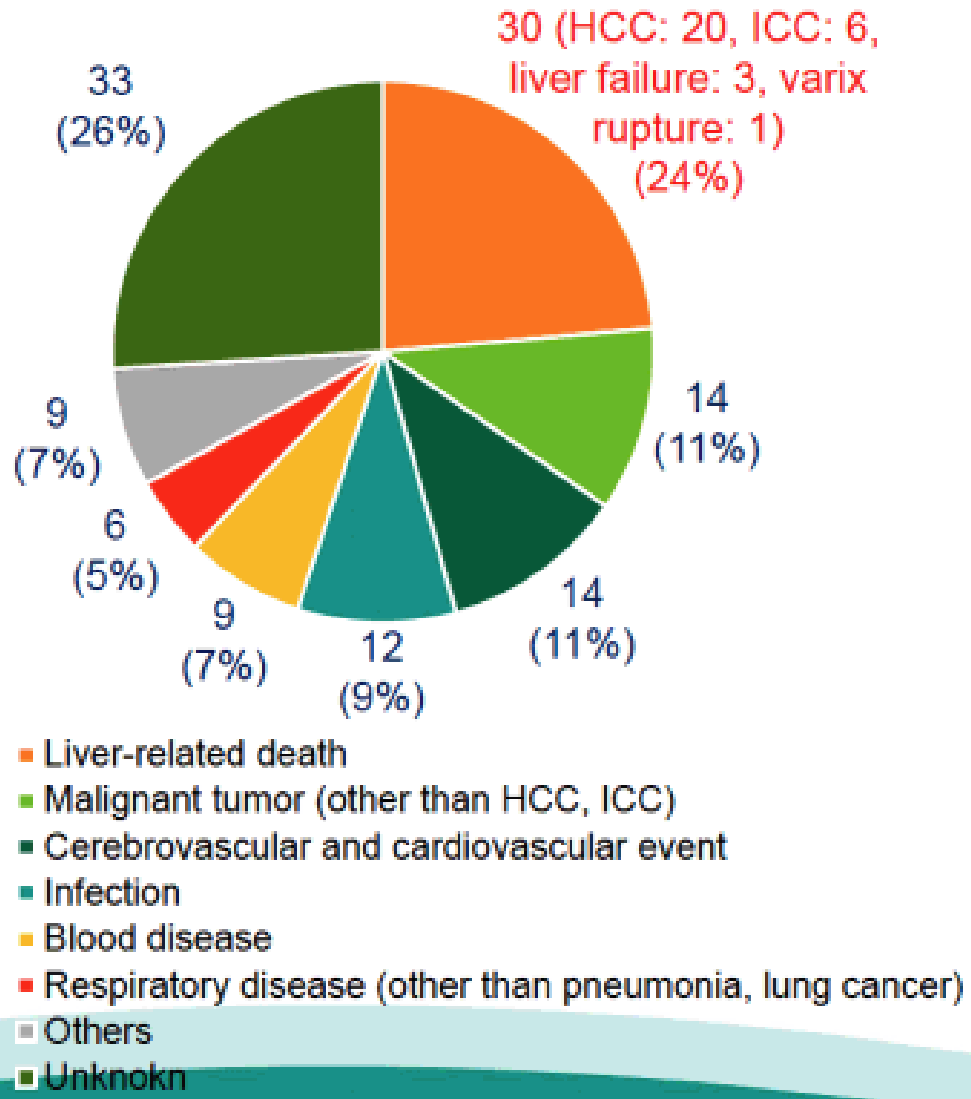
Yuki Tahata[1], Hayato Hikita[1], Hayato Hikita[1], Yasutoshi Nozaki[2], Hisashi Ishida[3], Naoki Hiramatsu[4], Masanori Miyazaki[5], Ryotaro Sakamori[6], Naoki Morishita[7], Kazuyoshi Ohkawa[8], Akira Kaneko[9], Fumihiko Nakanishi[10], Yoshinori Doi[11], Takayuki Yakushijin[12], Mitsuru Sakakibara[13], Kazuho Imanaka[14], Naruyasu Kakita[15], Akira Doi[1], Akira Nishio[1], Takahiro Kodama[1], Tomohide Tatsumi[1] and Tetsuo Takehara[1]

Aim: To clarify the risk factors for long-term prognosis according to liver-related and non-liver related death

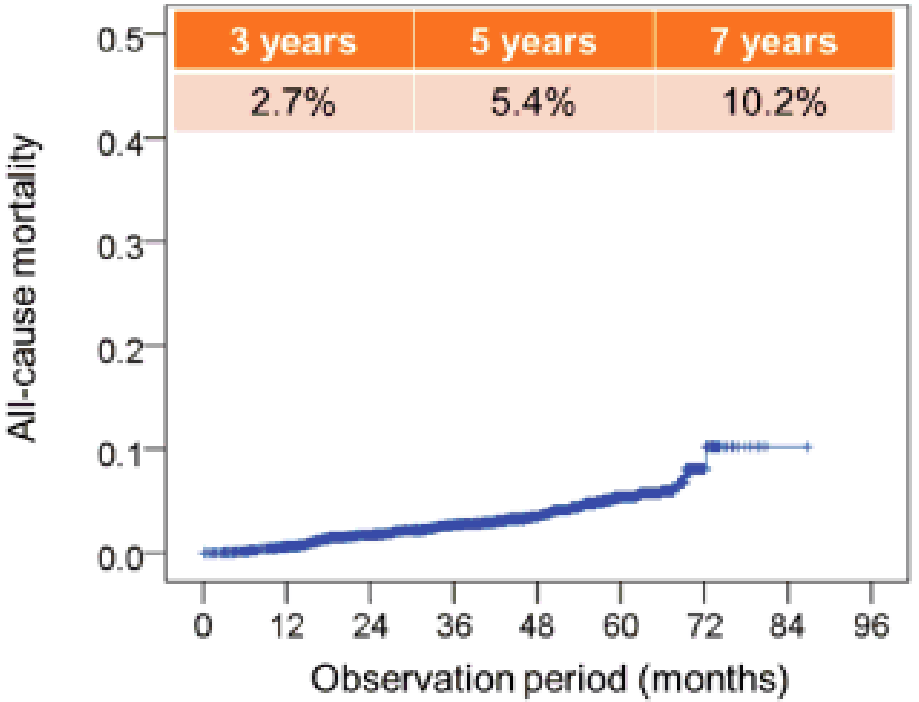
Methods: Prospective study included 3,238 HCV patients who started DAA treatment between September 2014 and June 2021 and achieved SVR in Japanese hospitals.
Factors associated with liver-related and non-liver related death after SVR were examined by Cox proportional hazard analysis. Liver-related death was defined as death from HCC, liver failure and varix rupture

Conclusion: Approximately 80% of deaths in SVR patients were non-liver-related cause, and older age, male sex and lower albumin level at SVR were significantly associated with non-liver-related death. In patients with a history of HCC, the risk of liver-related death persists over the long term after SVR.

All-cause mortality and causes of death after SVR



Observation period (from SVR): 50.4 (28.0-62.5) months
Death: 127 patients



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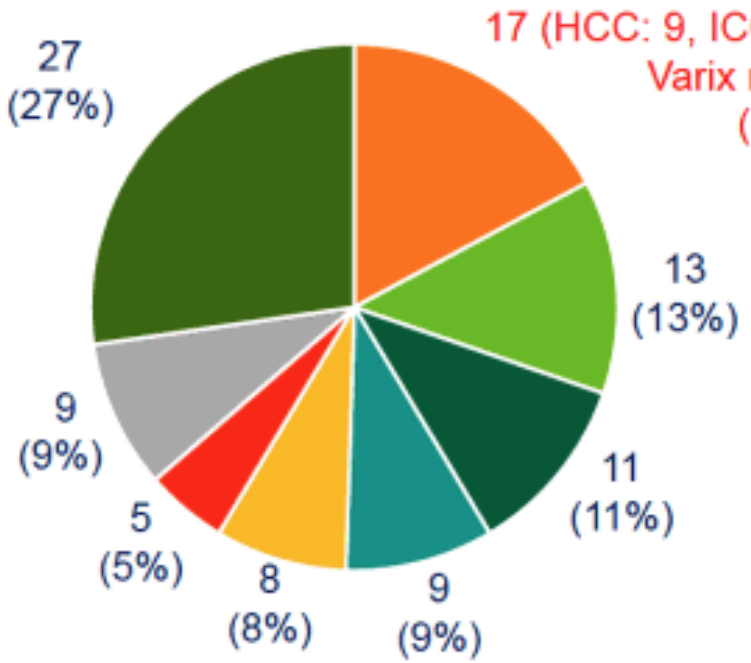
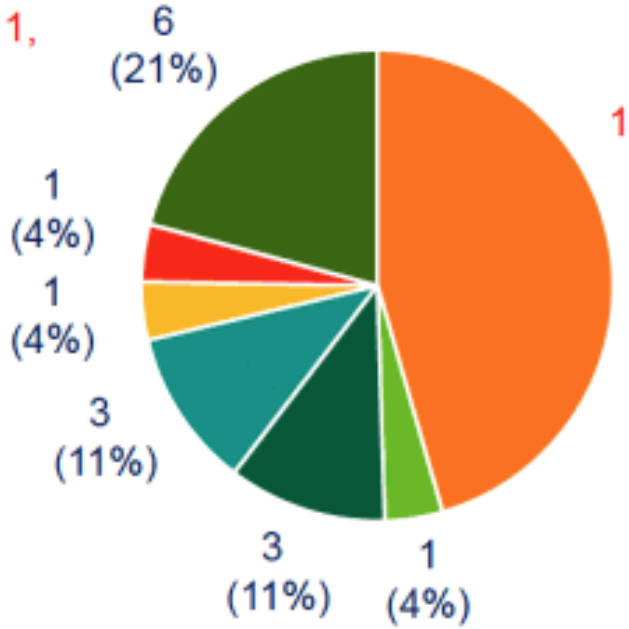
Cause of death according to history of HCC

Without a history of HCC



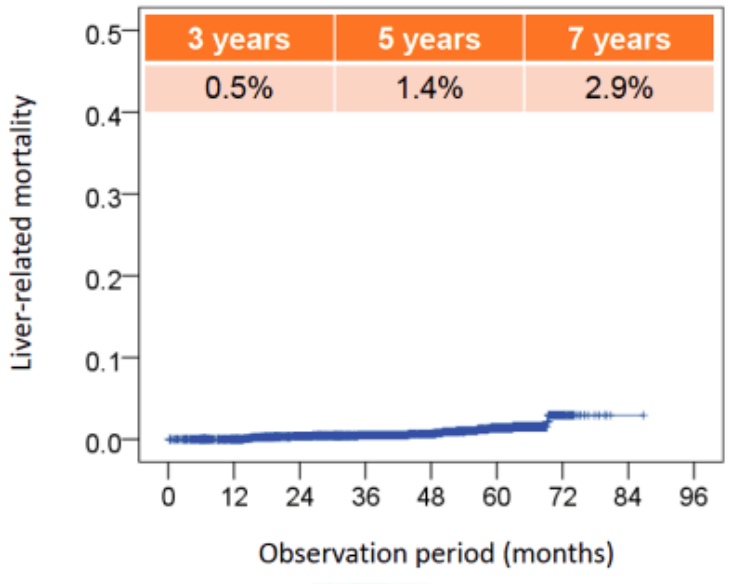
With a history of HCC



Proportion of liver-related death
p=0.001
(Chi square test)

- Liver-related death
- Malignant tumor (other than HCC, ICC)
- Cerebrovascular and cardiovascular event
- Infection
- Blood disease
- Respiratory disease (other than pneumonia, lung cancer)
- Others
- Unknown

Liver-related mortality after SVR



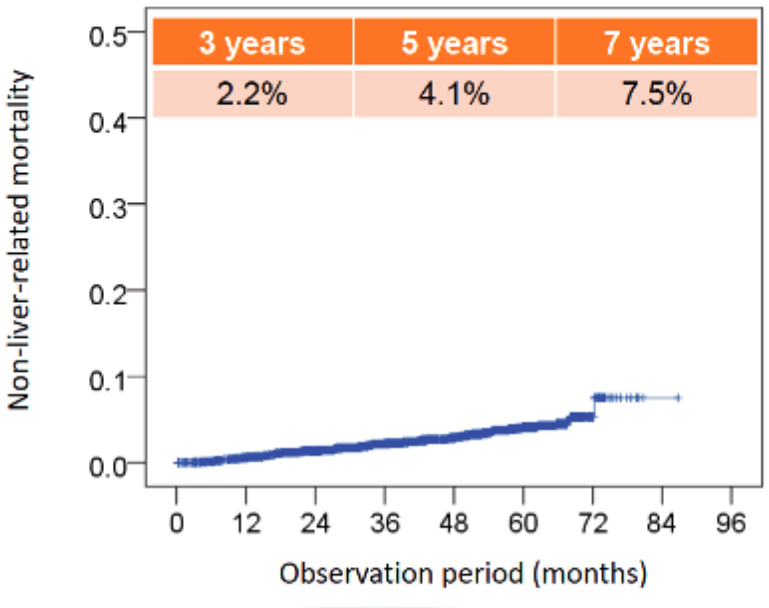
Observation period (from SVR24): 50.4 months
Death: 30 patients
HCC: 20
ICC: 6
Liver failure: 3
Varix rupture 1

Factors associated with liver-related mortality

Cox proportional hazard analysis

		Univariate analysis			Multivariate analysis		
Factor	Category	HR	95% CI	P value	HR	95% CI	P value
Age (years)	Per 1	1.095	1.043 – 1.149	< 0.001	1.069	1.017 – 1.123	0.009
Sex	Female/male	0.564	0.274 – 1.161	0.120			
BMI (kg/m^2)	Per 1	1.027	0.925 – 1.142	0.615			
Diabetes mellitus	Yes/no	2.503	1.191 – 5.260	0.016	1.651	0.770 – 3.539	0.198
Antiviral treatment	re-treatment/naïve	1.612	0.782 – 3.325	0.196			
History of HCC	Yes/no	7.089	3.432 – 14.644	< 0.001	3.179	1.485 – 6.803	0.003
Liver disease	CH/LC	4.993	2.426 – 10.275	< 0.001	1.537	0.656 – 3.605	0.323
Plt_svr24 (x10^4/μl)	Per 1	0.854	0.791 – 0.922	< 0.001	0.917	0.840 – 1.001	0.052
ALT_svr24 (U/l)	Per 1	1.002	0.972 – 1.032	0.907			
Total bilirubin_svr24 (mg/dl)	Per 1	1.733	1.053 – 2.850	0.030	1.245	0.616 – 2.516	0.542
creatinine_svr24 (mg/dl)	Per 1	1.003	0.509 – 1.975	0.994			
Albumin_svr24 (g/dl)	Per 1	0.139	0.061 – 0.319	< 0.001	0.270	0.104 – 0.01	0.007
AFP_svr24 (ng/ml)	Per 1	1.001	0.993 – 1.010	0.743			

Non-liver-related mortality after SVR

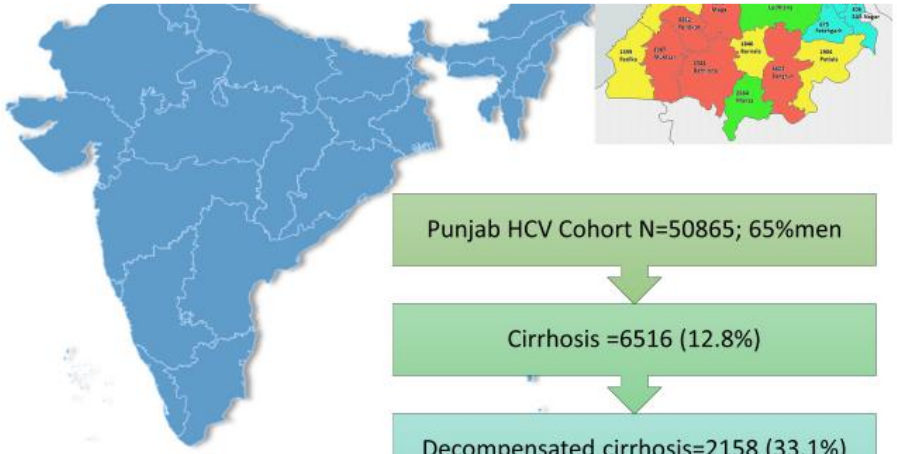


Observation period (from SVR24): 50.4 months
Death: 97 patients
Malignant tumor (other than HCC, ICC): 14
Cerebrovascular and cardiovascular event: 14
Infection: 12
Blood disease: 9
Respiratory disease (other than pneumonia, lung cancer): 6
Others: 9
Unknown: 33

Factors associated with non-liver-related mortality

Cox proportional hazard analysis

		Univariate analysis			Multivariate analysis		
Factor	Category	HR	95% CI	P value	HR	95% CI	P value
Age (years)	Per 1	1.062	1.036 – 1.087	< 0.001	1.051	1.020 – 1.082	0.001
Sex	Female/male	0.494	0.329 – 0.741	0.001	0.456	0.272 – 0.763	0.003
BMI (kg/m^2)	Per 1	0.947	0.887 – 1.010	0.099			
Diabetes mellitus	Yes/no	2.137	1.390 – 3.286	0.001	1.393	0.809 – 2.399	0.232
Antiviral treatment	re-treatment/naïve	0.725	0.471 – 1.115	0.143			
History of HCC	Yes/no	1.755	1.011 – 3.045	0.046	1.138	0.573 – 2.257	0.713
Liver disease	CH/LC	1.930	1.246 – 2.987	0.003	1.332	0.748 – 2.373	0.330
Plt_svr24 (x10^4/μl)	Per 1	0.993	0.962 – 1.026	0.689			
ALT_svr24 (U/l)	Per 1	0.987	0.966 – 1.008	0.230			
Total bilirubin_svr24 (mg/dl)	Per 1	0.575	0.303 – 1.092	0.091			
creatinine_svr24 (mg/dl)	Per 1	1.202	1.062 – 1.361	0.004	1.081	0.911 – 1.283	0.373
Albumin_svr24 (g/dl)	Per 1	0.160	0.101 – 0.255	< 0.001	0.271	0.147 – 0.501	< 0.001
AFP_svr24 (ng/ml)	Per 1	0.998	0.977 – 1.019	0.822			



Punjab HCV Cohort N=50865; 65%men

Cirrhosis =6516 (12.8%)

Decompensated cirrhosis=2158 (33.1%)

1152 Decompensated cirrhosis enrolled at PGIMER.

DAAs were given at 25 sites with the nodal referral centre being PGIMER, Chandigarh.

Between April 2018 and December 2022, of 6516 referred patients with cirrhosis, 1152 patients with decompensated cirrhosis were enrolled for this study.
(Mean age:53.2±11.5 years, 62.9% men, median MELDNa 18.5,73.5%-unsafe injection related,77.9% urban)
They were treated with DAAs as per the published NVHCP algorithm.

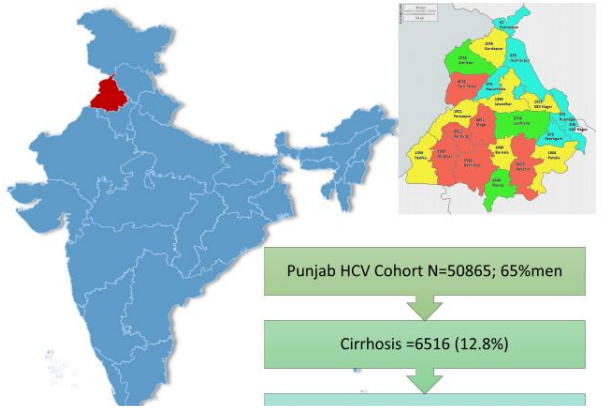
- Followed up for HCC, clinical events, progression of PHT
- Rate of recompensation was noted
- Predictors of failure to recompensate and progression of portal hypertension

In follow up at 2 years: A decrease in MELDNa occurred in 409 (35.5%) a final MELD score of <10 was achieved in 31.7%.

- Liver stiffness measurement (LSM) > 12.5 kPa, aspartate aminotransferase (AST)-to-platelet ratio index (APRI ≥2.0) and FIB-4 score (≥3.25) were used in making a diagnosis of cirrhosis.
- **Decompensated cirrhosis** was defined as the

Recompensation was defined per Baveno-VII if all the following criteria were met:

Recompensation of Chronic Hepatitis C-related decompensated cirrhosis following direct-acting antiviral therapy: real-world data from the Punjab HCV Elimination Model.



Punjab HCV Cohort N=50865; 65%men

Cirrhosis =6516 (12.8%)

The Mukh-Mantri Punjab Hepatitis C Relief Fund (MMPHCRF), launched on 18th June 2016, now merged with the National Viral hepatitis Control programme (NVHCP) provides free of-charge generic direct-acting antivirals (DAAs) with the goal to eliminate CHC from Punjab, India.

DAAs were given at 25 sites with the nodal referral centre being PGIMER Chandigarh.

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(Mean age:53.2±11.5 years, 62.9% men, median MELDNa 18.5,73.5%-unsafe injection related,77.9% urban)
They were treated with DAAs as per the published NVHCP algorithm.

aspartate aminotransferase (AST)-to-platelet ratio index (APRI ≥2.0) and FIB-4 score (≥3.25) were used in making a diagnosis of cirrhosis.

- **Decompensated cirrhosis** was defined as the appearance of any of the following manifestations: ascites, variceal bleeding, and/or hepatic encephalopathy (HE).

Recompensation was documented in 284/1152(24.7%).

SVR-12 was 81.8%. New HCC=29/6516 (0.45%)

Recompensation was defined per Baveno-VII if all the following criteria were met:

Resolution of clinical manifestations such as ascites (without the concurrent use of diuretics), HE (without the use of prophylactic medications), and absence of recurrent variceal bleeding for at least a duration of 12 months.	Removal or suppression of primary aetiological cause of liver disease such as alcohol abstinence or effective viral suppression.	Improvement in synthetic liver function such as serum albumin, International Normalized Ratio (INR), and bilirubin.

On multivariate Cox proportional hazards regression only higher age (aHR 1.013 ,95%CI:1.003-1.048,*P*=0.042) and higher MELDNa (aHR 1.213,95%CI: 1.003-1.028,*P*<0.033) predicted failure to recompensate.

Madhumita Premkumar* Radha K. Dhiman, Ajay K. Duseja, Anchal Sandhu, Arka De, Sunil Taneja, Ekta Gupta, Manoj Kumar, Gagandeep Singh Grover, Pankaj Gupta, Sahaj Rathi, Nipun Verma, Sreedhara B Chaluvashetty, Harish Bhujade, Naveen Kalra, Jasvinder Nain, Vishesh Kumar, Prerna Sharma, Surender Singh

Progression of PHT was noted in 158 patients (13.7%)

- rebleed in 45 (3.9%) during a follow-up period of 52 months (interquartile range, 18-68.5 months).
- Treatment failure (OR 1.8, 95%CI:1.3-4.9, *P*=0.002) and presence of HE (OR4.4, 95%CI:1.3-5.6, *P*=0.044) were associated with progression of PHT.
- Of 145 patients who died, and 6 underwent liver transplantation.

ΗΚΚ

11 εργασίες

58: LOW ANTIVIRAL TREATMENT RATE FOR PATIENTS WITH HEPATITIS C (HCV)-RELATED HEPATOCELLULAR CARCINOMA (HCC)– A REAL-WORLD NATIONWIDE U.S. STUDY

- **Primary objective,** is to determine the proportion of patients with HCV-related HCC who received DAA after 2014 and factors associated with treatment receipt. **Secondary outcome:** DAA treatment impact on the overall survival.

- **Methods:**

This **retrospective study**, patients with HCV-related HCC from **2015-2021**. Adults with HCV-related HCC and at least 6 months of insurance coverage, but without prior liver transplant, hepatitis B, D or HIV co-infection were included.

- **Results: 3,922 patients with HCV-related HCC - 922 (23.5%) received DAA.**
- Treatment rates were higher for patients with **cirrhosis** (both compensated and decompensated), those who received care from **gastroenterology (GI) or infectious disease (ID)** with or without oncology specialists. Compared to untreated patients, the DAA-treated group was also **younger** (65.2±7.5 vs. 66.4±7.5 years, P<0.001).
- In **multivariable** logistic regression, younger **age** (aHR 0.98, 95%CI: 0.97-0.99, P<0.001), being seen by a **GI/ID physician** (aHR 3.06, 95%CI: 2.13-4.51, P<0.001), having **cirrhosis** (compensated: aHR 1.60, 95%CI 1.18-2.21; P=0.003; decompensated: aHR 1.45, 95%CI 1.07-1.98, P=0.02) were associated with **higher odds of receiving DAA treatment**, but **not sex or race/ethnicity**.
- **DAA treated patients had significantly higher 5-year survival compared to untreated patients** (47.2% vs. 35.2%, P<0.001). Following adjustment for age, sex, race/ethnicity, Charlson Comorbidity Index, HCC treatment, receiving **DAA treatment remained significantly associated with lower mortality** (aHR:0.61, 95%CI: 0.53-0.69, P<0.001).

Leslie Yeeman Kam, Yee Hui Yeo, Fanpu Ji, Linda Henry, Ramsey Cheung

58: LOW ANTIVIRAL TREATMENT RATE FOR PATIENTS WITH HEPATITIS C (HCV)-RELATED HEPATOCELLULAR CARCINOMA (HCC)– A REAL-WORLD NATIONWIDE U.S. STUDY

Figure 1A. Treatment rates among HCV-related HCC patients in the total cohort by sex, cirrhosis, race, and care provider.

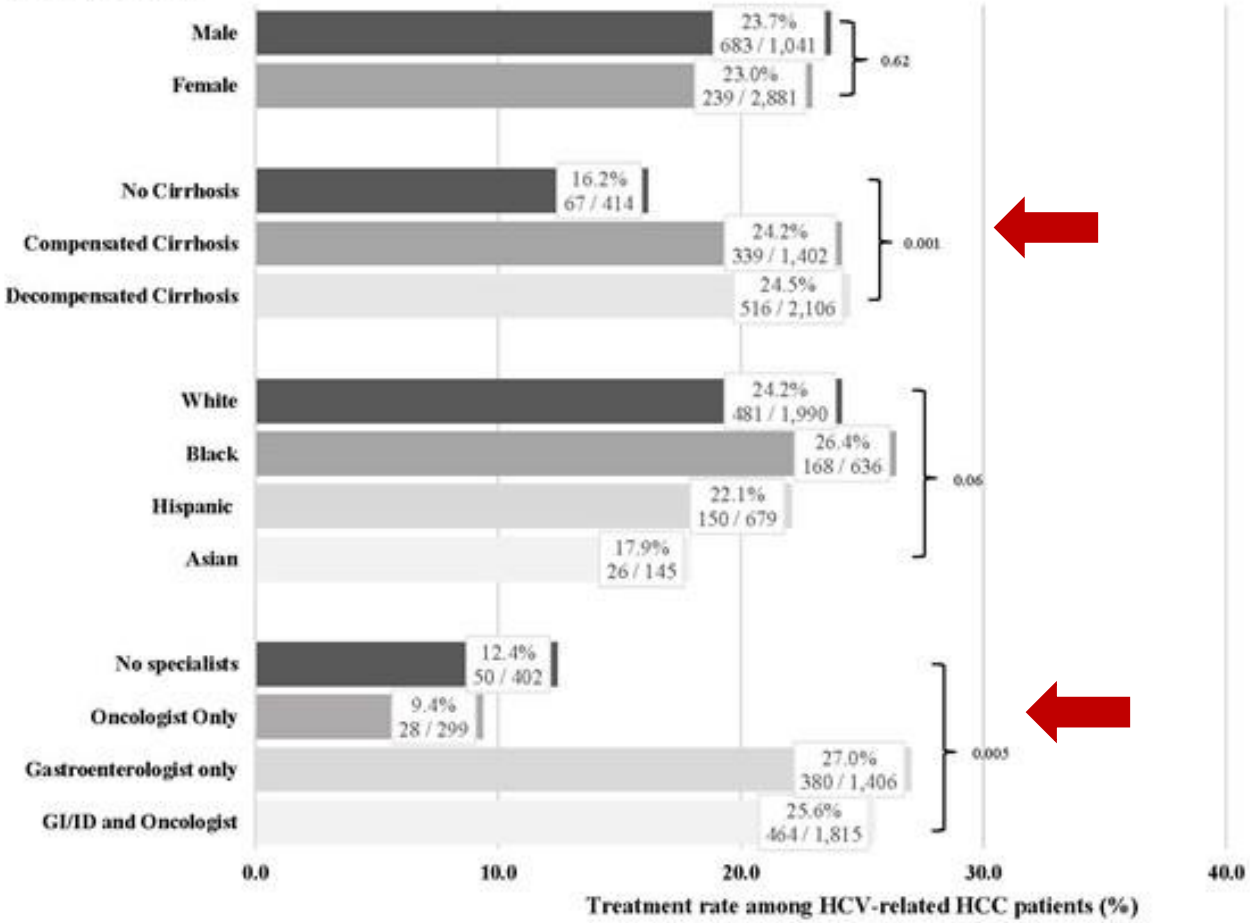
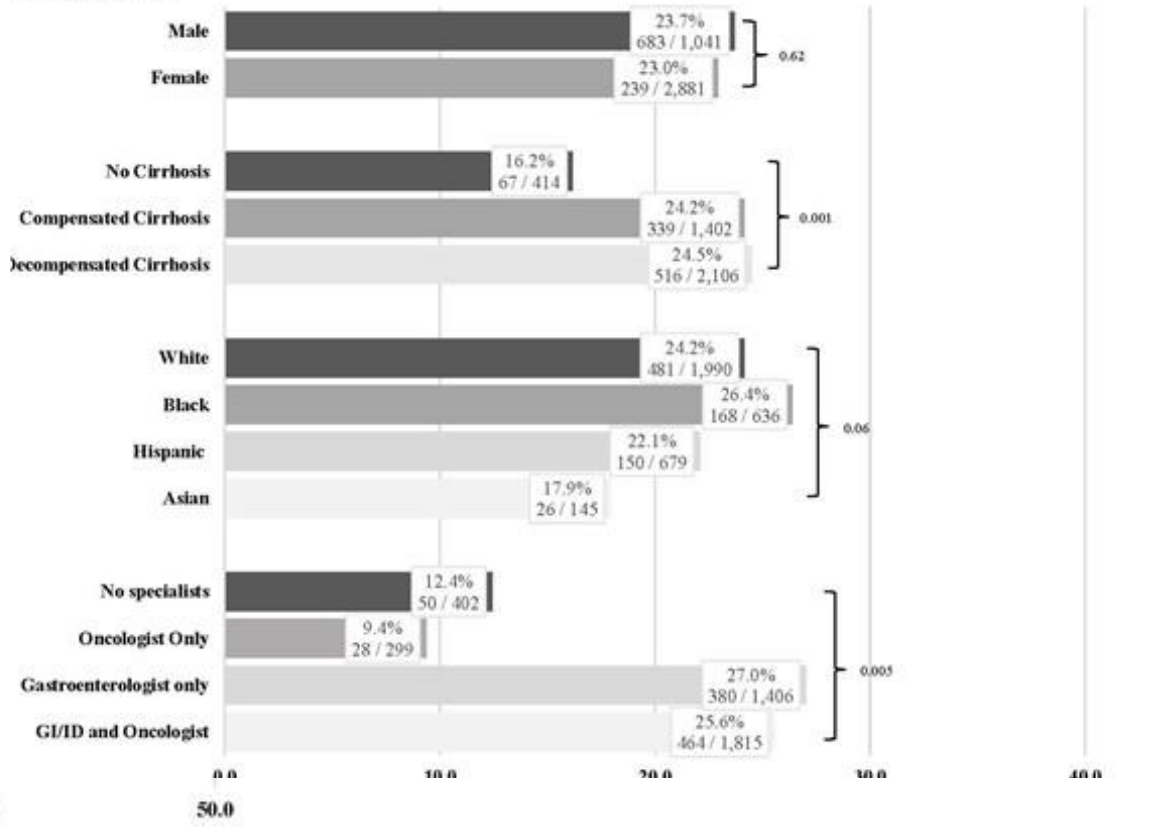


Figure 1A. Treatment rates among HCV-related HCC patients in the total cohort by sex, cirrhosis, care provider.



Abbreviations: HCV, hepatitis C virus; HCC, hepatocellular carcinoma; DAA, direct acting antiviral; GI, gastroenterologist/hepatologist; ID, infectious

58: LOW ANTIVIRAL TREATMENT RATE FOR PATIENTS WITH HEPATITIS C (HCV)-RELATED HEPATOCELLULAR CARCINOMA (HCC)– A REAL-WORLD NATIONWIDE U.S. STUDY

Figure 1A. Treatment rates among HCV-related HCC patients in the total cohort by sex, cirrhosis, race, and care provider.

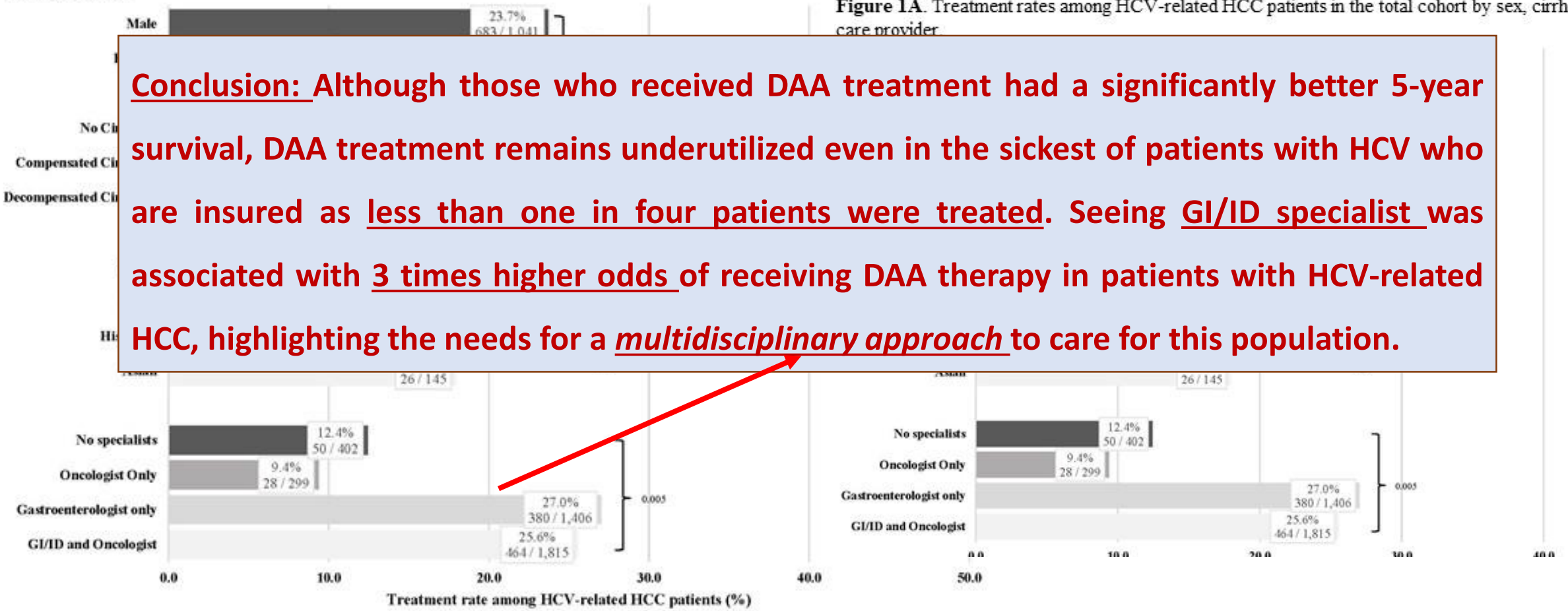


Figure 1A. Treatment rates among HCV-related HCC patients in the total cohort by sex, cirrhosis, care provider.

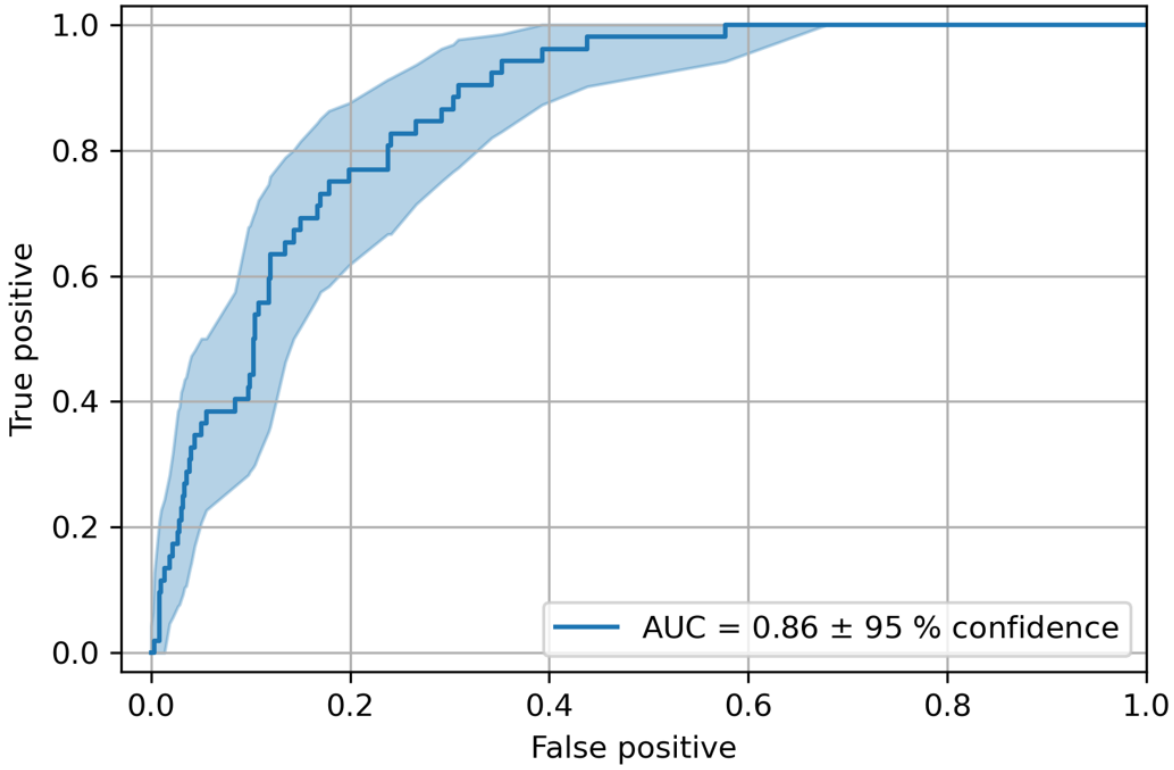
Conclusion: Although those who received DAA treatment had a significantly better 5-year survival, DAA treatment remains underutilized even in the sickest of patients with HCV who are insured as less than one in four patients were treated. Seeing GI/ID specialist was associated with 3 times higher odds of receiving DAA therapy in patients with HCV-related HCC, highlighting the needs for a *multidisciplinary approach* to care for this population.

Abbreviations: HCV, hepatitis C virus; HCC, hepatocellular carcinoma; DAA, direct acting antiviral; GI, gastroenterologist/hepatologist; ID, infectious

1801-A: AN ARTIFICIAL INTELLIGENCE MODEL FOR PREDICTION OF HEPATOCELLULAR CARCINOMA DEVELOPMENT AFTER ORAL ANTIVIRAL THERAPY IN PATIENTS WITH CHRONIC HEPATITIS C

Methods:
A total of **3,489 HCV patients who treated with DAAs** and had achieved **SVR** from ten hospitals in **South Korea.** HCC risk prediction models were developed using **machine learning** including Decision tree and Gradient Boosting.

Results:
Age, platelet, AST, ALT, bilirubin, and albumin. Prediction models using these parameters at **baseline** and **1 year after treatment** was showed good predictive abilities (**AUROC values of 0.83 to 0.86**).

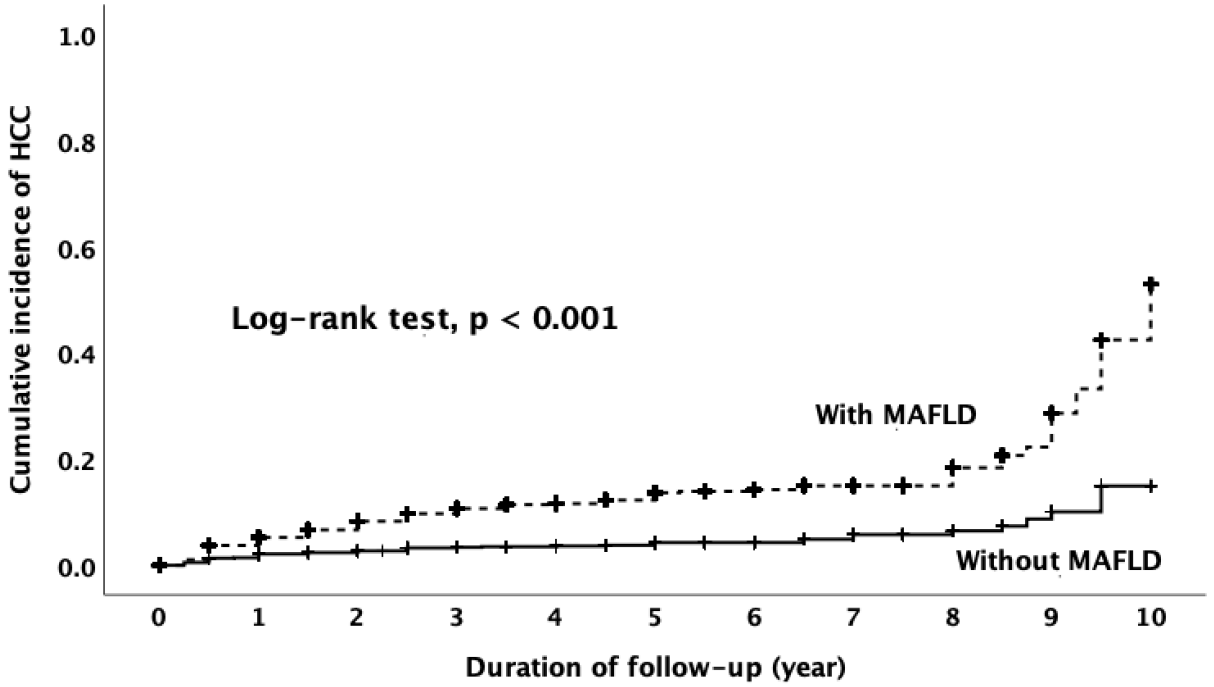


1839-A: INCREASED RISK OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CONCURRENT HEPATITIS C VIRUS INFECTION AND METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE AFTER ACHIEVING SUSTAINED VIROLOGIC RESPONSE WITH DIRECT-ACTING ANTIVIRALS

Methods: retrospectively analyzed a prospective cohort assessing the risk of HCC in patients with HCV after achieving SVR_{12} with DAAs at eight academic centers in Taiwan. MAFLD was defined as the presence of hepatic steatosis with a controlled attenuation parameter (CAP) of 248 dB/m or more, in combination with type 2 diabetes mellitus (DM), overweight or obesity, or lean/normal weight

Results: 2018 patients - median of post-SVR_{12} follow-up of 4.5 years, **164 (8.1%) of them developed HCC**.

Among patients with concurrent **MAFLD, those with type 2 DM** had a significantly higher cumulative incidence rate of HCC than those with overweight or obesity, or lean/normal weight (Log-rank test, p = 0.005).



Multivariate: age > 50 years (HR: 5.26 [95% CI: 2.80-9.88], p < 0.001), male (HR: 2.38 [95% CI: 1.71-3.32], p < 0.001), cirrhosis (HR: 4.98 (95% CI: 3.33-7.45, p < 0.001), ALBI grade (HR: 1.89 [95% CI: 1.23-2.92], p < 0.001), and MAFLD (HR: 1.96 (95% CI: 1.39-2.76, p < 0.001) were associated with HCC in patients achieving SVR_{12} with DAAs.

1804-A: HCC PREDICTION MODELS EFFECTIVELY ASSESS THE RISK OF HCC IN CHRONIC HEPATITIS C PATIENTS WITHOUT ADVANCED FIBROSIS AFTER ORAL ANTIVIRAL THERAPY: A MULTICENTER STUDY

Methods:

1,839 chronic hepatitis C patients **without advanced chronic** liver disease from 10 tertiary hospitals who were treated with DAA.

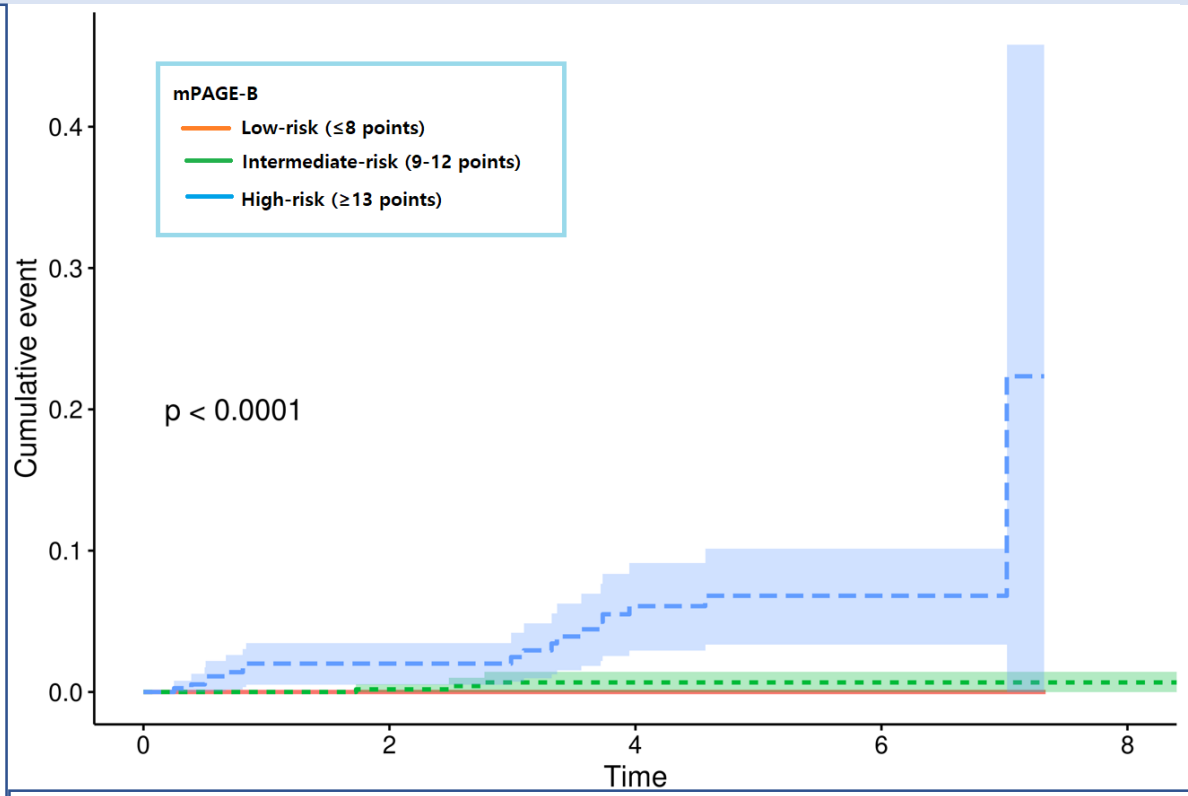
Advanced fibrosis: LSM >10 kPa, FIB-4 >3.25, or APRI >1.5 at baseline.

Results:

Median follow-up of 2.8 years - **1.5% patients developed HCC at a median of 2.77 years.**

Patients who developed HCC during follow-up: **older, lower platelet count and albumin level before antiviral treatment**, **higher FIB-4** score (*P*<0.001). Comorbidities (diabetes, hypertension) more common (*P*<0.05).

In multivariate analysis, old **age**, **platelet** count, **albumin** level, and **sodium** level **before treatment** were significantly associated with the occurrence of HCC (all *P*<0.05).



HCC prediction models aMAP and mPAGE-B

Incidence of HCC ranged from **1.5% to 7.4% at 3-years and from 3.8% to 24.2% at 5-years at SVR in high-risk patients**.

HCC **rarely occurred during the first 5-years** of follow-up in **low and intermediate-risk** patients defined by HCC risk scores.

Identifying the population at risk of HCC in non-ACLD chronic hepatitis C patients cured by direct-acting agents: A strategic approach

Yen-Chun Liu[1,2], Ya-Ting Cheng[1,2], Yi-Cheng Chen[1,2], Yi-Chung Hsieh[1,2], Wen-Juei Jeng[1,2], Chun-Yen Lin[1,2], Rong-Nan Chien[1,2], Dar-In Tai[1,2], I-Shyan Sheen[1,2]

1.College of Medicine, Chang Gung University,Taiwan 2. Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Linkou branch, Taiwan

AASLD The Liver Meeting® Nov. 10-14, 2023

INTRODUCTION

- Hepatocellular carcinoma (HCC) surveillance is recommended for chronic hepatitis C (CHC) patients with advanced fibrosis (F3) or cirrhosis (F4) after viral eradication.
- However, the risk of HCC still exists in CHC patients without advanced fibrosis or cirrhosis.

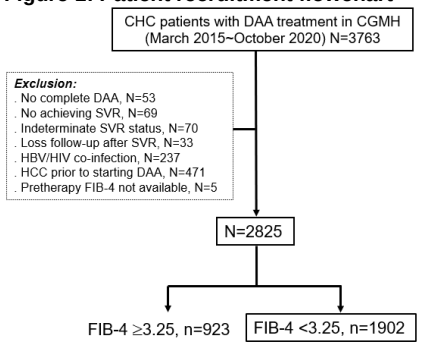
AIM

- The study aimed to identify the risk factors for HCC in patients with pretherapy FIB-4 scores <3.25 and develop a predictive model to stratify the population that would benefit from HCC surveillance.

MATERIAL & METHODS

- CHC patients achieved SVR by direct-acting antiviral agents (DAA) without HCC history before starting DAA in Chang Gung Memorial Hospital, Linkou branch, were enrolled (**Figure 1**).
- Cox regression analysis was performed to assess the occurrence of HCC, and predictive scores were derived based on adjusted hazard ratios.
- The cumulative incidences of de-novo HCC were calculated using the Kaplan-Meier method.

Figure 1: Patient recruitment flowchart



RESULTS

- Among 2825 enrolled patients with median follow-up duration of 42 (IQR: 30-51) months, the mean age was 62 years old, 43% patients were male, 60% were HCV genotype 1 and 1902 patients (67%) had FIB-4<3.25.
- In 1902 CHC patients with FIB-4 <3.25, multivariate cox regression showed male [adjusted hazard ratio (aHR): 4.11 (1.76-9.59), P<0.01], and FIB-4 ≥2.5 [aHR:4.30 (1.96-9.44), p<0.01] were predictors for HCC occurrence **(Table 1),** while AFP ≥10 ng/mL [aHR:2.66 (0.97-7.25), p=0.06] failed to achieved statistical significane.
- We derived a predictive model- FIBS score for HCC occurrence in patients with FIB-4 <3.25: 1 x (male:1, female:0) + 1 x (FIB-4 ≥2.5:1, FIB-4 <2.5:0), which ranged from 0-2 **(Table 2).**
- About 10% of FIB-4 <3.25 patients have FIBS score of 2.
- The 6-year cumulative HCC incidences for score 0, 1 and 2 were 0.4%, 3.1% and 11.7% (annual incidences: 0.11%, 0.45% and 2.40% person-year), log-rank p<0.01 **(Figure 2).**
- The sensitivity, specificity, PPV and NPV for HCC are the higher in patients with FIBS score of 2 than those with FIBS score <2 **(Table 2).**

Figure 2: Cumulative HCC incidences stratifying by FIBS score

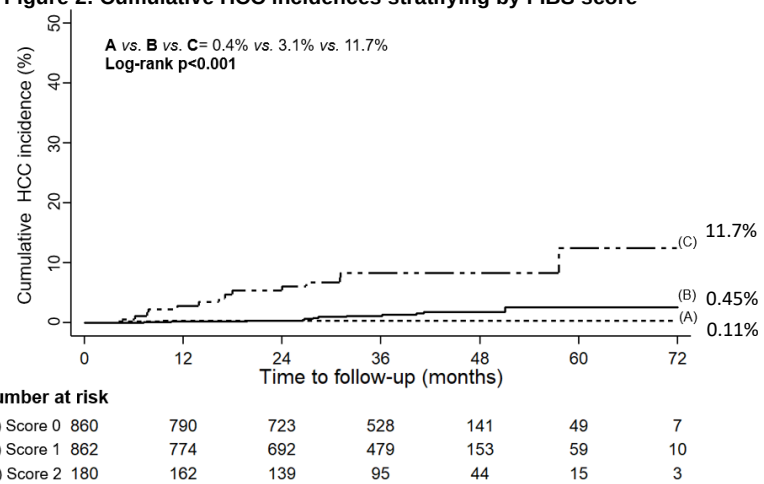


Table 1: Cox regression for HCC occurrence in DAA-treated

Variables	Crude HR (95%CI)	P value	Adjusted HR (95%CI)	P value
Age ≥65 years	2.18 (1.05-4.52)	0.04		
Male	3.09 (1.36-6.99)	<0.01	4.11 (1.76-9.59)	<0.01
Genotype 1 vs. non-1	1.80 (0.72-4.46)	0.21		
Sofosbuvir-based	0.82 (0.39-1.73)	0.61		
HCV RNA, Log_{10}IU/ml	0.92 (0.60-1.42)	0.71		
BMI, kg/m^2	1.02 (0.94-1.12)	0.61		
Diabetic mellitus	1.04 (0.44-2.46)	0.93		
Fatty liver	0.55 (0.26-1.15)	0.11		
ALT, U/L	1.00 (0.99-1.01)	0.88		
Bilirubin, mg/dL	1.82 (0.83-4.02)	0.14		
Albumin, g/dL	0.46 (0.17-1.23)	0.12		
Platelet, 10^3/uL	1.00 (0.99-1.00)	0.26		
AFP ≥6, ng/mL	2.83 (1.07-7.48)	0.04	2.66 (0.97-7.25)	0.06
MELD score	1.11 (0.88-1.39)	0.39		
FIB-4 ≥2.5	5.05 (2.33-10.93)	<0.01	4.30 (1.96-9.44)	<0.01

Table 2: Accuracy of the FIBS score for HCC prediction

FIBS score	0, n=860	1, n=862	2, n=180
HCC event, n	3	12	14
Annual incidence, person-year	0.11%	0.45%	2.40%
Sensitivity	10.3%	41.4%	48.3%
Specificity	54.3%	54.6%	91.1%
PPV	0.4%	1.4%	7.8%
NPV	97.5%	98.4%	99.1%

- A simple scoring system-FIBS score, utilizing the FIB-4 cut-off of 2.5 and gender can identify 10% of non-ACLD CHC patients with the FIBS score of 2, who are at higher HCC risk. These patient should be considered for inclusion in an HCC surveillance program.

DISCLOSURES

All authors have no conflict of financial interests to disclose.

CONTACT INFORMATION

Prof. Wen-Juei Jeng, E-mail: Rachel.jeng@gmail.com

Epidemiology of Hepatitis E Virus in Patients With Chronic Liver Disease Across South America

Pisano MB[1], Fantilli AC[1], Spencer Goble[2], Balderramo DC[3], Prieto JE[4], Arrese M[5], Carrera E[6], Díaz Ferrer J[7], Mattos AZ[8], Boonstra A[9], Debes JD,[2,9,10], Ré VE[1]

[1] Instituto de Virología "Dr. Vanella", Facultad de Ciencias Médicas, Universidad Nacional de Córdoba, Argentina, [2] Hennepin Healthcare, Minneapolis, Minnesota, [3] Hospital Privado Universitario de Córdoba, Córdoba, Argentina, [4] Centro de enfermedades hepáticas y digestivas (CEHYD), Bogotá, Colombia, [5] Facultad de Medicina, Pontificia Universidad Católica de Chile, [6] Universidad San Francisco de Quito, Ecuador, [7] Universidad de San Martin de Porres, Facultad de Medicina Humana, Lima, Perú , [8] Federal University of Health Sciences of Porto Alegre, Porto Alegre, Brazil, [9] Erasmus MC, University Medical Center, Rotterdam, The Netherlands, [10] University of Minnesota, Minneapolis, MN, USA

Introduction

- Enterically transmitted, zoonotic infection
- Cause of acute hepatitis
- Frequently asymptomatic
- **High mortality in pregnant women**
- Can **worsen pre-existing liver disease**
- Epidemiology is understudied in Latin America

Methods

The presence of IgG anti-HEV was evaluated for in 716 serum samples

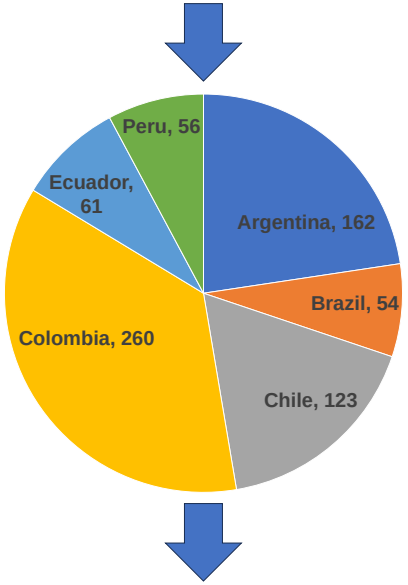


Figure 1. Prevalence calculated for each country and stratified by etiology of chronic liver disease

Results

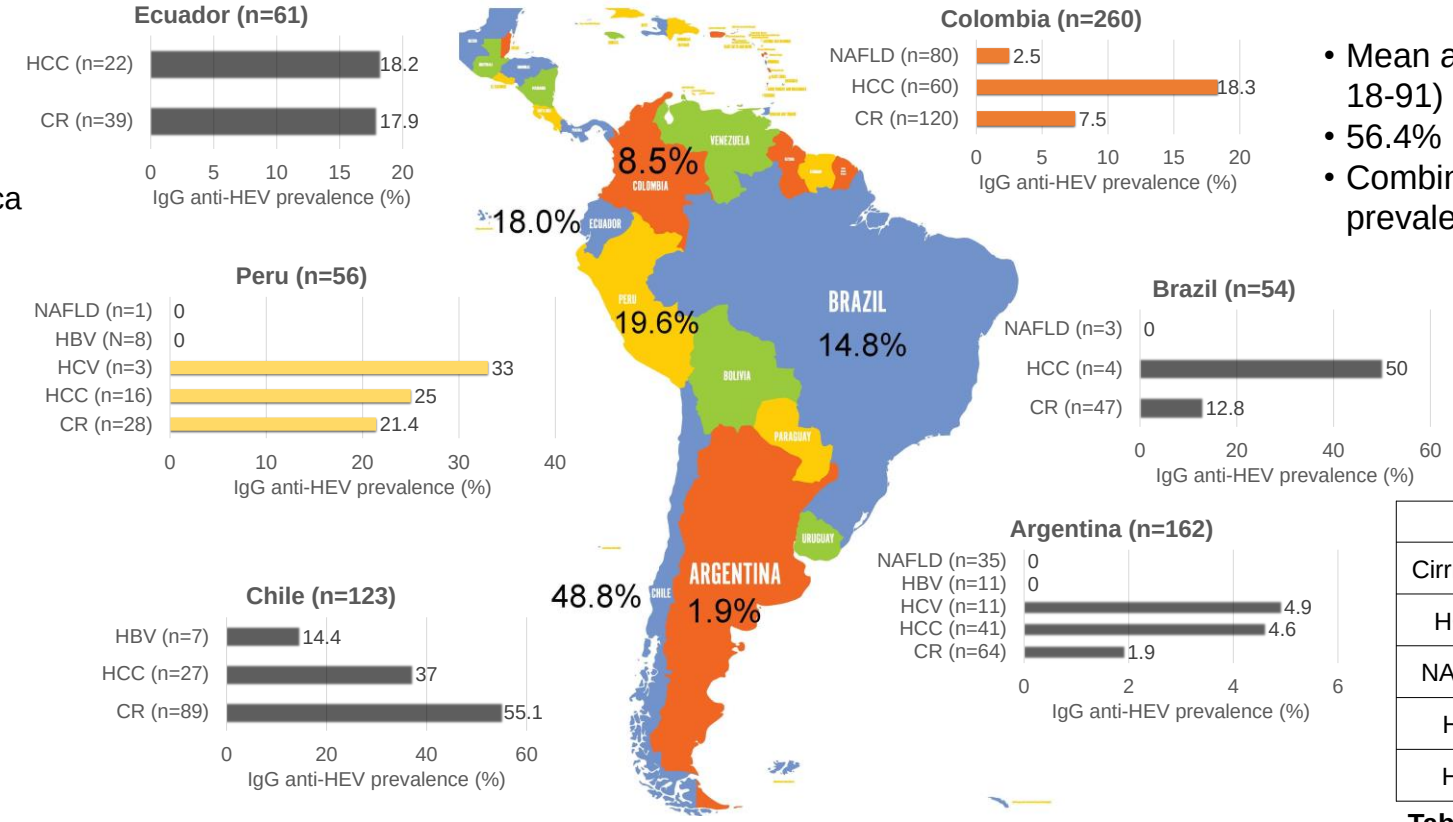


Figure 2. Prevalence of anti-HEV IgG in each evaluated country. Prevalence for each country is further stratified by etiology of subjects' liver disease

- Mean age 62.9 years (range 18-91)
- 56.4% male, 43.6% female
- Combined IgG anti-HEV prevalence of 16.1% (115/716)

Etiology	Proportion (%)
Cirrhosis (n=387)	20.1
HCC (n=170)	19.4
NAFLD (n=119)	1.7
HBV (n=26)	3.8
HCV (n=14)	7.1

Table 1. Etiologies of liver disease for the combined

Conclusion

- High prevalence of HEV seropositivity found in patients with chronic liver disease across South America
- Prevalence was particularly high in Chile and in patients with cirrhosis and HCC
- Further study are needed to address the differences in epidemiology and the potential clinical implications

Recent Increase in Hepatitis Cases (Acute Hepatitis of Unknown Origin in Children/Hepatitis A/Other Food Borne Hepatitis) Worldwide: A Possible COVID19 Linkage

Dr. Arvind Tomar[1] and Nishul Rani[2]

[1] Department of Pulmonary Medicine, Institute of Liver and Biliary Sciences, New Delhi, India

[2] Department of Genetics and Plant Breeding, C.C.S. University Meerut, Uttar Pradesh, India

*Corresponding author

BACKGROUND

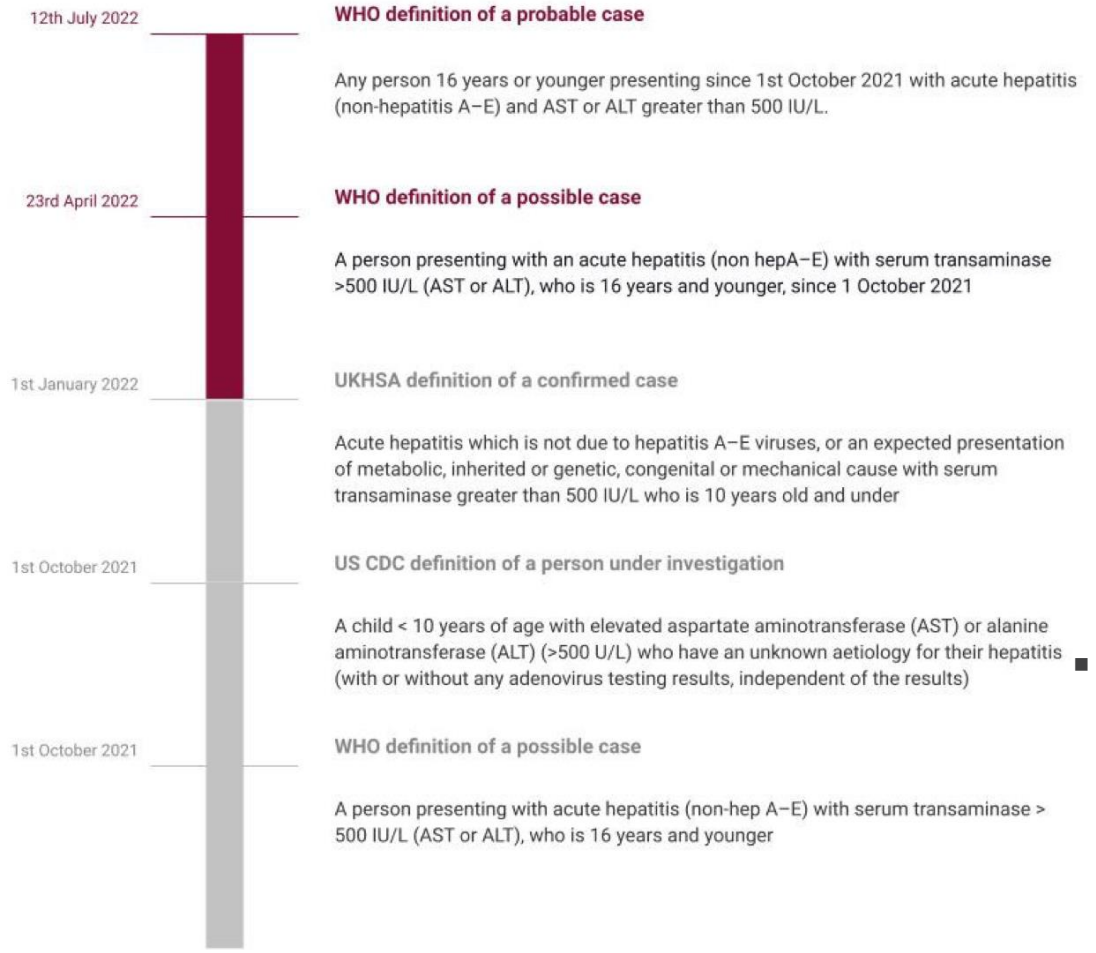


Figure 1. Timeline showing evolving definitions.

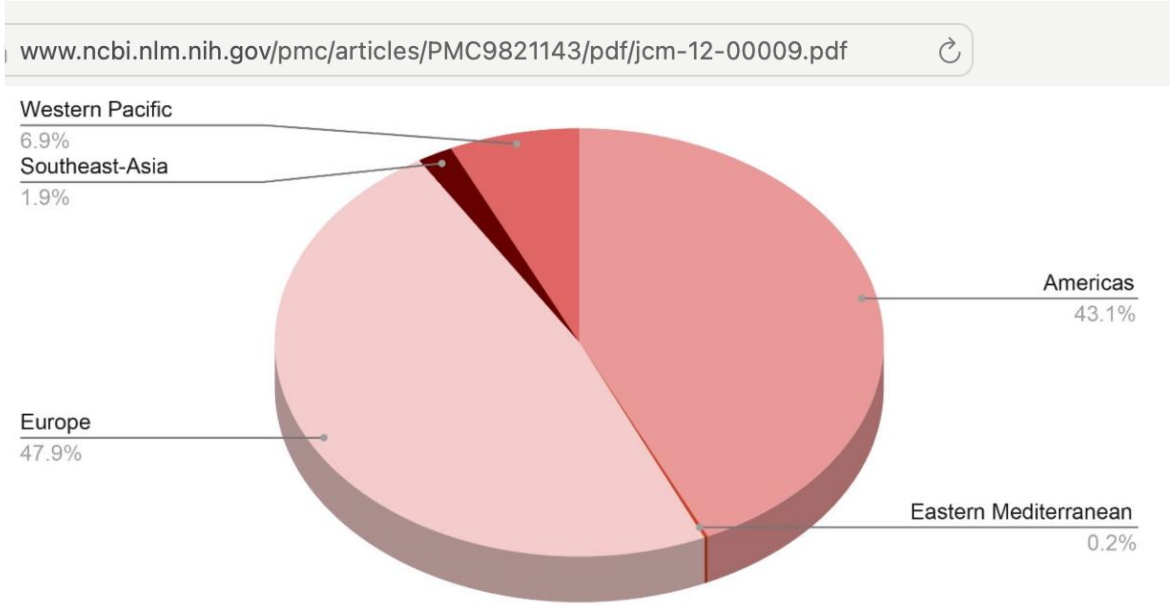
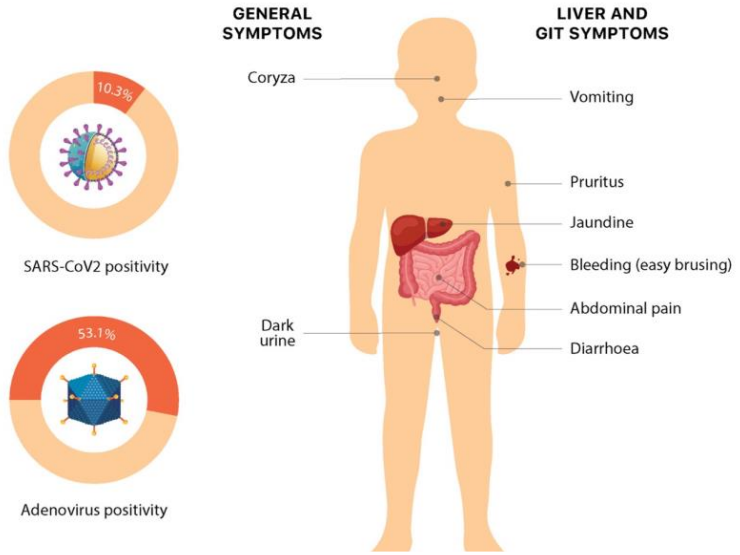


Figure 2. Distribution of probable cases of severe acute hepatitis of unknown origin across the WHO regions.



HYPOTHESIS

The emergence of novel SARS CoV2 virus led COVID-19 illness, a global pandemic as declared by World Health Organization (WHO) in early 2020, is accompanied by repeated and exuberant use of soap and alcohol-based sanitizers worldwide for cleaning the hands to curtail the virus transmission.

Alcohol-based sanitizing agents considered as potent virucidal agents against enveloped viruses, whereas non-enveloped viruses exhibited medium to high level of resistivity against these disinfectants.

Human innate cutaneous defense system i.e., RNases, an important barrier to prevent the entry of exogenous RNAs, may be compromised with these sanitizers and still be transmitting resilient non-enveloped enteric viruses such as adeno, hepatitis A virus and norovirus into the body.

The childrens are more prone for getting enteric viral infections because of typical playing/feeding habit and subsequent overreliance on alcohol-based sanitizers for cleaning the hands.

CONCLUSIONS

The possible linkage between COVID19 pandemic and emergence of frequent hepatitis A and acute hepatitis of unidentified etiology in children seems to increase enteric viral infections in the wake of overuse and reliance on alcohol-based hand sanitizers which are considered less effective against non-enveloped viruses.

Virus Category	Examples	Resistance to disinfectant
Enveloped virus	Herpes Simplex virus, Human Immunodeficiency virus (HIV), Influenza, Coronavirus	Low
Non-enveloped virus	Adenovirus, Poliovirus, Norovirus, Parvovirus, Enterovirus	Medium to high

PERSPECTIVE

SARS CoV2 infection is realized as an airborne infection, the unwarranted emphasis on alcohol-based sanitizers should now be guarded.

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HEPATIC TUBERCULOSIS: REAL WORLD EXPERIENCE FROM A TERTIARY CARE CENTRE

Souveek Mitra, MD,DM[1]; Ranajoy Ghosh, MD[1]; Dipankar Mondal, MD,DM[1] ;Srijan Majumdar MD,DM [1];Kishalaya MD,DM [1]; Abhijit Chowdhury MD,DM [2]

[1]Indian Institute of Digestive And Liver disease,, [2] IPGMER Kolkata

Introduction

Tuberculosis is an endemic communicable disease , in developing nations such as India . Despite being a preventable and curative disease more than a million people are affected with it , annually (1). Although , lung is the primary site of involvement , extrapulmonary tuberculosis accounts for about 15% of total cases ,globally . Abdominal tuberculosis, including liver is a common site for extrapulmonary involvement . Diagnosis of hepatic tuberculosis is a challenge , as the disease is usually paucibacillary ,causing very low yield for microbiological analysis . Coupled with that , nonspecific presentations that mimics various other disease , results in diagnostic confusions. Hepatic tuberculosis ,can also be a part of systemic involvement of tuberculosis.

Reed divided it into three forms: tuberculosis of the liver associated with generalized miliary tuberculosis, primary miliary tuberculosis of the liver, and primary tuberculoma or abscess of the liver (2)

Although ,microbiological yield from liver lesions are good , liver biopsy also has an excellent yield for granulomatous hepatitis (3). Hepatic tuberculosis should be considered in non-resolving liver abscess, hepatic space-occupying lesion(s) or infiltrative pattern of liver function tests with predominant alkaline phosphatase elevations.

In endemic countries like , India , tuberculosis is the most common cause of granulomatous liver disease (4).

In subjects suffering from chronic liver disease , concomitant tuberculosis might precipitate acute decompensation and can lead to further worsening of clinical status and might impact mortality . Also , concomitant active tuberculosis infection in cirrhotic patients , preclude liver transplantation. Anti tubercular therapy (ATT), might also lead to significant morbidity in form of ATT induced hepatoxicity , in those patients having underlying liver disease .

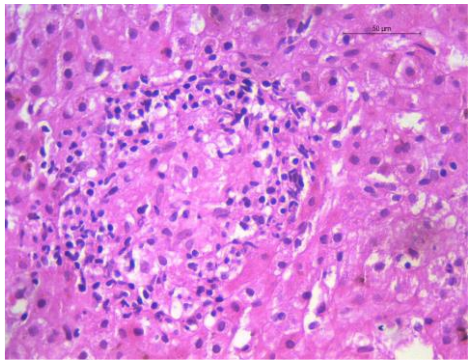

Figure 1. Tubercular Granuloma.

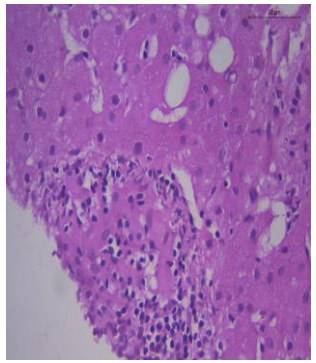

Figure 2. Tubercular Granuloma.

Methods and Materials

Retrospective analysis of all the cases , diagnosed as hepatic tuberculosis , at our institute , between , September 2018 to January 2023 , were done .

Diagnosis of hepatic tuberculosis were made if the patients fulfilled any of the following criteria's : i) Liver biopsy showing caseating granuloma , classical of tuberculosis
ii) Identification of acid fast positive(AFB) tubercle bacilli from liver biopsy or aspirate from any liver space occupying lesion .
ii)Positive culture for tuberculosis from any tissue /aspirate / pus obtained from liver .

All the subjects , diagnosed as hepatic tuberculosis were also assessed , regarding evidence of tuberculosis in other organs .

All demographic , biochemical data were analyzed . Subjects , having underlying evidence of liver disease were analyzed separately .

Results

Total number of subjects : 22 (Twenty two) . Male 16/ Female 6.
Mean Age : 53 years .
Underlying Comorbidity (%) : Diabetes (28%) / Cirrhosis (23%).
Aetiology of Cirrhosis (%) : Hepatitis B (20%) / Alcohol (40%) / NASH and cryptogenic (40%)

Index Presenting symptoms (Chart 1) : Most of the subjects asymptomatic either detected by isolated elevation of alkaline phosphatase (ALP) , or incidentally detected tubercular granuloma on liver biopsy . All preexisting cirrhotic subjects , presented as acute decompensation or ACLF like presentation . Those , who exhibited liver space occupying lesion (SOL) , 95% of them had a solitary SOL , rest had multifocal tuberculoma with evidence of extra abdominal involvement .

86% of the subjects underwent liver biopsies and tubercular granuloma was identified in all of them. Tubercular cultures were sent in 10% of the subjects , no growth yielded .

All 86% of the subjects that showed tubercular granuloma had no evidence of extrahepatic involvement .

Rest 14% of the subjects were identified via positive AFB ,and had evidence of disseminated tuberculosis.

Out of all the subjects three (3) expired during the study period , two of them were cirrhotic and presented with ACLF like syndrome , one subject presented with PUO, and had evidence of disseminated disease .

Mean time from symptom onset to start of antitubercular therapy : 6.8 months

Standard quadruple weight based anti tubercular therapy(ATT) regimen (HRZE) was offered to 27% of the subjects at initiation . Most of them were started on a modified regimen , with pyrazinamide being the most common drug to be substituted . Gradual titration of the drug dosage done based upon liver function tests .

63% of the total subjects could be put on first line therapy .
Mean treatment duration : 9.4 months

Chart 1. Presenting symptoms .

Discussion

we found that hepatic tuberculosis can exist as an isolated entity in a significant number of subjects .

Most of them might not have evidence of extrahepatic involvement or prior history of contact.

A significant chunk of subjects in our study were asymptomatic at presentation and required clinical acumen along with liver biopsy for diagnosis . Isolated elevation of ALP is the most common biochemical anomaly in the asymptomatic subjects.

Concomitant comorbidity can exist in about one fourth of the subjects and might worsen the outcome .

Tuberculosis can be an inciting factor of decompensation in cirrhotic subjects , even if there is no evidence of systemic tuberculosis .

All of our cirrhotic subjects presented with either acute decompensation or ACLF and had a significant poorer outcome , compared to non cirrhotic subjects .

Even in compensated cirrhotic , isolated hepatic tuberculosis can precipitate decompensation

Presence of diabetes , active alcohol use worsens the outcome in cirrhotic subjects .

Judicious use of antitubercular therapy is recommended for the therapy , due to the hepatotoxicity of the antitubercular drugs .

Individual weight-based regimen with gradual titration of the drug dosage ensured , first line therapy in most of the subjects .

Limitation of our study was relatively small sample size , retrospective analysis .

Being a single specialty tertiary care center there was significant referral bias .

Conclusions

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Even without evidence of systemic involvement , isolated hepatic tuberculosis is quite prevalent in endemic zone . Most of them being asymptomatic , judicious clinical judgement is required for the diagnosis . Liver biopsy showing classical caseating granuloma aids in diagnosis and should be offered to all subjects having high clinical suspicion of hepatic tuberculosis .

Outcome significantly worsens in , preexisting chronic liver disease subjects with tuberculosis acting as an inciting factor for decompensation and further worsening of clinical status .

Disseminated HSV-2 Hepatitis in a Liver Transplant Patient presenting as Fever of Unknown Origin

Kunal Elete DO, Machaiah Madhrira MD, Sridhar Allam MD, Ashraf Reyad MD, Randy Nguyen DO

Medical City Fort Worth

Introduction

Herpes simplex virus (HSV) is a rare cause of acute hepatitis with high mortality. Transplant recipients are at especially high-risk of opportunistic infections due to chronic immunosuppression. Here, we present a case of disseminated HSV-2 hepatitis in a liver transplant patient who presented with a fever of unknown origin (FUO).

Case Description

A 67-year-old female with a history of alcoholic cirrhosis s/p liver transplant (2017), and end-stage renal disease due to non-recovered hepatorenal syndrome s/p renal transplant (2022) initially presented with three-day history of recurrent fevers. The patient was initially hospitalized for 1 week due to FUO. While in the hospital, her fevers ranged from 100.4 °F to 102.6 °F. Her workup comprised of pan-cultures, a respiratory panel, and renal/liver allograft function testing were all negative. After treatment with empiric antibiotics (Vancomycin and Unasyn) and resolution of fevers, she was thought to have viral syndrome and discharged home on Augmentin.

However, symptoms recurred within 48 hours of improvement and she returned to the hospital. Additional workup included:

- Hepatitis panel
- Serologic testing for viral and fungal infections
- CT imaging of head/chest/abdomen
- Lumbar puncture
- Echocardiogram
- Gastroenterology consult for upper and lower endoscopies

Unfortunately, these were all unrevealing. While she continued to have persistent fevers, increases in serum creatinine and AST from initial values were noted (Graph 1). She also developed two ulcerated plaque lesions on her right thumb and lower abdomen. Given these developments, MRI of abdomen (Figure 1) and biopsy of skin lesions and kidney and liver transplants were pursued. Kidney biopsy was unremarkable. Liver allograft biopsy was positive for HSV hepatitis with extensive necrosis (Figure 2). Skin punch biopsies showed HSV infection as well (Figure 3) and serologic testing for HSV resulted positive for HSV-2 IgG and DNA PCR. She was started on IV Acyclovir at 10mg/kg with resolution of fevers, normalization of AST, and improvement of skin ulcers. On discharge, she was transitioned to oral Valacyclovir for an additional 3-6 months of therapy.

Figures & Results

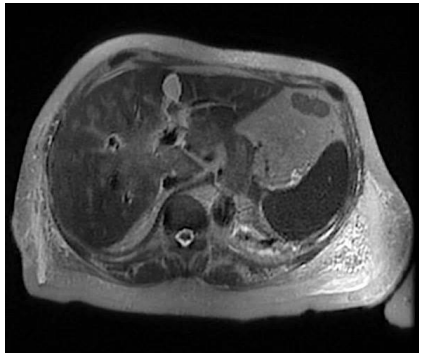


Figure 1: T2 MRI Abdomen showing heterogenous liver parenchyma with haziness somewhat more pronounced in the superior liver and centered around the vessels, which is favored to represent edema.

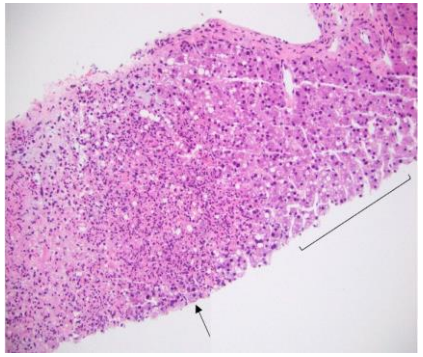


Figure 2: High magnification of liver biopsy with foci of acute inflammation and necrosis (arrow). Normal liver hepatocytes (bracket)

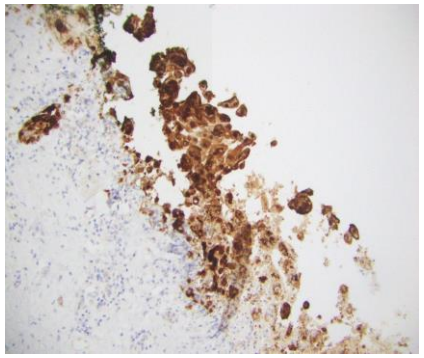
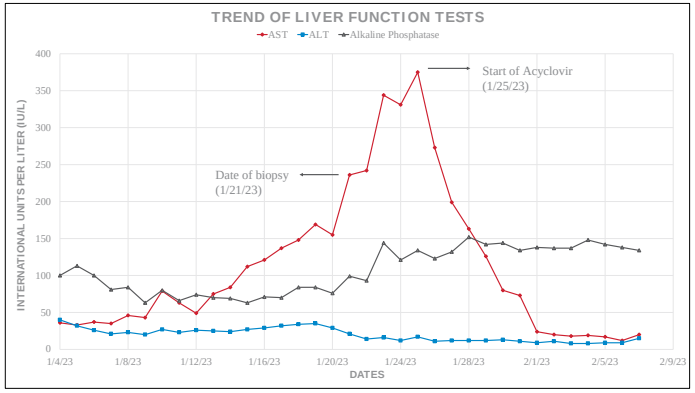


Figure 3: HSV 1-II immunostaining of skin punch biopsy



Graph 1: This graph depicts the trend of patient's LFTs. Her AST up-trended significantly up until and after biopsy. However, with treatment, her lab values returned to within normal range.

Discussion/Conclusion

Fever of unknown origin (FUO) is defined by recurrent temperatures exceeding 38.3°C over a span of at least three weeks, with no clear underlying cause identified following a one-week evaluation in the hospital. In addition to thorough medical history (travel, animal exposure, immunosuppression, drug/toxin use) and physical exam, initial laboratory tests should be used to rule out common infectious, inflammatory, autoimmune, and neoplastic causes. Further diagnostic tools include imaging studies, serologic assays, and biopsies along with collaboration with specialists. FUO can be challenging to diagnose, requiring a multidisciplinary and patient-centered approach to uncover its underlying etiology

HSV-2 typically causes genital herpes, but it can also cause systemic infections in immunocompromised hosts. **Hepatitis secondary to infection with HSV-1 or HSV-2 is a rare complication that can lead to acute liver failure (ALF)** if not promptly diagnosed and treated. In one study, HSV hepatitis occurred most frequently in the setting of disseminated herpes in solid organ transplant patients. Our patient was unusual with her fairly indolent course, whereas most of the literature describes patients with more fulminant courses. **Early recognition, diagnosis and initiation of treatment with IV Acyclovir can help prevent ALF.**

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HCA Healthcare

Validation of prognostic scores for predicting acute liver failure and in-hospital death in patients with dengue-induced severe hepatitis

Tongluk Teerasarntipan, Kessarin Thanapirom, Roongruedee Chaiteerakij, Piyawat Komolmit, Sombat Treeprasertsuk

Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

BACKGROUND

Acute liver failure (ALF) in dengue is rare but fatal. MELD score was generally used in predicting liver-related prognosis. However, the complex calculation might limit its applicability. Recently, simple prognostic scores, including the ALBI, EZ-ALBI and PALBI scores, have been developed in determining prognosis in various aspects of liver injury. Therefore, we aimed to validate prognostic scores for predicting ALF and in-hospital mortality in patients with dengue-induced severe hepatitis (DISH).

METHODS

We retrospectively reviewed 2,532 serology-confirmed hospitalized adult dengue patients during the 16-year study period (2007-2022) at the King Chulalongkorn Memorial Hospital, Thailand. Patients with DISH [n=193 (7.62%)], defined as transaminases > 10 times from the normal reference level, and DISH with subsequent ALF, defined by the EASL 2017 criteria, were included.

Univariate regression analysis was used to identify potential factors associated with adverse outcomes. Youden's index in conjunction with receiver operating characteristics (ROC) analysis was used to determine the best cut-off value of prognostic scores in predicting ALF and in-hospital death and area under ROC (AUROC) curves were compared using a paired data nonparametric ROC curve estimation.

RESULTS

Figure 1 AUROC curves of prognostic scores predicting ALF from DISH

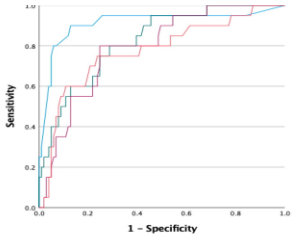
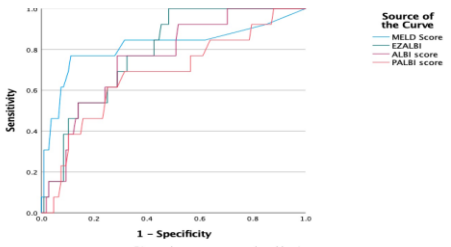


Figure 2 AUROC curves of prognostic scores predicting in-hospital death from DISH



Of the 193 DISH patients, 20 patients developed ALF (0.79%). Mortality rates in patients with ALF and without ALF were 60.0% (12/20) and 0.58% (1/173), respectively. Regression analysis showed that INR, bilirubin, albumin, and creatinine were independent laboratory markers associated with ALF and death.

Liver prognostic scores (MELD, EZ-ALBI, ALBI, PALBI scores) had excellent performance predicting adverse outcome from DISH. (Table 1) A paired sample ROC curve estimation showed non-different performance between MELD score and EZ-ALBI score, in predicting ALF (z=1.688, p=0.091, 95%CI of -0.014-0.194) and in-hospital death (z=0.322, p=0.747, 95%CI -0.141-0.197).

Table 1 Diagnostic performance of each prognostic score in predicting acute liver failure and in-hospital death in patients with dengue-induced severe hepatitis

Scores	Acute Liver Failure					In-hospital Death				
	AUROC	P value	Cut-off	Sn (%)	Sp (%)	AUROC	P value	Cut-off	Sn (%)	Sp (%)
MELD	0.917	<0.001	15	90.0	88.4	0.823	<0.001	18	76.9	89.1
EZ-ALBI	0.835	<0.001	-30	80.0	72.7	0.808	<0.001	-30	76.9	69.3
ALBI	0.806	<0.001	-2.00	80.0	77.4	0.799	0.001	-2.00	76.9	74.3
PALBI	0.785	<0.001	-0.78	75.0	78.0	0.699	0.018	-0.81	69.2	71.2

CONCLUSIONS

MELD score was the best predictor of ALF and death in DISH patients. EZ-ALBI score, a simple and easy-to-use score, had excellent predictive performance and therefore might be considered as an alternative tool to predict prognosis in dengue patients.

There is no conflict of interest to declare.

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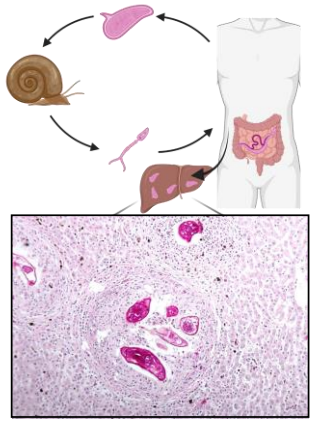


Fig. 1: Life cycle of *S. mansoni*
PAS staining of eggs in liver tissue of *S. mansoni*-infected hamsters.

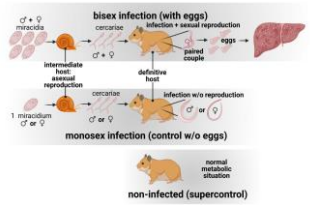


Fig. 2: Hamster infection model
Infection of hamsters with *S. mansoni* cercariae of both sexes (bs-infection) or with clonal cercariae of one sex (ss- infection) in order to compare egg-induced vs. worm-only effects[4].

Introduction

Schistosomiasis is one of the most common parasitic infections of humans worldwide with at least 236 million people that required preventive treatment in 2019[1]. The eggs of *Schistosoma mansoni* induce chronic liver inflammation. We have previously shown that *S. mansoni* eggs and soluble egg antigens (SEA) induce metabolic exhaustion and a strong redox imbalance, which is critical for hepatocellular DNA integrity[2,3]. However, the impact of egg-induced oxidative stress for the regulation of cell cycle remains elusive[4].

Methods

Female hamsters (n=5) were infected either with both genders (bisex, bs; producing eggs) or unisexual *S. mansoni* cercariae (single-sex, ss; no eggs produced) or non-infected (ni, control) as shown in Fig. 2. Liver tissue of these hamsters was investigated by western blotting and qRT-PCR. HepG2 cells were treated with SEA and/or the ROS scavenger L-gluthation (GSH). Human liver biopsy of a *S. mansoni*-infected patient was stained for cyclin D1 by IHC. Cartoons created with biorender.

Results

Analysis of mRNA expression levels showed that *S. mansoni* infection induced a strong upregulation of hepatic *Mcm 7* in bisex-infected hamsters (bs; final host infections with both schistosome genders), in which massive egg production occurs due to the presence of couples (Fig. 3A). Fig. 3 B shows that SEA caused an elevation of the *Mcm7* mRNA level in HepG2 cells.

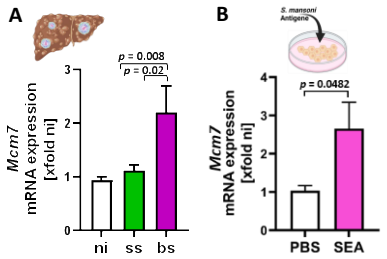


Fig. 3: *S. mansoni* infection modulated the expression of hepatic replication licensing.
Expression of hepatic *Mcm7* was significantly upregulated in *S. mansoni* bs-infected livers (A) and HepG2 cells treated with *S. mansoni* SEA (B).

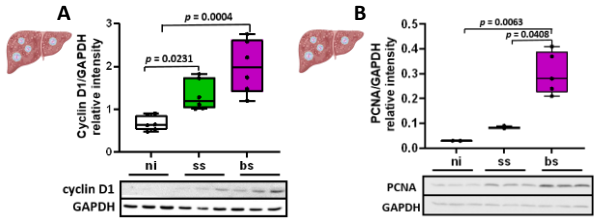


Fig. 4: *S. mansoni* infection modulates hepatic Cyclin D1 and PCNA
Hepatic Cyclin D1 (A) and PCNA (B) were strongly upregulated in livers of bs-infected hamsters as demonstrated by western blot analysis.

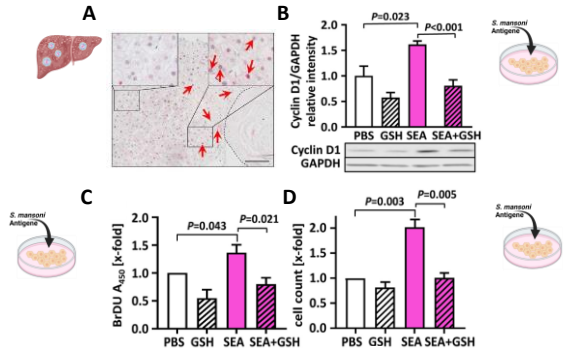
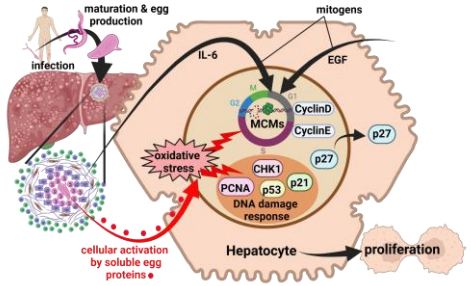


Fig. 5: Hepatocellular oxidative stress caused aberrant proliferation upon *S. mansoni* infection
(A) Cyclin D1 staining in nuclei of perigranulomatous hepatocytes in a patient infected with *S. mansoni.* (B-D) HepG2 cells treated with SEA and/or GSH were analysed by westernblotting for Cyclin D1 and cell proliferation (C-D).

Cyclin D1, a key player that controls the transition from G1 to S phase, was strongly elevated by *S. mansoni* infection (Fig. 4 A). The expression level of hepatic PCNA, which serves as master coordinator of DNA replication and repair, was also enhanced upon *S. mansoni* infection, most significantly upon bs-infection (Fig. 4 B). Immunohistochemistry analysis with liver tissue of a patient infected with *S. mansoni* also provided evidence of hepatocellular nuclear Cyclin D1 accumulation (Fig. 5 A). Finally, the addition of GSH diminished SEA-induced Cyclin D1 to control levels (Fig. 5B). Furthermore, SEA-induced proliferation was inhibited by GSH in HepG2 cells (Fig. 5 C-D).

Conclusion

Our study provides evidence that cell proliferation is triggered in hepatocytes by *S. mansoni* egg antigen-induced oxidative stress. By using livers of single-sex-infected hamsters as controls containing no eggs and *in vitro* experiments with egg antigens, we were able to demonstrate that *S. mansoni* egg secreting factors are responsible for interfering with the hepatic replication process.



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Mail: verena.von-buelow@innere.med.uni-giessen.de, phone +49 641 9941561