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MORTALITY RATES AMONG PATIENTS SUCCESSFULLY TREATED FOR HEPATITIS C: A REALWORLD MULTINATIONAL COHORT STUDY

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BACKGROUND/AIM

Interferon-free DAAs have transformed the treatment of chronic hepatitis C infection, treatment is successful in more than 95% of patients. Patients who are successfully treated show better health outcomes than untreated patients (eg, liver disease progression, HCC, diseases outside the liver). HCV cure with SVR following DAA treatment reduces mortality risk, but data on risk factors associated with mortality following DAA-associated SVR are sparse.

We aimed to quantify mortality rates and risk factors associated with mortality for patients with DAA-associated SVR.

METHOD

Study Design:

- Open label observational chart review registry for retrospective analysis.
- The primary outcome was mortality after DAA-SVR12.

Study Population:

- **10,034** CHC patients receiving IFN-free DAA from 39 REAL-C clinical sites from the Western Pacific region, North America and Europe.
- Any genotypes CHC patients with or without cirrhosis and prior treatment history received DAA and achieved SVR12.

Inclusion criteria

- Any ethnicity
- Adult >18 years old
- IFN-free DAAs treatment between 07/012017-07/012021 and achieved SVR12

Exclusion criteria

- Recipient of solid organ transplantation before DAA treatment
- Significant immunosuppression agents within 3 months of the initiation with IFN-free DAA regimens
- HBV or HIV co-infection
- Baseline HCC and developed HCC within six months end of treatment.

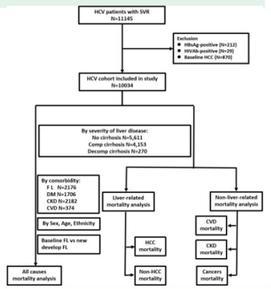


Figure 1. Analysis of mortality outcomes in HCV patients with SVR. In total, 10,034 patients who were successfully treated for HCV were included in the analysis including 5,611 non-cirrhosis, 4,153 compensated and 270 decompensated cirrhosis.
HCV: Hepatitis C virus; DAA: Direct-acting antiviral; DM: Diabetes mellitus; CKD: Chronic kidney disease; CVD: Cardiovascular disease

RESULTS

Totally, 491 (4.9%) death for analysising all causes mortality, and liver and non-liver-related mortality during mean 4.7 years follow-up after SVR.

Table 1. Baseline characteristics of HCV patients with SVR after DAA treatment.

Characteristics	Overall population (n=10,034)	No-Cirrhosis (n=5,611)	Compensated cirrhosis (n=4,153)	Decompensated cirrhosis (n= 270)
Age, year	62.5±12.9	59.8±13.6	66.1±11.2	61.3±10.1
Male, n (%)	4,767 (47.5)	2,779 (49.5)	1,835 (44.2)	153 (56.7)
Ethnicity, n (%)				
Asian	9040 (90.1)	5162 (92.0)	3721 (89.6)	157 (58.2)
Asian from Asia	8609 (85.8)	4883 (87.0)	3585 (86.3)	141 (52.2)
Asian American	431 (4.3)	279 (5.0)	136 (3.3)	16 (5.9)
Non-Asian	994 (9.9)	449 (8.0)	432 (10.4)	113 (41.9)
Regions, n (%)				
East	8,612 (85.8)	4885 (87.1)	3,586 (86.4)	141 (52.2)
West	1,422 (14.2)	726 (12.9)	567 (13.7)	129 (47.8)
Fatty liver, n (%)	2176 (22.1)	1179 (21.5)	953 (23.3)	44 (16.5)
Diabetes mellitus, n (%)	1,706 (17.7)	764 (14.3)	869 (21.6)	73 (29.6)
CKD,	2,182 (23.9)	1,123 (22.8)	1,006 (25.5)	53 (21.2)
CVD, n (%) (n=6,013)	374 (6.2)	186 (5.6)	172 (7.0)	16 (6.8)
Follow-up years	4.7±2.5	4.6±2.4	4.9±2.5	4.1±2.2
Follow-up person-years	47102	25621	20381	1099

Comorbidity: 21.7% patients with fatty liver, 17% diabetes mellitus, 21.7% chronic kidney disease; 3.7% cardiovascular disease. Mortality: 491 (4.9%) participants died during mean 4.7 years follow-up after SVR.

Table 2. Factors associated with mortality among HCV patients with SVR.

Factors	Category	Univariate Analysis Hazard Ratio (95% CI)	P Value	Multivariate Analysis Hazard Ratio (95% CI)	P Value
Age, years	< 45	1 (Referent)		1 (Referent)	
	45-65	3.71 (1.9-7.26)	<0.001	1.57 (0.79-3.11)	0.20
	>65	5.98 (3.08-11.6)	<0.001	3.25 (1.63-6.45)	<0.001
Sex	Female	1 (Referent)		1 (Referent)	
	Male	1.34 (1.12-1.6)	<0.001	1.50 (1.20-1.89)	<0.001
Ethnicity	Asian from Asia	1 (Referent)		1 (Referent)	
	Asian American	1.62 (1.01-2.61)	0.045	1.41 (0.86-2.33)	0.17
	Non-Asian	2.76 (2.19-3.48)	<0.001	2.12 (1.55-2.89)	<0.001
Liver fibrosis	Non cirrhosis	1 (Referent)		1 (Referent)	
	Compensated cirrhosis	2.07 (1.7-2.52)	<0.001	1.81 (1.39-2.37)	<0.001
	Decompensated cirrhosis	10.45 (7.84-13.93)	<0.001	7.58 (5.35-10.74)	<0.001
Fatty liver	No	1 (Referent)		1 (Referent)	
	Yes	0.81 (0.64-1.01)	0.07	0.83 (0.61-1.13)	0.24
DM	No	1 (Referent)		1 (Referent)	
	Yes	1.85 (1.52-2.25)	<0.001	1.53 (1.20-1.95)	<0.001
CKD	No	1 (Referent)		1 (Referent)	
	Yes	1.47 (1.21-1.79)	<0.001	1.26 (0.97-1.64)	0.08
CVD	No	1 (Referent)		1 (Referent)	
	Yes	1.95 (1.41-2.69)	<0.001	1.41 (0.99-2.00)	0.050

In multivariable analyses:
older age (>65 years: 3.25 times),
male (1.5 times),
fibrosis severity (7.6/1.8 times for decom/compensated cirrhosis),
baseline DM (1.5 3times),
Non-Asian (2.12 times)
were significantly associated with higher mortality.

Table 3. Incidence rates for all cause mortality outcomes in DAA-SVR patients with chronic hepatitis C by severity of liver disease, comorbidity and ethnicity.

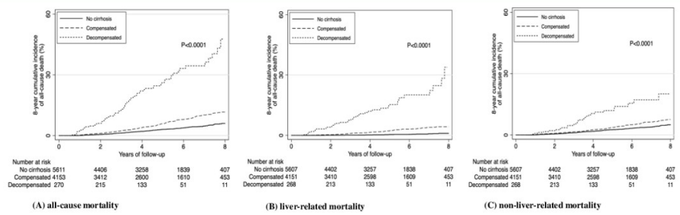
	Patient	Event	Incidence rate per 1000 patient-years(95%CI)	*P* value	3-years survival	5-years survival	*P* value
Total Mortality for Overall Patients	10034	491	10.4 (9.66-11.4)		97.8 (97.6-98.3)	95.1 (94.5-95.6)	
No baseline cirrhosis	5611	158	6.2 (5.3-7.2)	<0.0001	98.8 (98.4-99.1)	97.0 (96.4-97.5)	<0.0001
Compensated cirrhosis	4153	267	13.1 (11.6-14.8)		97.6 (97.0-98.1)	94.1 (93.2-94.9)	
Decompensated cirrhosis	270	66	60.0 (47.2-76.4)		87.5 (82.4-91.1)	73.9 (67.0-79.5)	
Fatty liver	7675	383	10.6 (9.6-11.8)	0.07	97.9 (97.5-98.2)	95.0 (94.4-95.6)	0.29
Fatty liver	2176	93	8.8 (7.2-10.8)		98.3 (97.6-98.8)	95.7 (94.5-96.6)	
Non-diabetes mellitus	7919	340	9.1 (8.2-10.1)		98.3 (98.0-98.6)	95.7 (95.1-96.2)	<0.0001
Diabetes mellitus	1706	142	17.2 (14.6-20.2)		96.1 (95.0-97.0)	92.1 (90.5-93.5)	
Non-chronic kidney disease	6952	301	9.4 (8.4-10.6)	<0.0001	98.1 (97.7-98.4)	95.3 (94.7-95.9)	0.02
Chronic kidney disease	2182	149	14.0 (11.9-16.5)		97.6 (96.8-98.2)	93.8 (92.4-94.9)	
	5639	289	12.3 (10.9-13.8)	<0.0001	97.8 (97.4-98.2)	94.3 (93.5-95.1)	0.0002
Cardiovascular disease	374	42	24.8 (18.3-33.6)		95.2 (92.2-97.1)	88.9 (84.4-92.2)	
Asian from Asia	8609	384	9.2 (8.3-10.1)	<0.0001	98.2 (97.8-98.4)	95.6 (95.0-96.1)	<0.0001
Asian American	431	18	12.5 (7.9-19.8)		98.2 (95.7-99.3)	94.1 (89.2-96.9)	
Non-Asian	994	89	23.4 (19.0-28.7)		96.1 (94.3-97.3)	89.8 (86.9-92.1)	

- The overall mortality is **10.4** per 1000 patient-years, all-cause mortality rates per 1000 person-years of **6.2, 13.1,** and **60.0** for patients non-cirrhosis, compensated and decompensated cirrhosis, respectively.
- The 3-years and 5-years overall survival of overall cohort were 97.8 (97.6-98.3) and 95.1 (94.5-95.6).
- Patients with decompensated cirrhosis have lowest 3-years (87.5%) and 5-years (73.9%) survival.

Table 4. Incidence rates for all cause mortality outcomes in patients by severity of liver disease and by sex, age and diabetes mellitus.

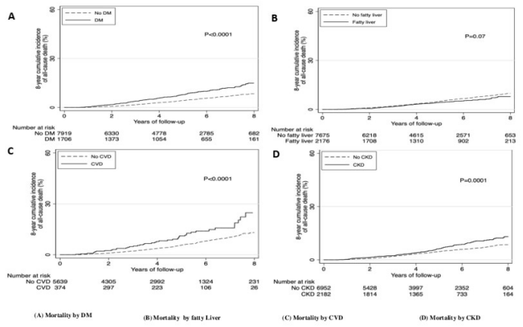
			No cirrhosis			Compensated cirrhosis			Decompensated		
Sex	Diabetes mellitus	Age	No. of pts	No. of deaths	Incidence rate per 1000 patient-years (95%CI)	No. of pts	No. of deaths	Incidence rate per 1000 patient-years (95%CI)	No. of pts	No. of deaths	Incidence rate per 1000 patient-years (95%CI)
Male	No	Age<65	1,516	26	4.1 (2.8-6.1)	643	27	9.3 (6.4-13.5)	69	20	71.9 (46.4-111.4)
		Age≥65	730	40	11 (8.0-14.9)	700	59	16.4 (12.7-21.2)	28	4	33.2 (12.5-88.5)
	Yes	Age<65	188	9	10.2 (5.3-19.6)	201	8	8.7 (4.3-17.3)	35	12	87.2 (49.5-153.5)
		Age≥65	219	22	21.3 (14.1-32.4)	250	27	21.5 (14.8-31.4)	7	3	95.9 (30.9-297.3)
Female	No	Age<65	1,265	9	1.6 (0.8-3.0)	644	27	8.8 (6.0-12.8)	44	9	49.1 (25.5-94.3)
		Age≥65	1,083	34	6.4 (4.6-9.0)	1,164	80	13.3 (10.7-16.6)	33	5	34.4 (14.3-82.6)
	Yes	Age<65	145	2	2.8 (0.7-11.2)	144	11	14.6 (8.1-26.3)	17	6	83.5 (37.5-185.8)
		Age≥65	212	14	13.0 (7.7-21.9)	274	22	16.4 (10.8-24.9)	14	6	120.7 (54.2-268.7)

Female without cirrhosis and DM and aged <65 years old have a lowest mortality of 1.6 per 1000 patient-years. However, patients with decompensated cirrhosis and DM and aged >65 years old have a highest mortality of 95.9-120.7 per 1000 patient-years.



(A) all-cause mortality (B) liver-related mortality (C) non-liver-related mortality

Figure 2. The 8-year estimated cumulative incidence of mortality is 6.0%, 11.6% and 47.7% for non-cirrhosis, compensated and decompensated cirrhosis patients with DAA-SVR.



(A) Mortality by DM (B) Mortality by fatty Liver (C) Mortality by CVD (D) Mortality by CKD

Figure 3. Kaplan-Meier curves on all cause mortality among DAA-SVR HCV patients by comorbidity. Baseline diabetes mellitus, cardiovascular disease , chronic kidney disease, but not fatty liver associated with higher risk of all causes mortality.

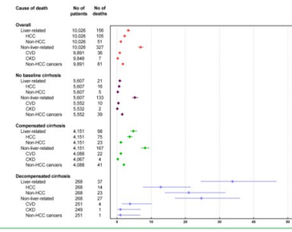


Figure 4. Liver and non-liver mortality outcomes in DAA-SVR patients by severity of liver disease. Non-liver related mortality (5.2-8.2 per 1000 patient-years) is the main cause of death in patients without cirrhosis and compensated cirrhosis, however, the liver related mortality (33.8 per 1000 patient-years) is the main cause of death in patients with decompensated cirrhosis.

CONCLUSIONS

- Patients with SVR after DAAs face different risks of death. with mortality strongly influenced by pre-DAA liver disease severity.
- Baseline factors including advanced age, male, cirrhosis, no-Asian and DM associated with mortality after DAA-SVR.
- The 8-year estimated cumulative incidence of mortality is 6.0%, 11.6% and 47.7% for non-cirrhosis, compensated and decompensated cirrhosis patients with DAA-SVR.
- Non-liver related mortality is the main cause of death in patients without cirrhosis and compensated cirrhosis, however, the liver related mortality is the main cause of death in patients with decompensated cirrhosis.

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