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ORIGINAL ARTICLE

Liver and cardiovascular mortality after hepatitis C virus eradication by DAA: Data from RESIST-HCV cohort

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Abstract

Real-world evidence on the course of Hepatitis C Virus (HCV) chronic liver disease after Sustained Virologic Response (SVR) obtained with direct-acting antiviral drugs (DAAs) are still limited, and the effects on mortality remain unclear. We evaluated the post-treatment survival of 4307 patients in the RESIST-HCV cohort (mean age 66.3 ± 11.6 years, 56.9% males, 24.7% chronic hepatitis, 66.9% Child-Pugh

Abbreviations: AEs, adverse events; CKD, chronic kidney disease; CP, Child-Pugh score; CV, cardiovascular deaths; DAAs, direct-acting antiviral drugs; EGS, oesophageal gastroscopy; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ITT, intention to treat analysis; LR, liver-related; mITT, modified intention to treat analysis; PSE, portosystemic encephalopathy; SVR, sustained virologic response.

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A cirrhosis and 8.4% Child-Pugh B cirrhosis) treated with DAAs between March 2015 and December 2016 and followed for a median of 73 weeks (range 16–152). Proportional cause-specific hazard regression for competing risks was used to evaluate the survival and to assess the predictors of liver and cardiovascular death. Overall, 94.7% of patients achieved SVR while 5.3% were HCV RNA-positive at last follow-up. Sixty-three patients (1.4%) died during the observation period. SVR was associated with a decreased risk of liver mortality (hazard ratio,HR0.09, beta −2.37, $p < .001$). Also, platelet count (HR 0.99, beta-0.01, $p = .007$) and albumin value (HR 0.26, beta −1.36 $p = .001$) were associated with liver mortality by competing risk analysis. SVR was associated with a reduced risk of cardiovascular mortality regardless of presence of cirrhosis (HR 0.07, beta-2.67, $p < .001$). Presence of diabetes (HR 3.45, beta 1.24, $p = .014$) and chronic kidney disease class ≥3 (HR 3.60, beta 1.28, $p = 0.016$) were two factors independently associated with higher risk of cardiovascular mortality. Patients with SVR to a DAA therapy have a better liver and cardiovascular survival, and the effects of HCV eradication are most evident in patients with compensated liver disease.

KEYWORDS
chronic hepatitis, cirrhosis, competing risks, survival

1 | INTRODUCTION

Globally, 71 million people live with chronic hepatitis C virus (HCV) infection[1] and a significant proportion of these are at risk of developing cirrhosis.[2] Patients with HCV cirrhosis have a risk of 2 to 5% and 3 to 6% per year to develop hepatocellular carcinoma (HCC) and liver decompensation, respectively.[3–5] Liver decompensation increases the risk of death to 15–20% per year.[6,7] Patients with HCV infection, especially those with diabetes, are also at increased risk of death due to cardiovascular disease.[8–11]

HCV infection can be eliminated through the use of direct-acting antiviral (DAA) drugs,[12,13] a treatment indicated for all patients, even those with decompensated cirrhosis.[14–16] Several real-world studies have demonstrated that patients with chronic HCV achieving a sustained virologic response (SVR) with interferon-based or DAA treatment are at lower risk of developing liver complications.[17–23] However, these studies failed to offer clear conclusions about the effects of SVR on clinical end points such as liver transplantation and mortality.[24,25] In this rapidly evolving scenario, it is necessary to demonstrate that treatment provides benefit for individual patients as well as general utility at the population level[26] to justify expansion of treatment and efforts for global elimination of HCV infection.[27]

Here, we report the results of a large prospective observational real-world cohort study, in order to assess the rate of disease outcomes and overall survival in patients with chronic HCV disease treated with DAAs, to analyse the rate of liver-related (LR) and cardiovascular (CV) deaths, and to identify risk factors associated with mortality, thereby stratifying patients according to their stage of liver disease.

Significance Statement

Direct-acting antiviral agents (DAAs) increase the likelihood of HCV clearance in all patients, even those with advanced liver disease. Several real-world studies have demonstrated that sustained virologic response (SVR) is associated at lower risk of developing liver complications. This large prospective observational real-world cohort study evaluated the rate of liver-related and cardiovascular deaths in HCV patients treated by DAAs, and identified the risk factors associated with mortality. The results of our analysis confirmed that patients with SVR have a better liver and cardiovascular survival and the effects of HCV eradication are most evident in patients with compensated liver disease.

2 | PATIENTS AND METHODS

As previously reported,[20] the Sicily network for therapy of patients with chronic HCV infection (RESIST-HCV, REte SIcilia Selezione Terapia-HCV) comprises a web-based regional database approved by the regional sanitary authority since March 2015. Registration of clinical and virologic data into the RESIST-HCV database was mandatory before DAA treatment could begin in any of the 22 authorized academic and community liver centres, and each patient at first contact with the liver centre signed their informed consent allowing

for use of all registered data. The database included information on liver disease stage, diabetes, arterial hypertension, chronic kidney disease (CKD) stage, cardiovascular diseases, virologic characteristics, DAA regimens, adverse events (AEs), SVR and disease outcomes, including mortality and cause of death after DAA treatment.

A diagnosis of cirrhosis was defined as meeting at least one of the following clinical criteria: a previous liver biopsy with stage 4 fibrosis by METAVIR score and/or the presence of oesophageal and/or gastric varices at oesophageal gastroscopy (EGS) and/or a liver stiffness 12 KPa by Fibroscan.[28] Serum values of bilirubin, albumin, international normalized ratio (INR) and platelets were included in the database, and the Child-Pugh (CP) score was used to indicate functional class of cirrhosis. The database included the diagnosis of diabetes, arterial hypertension, the cause of cardiovascular diseases (coronary heart diseases and cerebrovascular diseases by International Classification of Diseases), the evaluation of CKD stage based on the glomerular filtration rate (GFR) and therapies indicated for the co-morbidity.

Physicians at each RESIST-HCV centre established the DAA treatment and use of ribavirin according to European Association for the Study of the Liver recommendations[14] and Italian Drug Agency criteria.

Regional health authorities requested serum HCV RNA results 12 weeks after the end of therapy to evaluate SVR. Clinical follow-up and HCC surveillance were performed every 6–12 months as suggested by guidelines.[29] The recording of virologic and clinical data was performed by four expert clinical monitors together with the physicians at 22 RESIST-HCV centres.

Physicians recorded data about diagnosis of HCC, complications of liver disease, causes of LR and CV death on the web platform. Patients who did not attend clinical control were called by telephone in order to verify the occurrence of liver events. For patients who were not reachable by telephone, clinical data and/or cause of death were obtained from the Regional Office of Health responsible for the epidemiologic survey in Sicily. Patients who did not have any clinical data were considered dropouts and were censored at the last available visit.

2.1 | Statistical analysis

We analysed the records of all patients included in the RESIST-HCV database from 1 March 2015 to 31 December 2016, in order to evaluate all patients who had concluded the antiviral therapy, had been evaluated for SVR and had a clinical follow-up to assess the difference in the incidence of events between patients who had or did not achieve the SVR. Data were transferred from the web platform to an Excel database using an automatic procedure and statistical analyses were performed using both SPSS and R software. The follow-up time of patients who did not respond to DAA therapy or who showed a relapse after the end of treatment was censored until the start of a second DAA treatment. Patients with previous diagnosis of HCC or liver transplant and patients with hepatitis B and/or human immunodeficiency virus co-infection were excluded from analysis. We performed an intention to treat (ITT) analysis to evaluate therapeutic efficacy in the entire population. To evaluate the effect of SVR on disease events, we applied a modified ITT (mITT) analysis which assessed only patients who completed therapy and follow-up.[30] Patients with SVR were compared to patients who did not achieve SVR.

Data for continuous variables are presented as mean and SD or as median and range, and data for categorical variables are presented as frequency and percentage. Differences between continuous data were analysed by Student's *t* test. Chi-squared tests with Yates' continuity correction were used for dichotomous or categorical variables. A *p*-value <.05 was considered statistically significant.

Univariate Cox regression analysis was used to identify baseline variables such as age, sex, body mass index, bilirubin, albumin, international normalized ratio (INR), platelets, diagnosis of arterial hypertension, cardiovascular diseases, diabetes, CKD stage 3 and SVR associated with LR and CV. The proportional cause-specific hazard model was fitted in order to estimate the effect of covariates on the risk of LR mortality, while CV mortality was considered as a competing risk and vice versa. The cause-specific hazard distribution for LR or CV mortality estimates the effect of covariates on the rate at which events occurred in subjects who were event-free until a given point of follow-up.[31] Moreover, the proportional sub-distribution hazard model by Fine and Gray was fitted in order to estimate the effect of covariates on the cumulative incidence of LR or CV mortality, while CV or LR mortality was respectively considered as a competing risk.[32]

Covariates used for multivariate analyses included SVR, platelet count, albumin, bilirubin, INR, body mass index, CKD stage 3, diagnosis of cardiovascular diseases and diabetes. They were chosen based on their significance in the Cox univariate analysis ($p < .10$). Variables in the final model with a *p*-value <.05 were considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics of patients

From March 2015 to December 2016, 5153 patients were added to the RESIST-HCV database. Of these patients, 691 (13.4%) were excluded from analysis because they had a previous diagnosis of HCC (199 patients) or had received a liver transplant (299 patients) or had HBV and/or HIV co-infection (193 patients). Among the 4462 patients evaluated at baseline, 116 (2.6%) were excluded because they lacked an SVR assessment; 14 (0.3%) because they had withdrawn from therapy due to AEs; and 25 (0.6%) because they had died during therapy or before SVR evaluation (Figure 1). Rates of SVR by ITT analysis and rates of dropout or death during therapy according to baseline liver disease stage are shown in Supplementary Table S1.

The analysis to evaluate LR and CV mortality was performed on 4307 patients who had all completed the full course of DAA regimen, had available SVR data, and underwent follow-up after treatment (Table 1). Chronic hepatitis was diagnosed in 1064 (24.7%) patients,

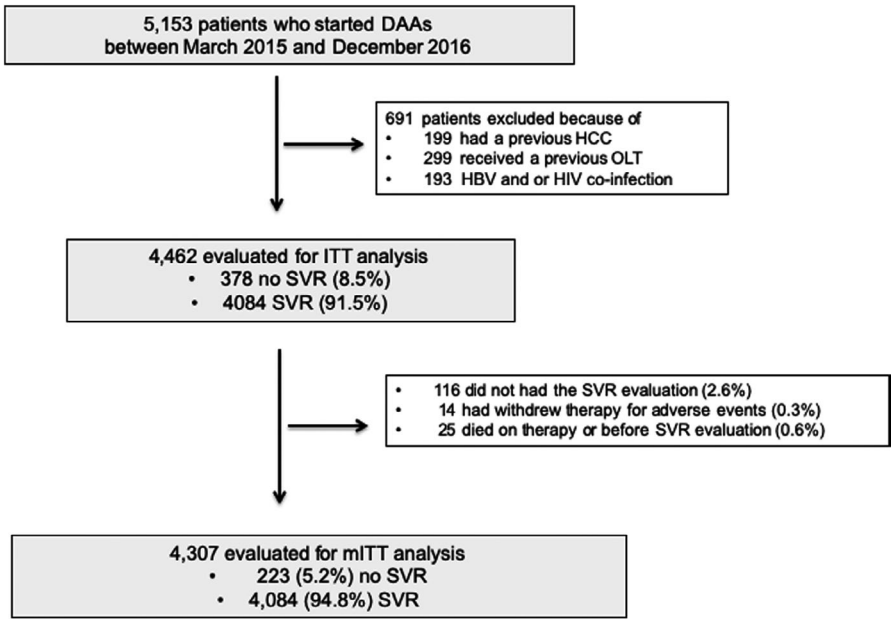

FIGURE 1 Flow-chart of the RESIST—HCV cohort

CP class A cirrhosis in 2883 (66.9%), and CP class B cirrhosis in 360 (8.4%). Mean age was significantly lower in patients with chronic hepatitis as compared to patients with CP-A and CP-B cirrhosis (63.3, 67.4, and 66.6 years, respectively, $p < .001$). The rate of male gender was similar across the three groups (56.4%, 57.1% and 57.2%, respectively, $p = .79$) and the most frequent HCV genotype was 1b in all stages of disease (69.5%, 70.3%, and 70.8%, respectively, $p = .49$). As expected, mean platelet count, albumin, bilirubin and INR values were significantly different according to stage of liver disease. The prevalence of diabetes, arterial hypertension and cardiovascular diseases were significantly lower in patients with chronic hepatitis as compared to those with CP-A and CP-B cirrhosis ($p < .001$, $p = .006$ and <.001, respectively). Even the prevalence of CKD stage ≥3 was significantly lower in patients with chronic hepatitis as compared to those with cirrhosis ($p = .025$).

3.2 | Virologic response to DAAs

According to the modified ITT analysis, SVR was achieved in 4084 of the 4307 examined patients (94.8%) while 223 (5.2%) remained HCV RNA-positive at the last clinical control. There was a significant difference in SVR rates between patients with chronic hepatitis and those with CP-A and CP-B cirrhosis (96.5%, 94.9%, and 88.9%, respectively; $p < .001$; chronic hepatitis vs. CP-A cirrhosis $p = .035$; CP-A vs. CP-B cirrhosis $p < .001$). Baseline clinical and viral features according to virological response are shown in Table 2.

3.3 | Liver disease outcomes

One hundred eighty-three patients (4.2%) experienced liver disease complication during follow-up. Eighty-five (1.9%) of them developed one or more events related to liver decompensation: 62 developed ascites, 22 experienced Portosystemic Encephalopathy (PSE), and 6 had oesophageal varices bleeding, and all of them had a diagnosis of cirrhosis at baseline. The occurrence of liver decompensation was significantly different between patients with CP-A cirrhosis who achieved SVR or not ($p = .001$). By contrast, in patients with CP-B cirrhosis, the rate of liver decompensation was not significantly associated with SVR ($p = .44$).

De novo HCC occurred in 98 patients (2.2%). Three out of 1064 patients (0.3%) with chronic hepatitis, 70 out of 2883 patients (2.4%) with CP-A cirrhosis and 25 out of 360 patients (6.9%) with CP-B cirrhosis developed HCC. The rate of HCC was significantly different in CP-A cirrhosis with and without SVR (2.1% vs. 8.2%; $p < .001$), while de novo HCC occurrence in patients with CP-B cirrhosis was not affected by SVR (6.9% in SVR patients vs. 7.5% in no SVR patients, $p = .69$). Five patients, all with CP-B cirrhosis, received a liver transplant during follow-up (Table 3).

3.4 | Mortality

Patients were observed for a median of 72 weeks (range 2–152) and 59 patients (1.4%) died during the observation: 27 patients due to LR causes, 18 due to CV causes and 14 due to other causes (5 extrahepatic cancer, 3 sepsis, 3 chronic lung disease, 2 car accidents and one suicide) (Supplementary Table S2).

LR deaths occurred in 15 patients with CP-A (0.5%) and 12 patients with CP-B (3.3%) cirrhosis, and in no patients with chronic hepatitis. CV deaths occurred in all classes of liver disease: 0.5% of chronic hepatitis, 0.2% of CP-A cirrhosis and 1.9% of CP-B cirrhosis patients (Table 3).

Univariate Cox regression analysis showed that INR (HR 4.17, $p < .001$), albumin (HR 0.13, $p < .001$), bilirubin (HR 1.83, $p < .001$), platelet count (HR 0.98, $p < .001$) and absence of SVR (HR 14.59, $p < .001$) were associated with LR mortality. There was no correlation

TABLE 1 Baseline clinical and virological features of 4307 patients included in RESIST-HCV cohort

Variables	Chronic Hepatitis 1064 pts (24.7%)	CTP A Cirrhosis 2883 pts (66.9%)	CTP B Cirrhosis 360 pts (8.4%)	*p* value
Age (years, mean ± SD)	63.3 ± 12.6	67.4 ± 10.9	66.6 ± 12.1	<.001
Gender (males, %)	600 (56.4)	1646 (57.1)	206 (57.2)	.79
BMI ($Kg/m^{2,\ mean\ \pm\ SD}$)	25.5± 3.9	26.2 ± 3.8	26.1± 4.1	.005
ALT (IU/L, mean ± SD)	75.8 ± 55.7	90.2 ± 62.3	77.6 ± 64.0	<.001
Platelets ($\times 10^{9/L,\ mean\ \pm\ SD}$)	191.3 ± 82.7	136.2 ± 73.1	119.7 ± 100.0	<.001
INR (mean ± SD)	1.05 ± 0.19	1.09 ± 0.16	1.38 ± 0.49	<.001
Bilirubin (mg/dl, mean ± SD)	0.8 ± 0.5	1.0 ± 0.4	1. 8 ± 1.2	<.001
Albumin (g/dl, mean ± SD)	4.0 ± 0.4	3.8 ± 0.4	3.3 ± 0.6	<.001
Creatinin (mg/dl, mean ± SD)	0.9 ± 0.4	0.8 ± 0.2	0.9 ± 0.3	.01
eGFR (ml/min)	90.7 ± 33.2	89.4± 33.3	87.7 ± 38.2	.08
CKD stage ≥3	164 (15.4)	518 (18.0)	79 (21.9)	.025
Diabetes (%)	173 (16.3)	797 (27.6)	108 (30.0)	<.001
Arterial hypertension (%)	420 (39.5)	1281(44.4)	137 (38.1)	.006
Cardiovascular disease (%)	72 (6.8)	256 (8.9)	55 (15.3)	<.001
IFN-based therapy:				<.001
Naive (%)	576 (54.4)	1384 (48.4)	210 (58.1)	
Experienced (%)	466 (45.6)	1413 (51.6)	142 (41.9)	
HCV genotype				.49
1b	740 (69.5)	2028 (70.3)	255 (70.8)	
1a	95 (8.9)	248 (8.6)	37 (10.3)	
2	99 (9.3)	287 (10)	25 (6.9)	
3	82 (7.7)	197 (6.8)	35 (9.7)	
4	46 (4.3)	116 (4.0)	7 (1.9)	
Others	2	7	1	
Serum HCV RNA (IU/ml; mean, range)	2,925,962 (739–40,097,856)	2,256,938 (728– 52,000,000)	1,537,764 (749 –60,200,000)	<.001

between LR mortality and baseline age, gender, BMI, diabetes, arterial hypertension, CV diseases and CKD stage ≥3.

Univariate Cox regression analysis showed that diagnosis of diabetes (HR 3.35, $p = .009$), CV diseases (HR 2.92, $p = .045$), CKD stage 3 (HR 3.81, $p = 0.005$), INR (HR 3.61, $p = .006$) and absence of SVR (HR 14.42, $p < 0.001$) were associated with CV mortality. There was no correlation between the incidence of CV mortality and baseline age, gender, BMI, arterial hypertension, platelet count, bilirubin and albumin values.

3.5 | Competing risk analysis on hepatic and cardiovascular mortality

Using a Cox proportional cause-specific hazard model (Table 4) for LR and CV mortality, we confirmed that SVR (HR 0.09, beta −2.37, $p < .001$) significantly reduces the hazard of LR mortality. Also, platelet count (HR 0.99, beta −0.01, $p = .007$) and serum albumin (HR 0.26, beta −1.36, $p = .001$) were significantly associated with LR mortality. CV mortality was significantly associated with SVR (HR 0.07, beta −2.61, $p < .001$) with CKD stage 3 (HR 3.60, beta 1.28, $p = .016$) and diabetes (HR 3.45, beta 1.24, $p = .014$). Considering the Fine and Gray model (Supplementary Table S3) for the sub-distribution hazard of LR mortality and considering CV mortality as a competing risk, we confirmed that SVR (HR 0.10, beta −2.33, $p < .001$), platelet count (HR 0.32, beta −1.13, $p = 0.003$) and albumin value (HR 0.52, beta −0.66, $p = .001$) were significantly associated with LR mortality. Similarly, SVR was associated with a reduction of CV mortality (HR 0.08, beta −2.6, $p < .001$). CKD stage 3 (HR 3.49, beta 1.25, $p = .016$) and diagnosis of diabetes (HR 3.43, beta 1.23, $p = .012$) were associated with a significant increase of CV mortality.

3.6 | Cumulative incidence of LR and CV mortality

The cumulative incidence functions were performed using the parameter estimates of the cause-specific hazard model. In the first analysis (Figure 2), we considered the patient profile with mean values of continuous variables (platelet count, albumin, INR and bilirubin), CKD stage <3 and without diabetes. At 96 weeks of follow-up, the probability of LR death in subjects without SVR was greater than

TABLE 2 Baseline clinical and virological features of 4307 patients included in RESIST-HCV cohort according to virological response

Variables	No SVR 223 pts (5.2%)	SVR 4084 pts (94.8%)	*p* value
Age (years, mean ± SD)	63.2 ± 12.3	66.5 ± 11.5	<.001
Gender (males, %)	150 (67.3)	2302 (56.4)	.001
BMI ($Kg/m^{2,\ mean \pm SD}$)	26.4 ± 4.4	26.0 ± 3.8	.18
ALT (IU/L, mean ± SD)	90.8 ± 67.4	85.3 ± 60.8	.19
Platelets ($\times 10^{9/L,\ mean \pm SD}$)	141.4 ± 105.2	148.8 ± 80.5	.30
INR (mean ±SD)	1.15 ± 0.3	1.09 ± 0.2	.007
Bilirubin (mg/dl, mean ± SD)	1.2 ± 0.9	1.0 ± 0.6	<.001
Albumin (g/dl, mean ± SD)	3.7 ± 0.5	3.8 ± 0.5	.012
Stage of disease (number, %)			<.001
Chronic Hepatitis	37 (16.6)	1027 (25.1)	
Child-Pugh A cirrhosis	146 (65.5)	2737 (67.0)	
Child-Pugh B cirrhosis	40 (17.9)	320 (7.8)	
Creatinin (mg/dl, mean ± SD)	0.9 ± 0.3	0.9 ± 0.4	.52
CKD stage ≥3 (number %)	30 (13.5)	731 (17.9)	.09
Diabetes (number, %)	69 (29.6)	1009 (24.7)	.036
Arterial hypertension (number, %)	79 (35.4)	1759(43.1)	.025
CV diseases (number, %)	19 (8.5)	364 (8.9)	.93
IFN-based therapy (number, %)			.50
Naïve	110 (49.3)	2119 (51.9)	
Experienced	113 (50.7)	1965 (48.1)	
HCV genotype (number, %)			<.001
1b	129 (57.8)	2894 (70.9)	
1a	16 (7.2)	364 (8.9)	
2	25 (11.2)	386 (9.5)	
3	38 (17.0)	276 (6.8)	
4	14 (6.3)	155 (3.8)	
Others	1	9	
Serum HCV RNA (IU/ml; mean, range)	2,595,185 (739–63,400,000)	2,348,587 (728–102,200,930)	.53

in subjects with SVR (0.01 vs. 0.001). The probability of CV death was also greater for subjects without SVR than for those with SVR (0.005 vs. 0.0004).

In the second analysis (Figure 3), we considered the patient profile with mean values of continuous variables (platelet count, albumin, INR and bilirubin), CKD stage 3 and with diabetes. Again, the probability of LR death at 96 weeks was higher in patients without than with SVR (0.05 vs. 0.01). Furthermore, for CV, the probability of dying is greater in subjects without SVR (0.54 vs. 0.04 at 96 weeks).

4 | DISCUSSION

The reduction of mortality is the main goal of antiviral therapy in patients with HCV infection. The benefit and utility of any treatment need to be evaluated in real-world settings[33] because the analysis of only carefully controlled studies can produce biased results.[34] Several studies and meta-analysis suggest that HCV infection increases the cardiovascular risk, particular for individuals who already have cardiovascular risk factors such as diabetes and hypertension.[11] Others studies have identified correlations between cardiovascular diseases and the proinflammatory-profibrogenetic HCV-related environment and/or the severity of liver damage. A direct viral activity could also potentially explain these correlations have also been reported.[35]

For this reason, several studies have evaluated the impact of HCV elimination on survival, demonstrating that in patients with SVR, LR and all-cause mortality were lower than in patients without SVR or who had never been treated.[17,18,36]

In the era of interferon-based regimens, elderly patients, patients with advanced liver disease and patients with other diseases were excluded from treatment because of the high probability of AEs; now, these groups routinely receive DAA therapy. Recently, a large cohort from the Veterans' Affairs system was evaluated for the effects of SVR by DAA on mortality. In patients with mild or

TABLE 3 Liver disease outcomes of 4307 patients included in RESIST-HCV cohort and treated with DAAs: mITT analysis

	Chronic Hepatitis 1064 patients (24.7%)			Child-Pugh A cirrhosis 2883 patients (66.9%)			Child-Pugh B cirrhosis 360 patients (8.4%)		
Disease events	**SVR* 1027 pts (96.5%)**	**No SVR 37 pts (3.5%)**	***p***	**SVR* 2737 pts (94.9%)**	**No SVR 146 pts (5.1%)**	***p***	**SVR* 320 pts (88.9%)**	**No SVR 40 pts (11.1%)**	***p***
Liver decompensation (%)	0	0	-	44 (1.6)	8 (5.5)	<.001	28 (9.0)	5 (12.5)	.44
de novo HCC (%)	3 (0.28)	0	.86	58 (2.1)	12 (8.2)	<.001	22 (6.9)	3 (7.5)	.69
Liver Transplant (%)	0	0	-	0	0	-	4 (1.3)	1 (2.5)	.56
Overall death (%)	5 (0.46)	3 (7.9)	<.001	18 (0.7)	12 (8.2)	<.001	15 (4.7)	6 (15.0)	.005
LR death (%)	0	0		9 (0.43)	6 (4.1)	<.001	9 (2.8)	3 (7.5)	.07
CV death (%)	3 (0.3)	2 (5.4)	<.001	3 (0.1)	3 (2.1)	<.001	5 (1.6)	2 (5.0)	.09

TABLE 4 Competing risk analysis by Cox proportional cause specific hazard model for LR and CV mortality in 4307 HCV patients treated with DAAs

	Cox proportional cause specific hazard model							
	Liver-related mortality				Cardiovascular mortality			
	Beta	**Standard Error**	**HR**	***p* value**	**Beta**	**Standard Error**	**HR**	***p* value**
SVR	−2.37	0.45	0.09	<.001	−2.67	0.54	0.07	<.001
Platelets	−0.01	0.005	0.99	.007	−0.003	0.004	0.9	.48
Albumin	−1.36	0.41	0.26	.001	−0.53	0.53	0.59	.32
INR	0.78	0.59	2.18	.18	1.10	0.57	3.01	.06
Bilirubin	0.20	0.22	1.23	.35	−0.22	0.42	0.80	.60
CV diseases	0.77	0.47	2.17	.10	0.90	0.56	2.46	.11
CKD Stage ≥3	0.22	0.53	1.24	.68	1.28	0.53	3.60	.016
Diabetes	−0.08	0.43	0.92	.86	1.24	0.51	3.45	.014

moderate liver fibrosis, SVR was independently associated with reduced risk of death compared to those without SVR and untreated patients.[37] In patients with advanced liver disease, those with SVR showed a reduced risk of death as compared to those without SVR, but the risk of death was independently associated with the severity of liver disease and the reduction of serum albumin values.[38] However, this study was retrospective, comprised mostly (95%) male subjects with different risk factors and comorbidities, and did not report the causes of death. Similarly, the large prospective French Hepather cohort study reported that DAA treatment was associated with a decrease in all-cause mortality, but did not report the causes of mortality and did not perform a targeted analysis on cardiovascular mortality.[22] Finally, the analysis of a cohort of HCV-infected veterans reported that patients treated with DAA regimens who achieved SVR had a lower risk for CV disease events.[39]

Our study, conducted on a large prospective cohort, is the first one to our knowledge that evaluates the impact of SVR on LR and CV mortality using a competing risk model. We demonstrated that achievement of SVR conferred a significantly reduced risk of LR and CV mortality. As expected, baseline platelet count and albumin values were also significantly associated with LR mortality.

Considering CV mortality, SVR, CKD stage 3 and diagnosis of diabetes were all significantly associated. Thus, we are aware that in order to evaluate the prognosis of patients with chronic HCV infection, we need to perform a well-defined staging of liver disease at the beginning of therapy.[6,7] In the RESIST-HCV platform, the stage of liver disease and all variables included in the Child-Pugh score to sub-classify patients with cirrhosis were defined, and co-morbidities were recorded. Using these criteria, it was possible to evaluate mortality according to liver function and to correlate the risk of death with the presence of any co-morbidities.

Patients who failed to achieve SVR were ten times more likely to die from CV events than those who achieved SVR. The association between CV mortality and SVR was confirmed both in the best patient profiles (i.e., patients without diabetes and without severe chronic kidney disease) and in the worst patient profile (i.e., presence of diabetes and CKD class 3), where the probability of CV death is higher.

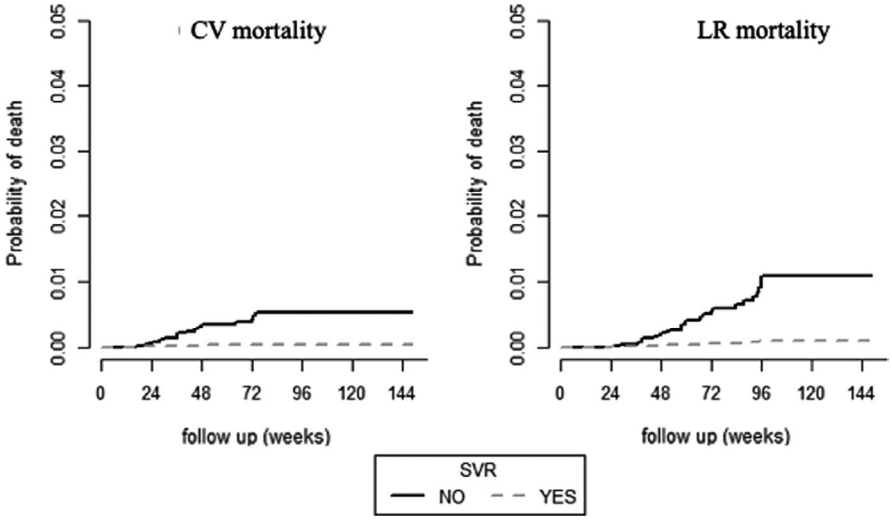

FIGURE 2 Cumulative incidence functions for LR and CV mortality performed using the parameter estimates of the cause-specific hazard model and considering the best patient profile for continuous variables (PLT, Albumin, INR and bilirubin) in subjects with CKD <3 and without diabetes

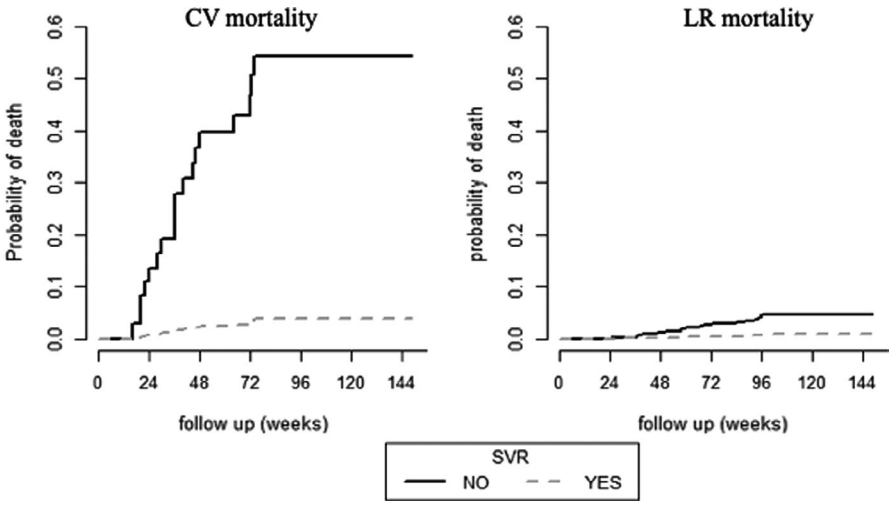

FIGURE 3 Cumulative incidence functions for LR and CV mortality performed using the parameter estimates of the cause-specific hazard model and considering the worst patient profile for continuous variables (PLT, Albumin, INR and bilirubin) in subjects with CKD stage 3 and diabetes

Our analysis also showed that in the worst patient profile, SVR seems to have a lower impact on the probability of LR death. This result can be explained considering the fact that most patients with diabetes and severe renal disease had CP-B cirrhosis. These patients retain a significant risk of HCC, decompensation, and death after HCV eradication in keeping with the marginal association of LR mortality and virologic response; in patients with advanced liver disease, the benefit of antiviral treatments is less evident.[17,20]

The main limitation of our study was the short follow-up after SVR. Such a short observation time may increase the variability in event frequency for different stages of liver disease, but the large number of patients observed and the small proportion of dropouts can help to offset this. Another limitation of this study lies in the heterogeneity of clinical centres participating in RESIST-HCV: each centre will conduct patient surveillance and data recording in a slightly different way. We believe this limitation has been overcome through the evaluation of an objective outcome (death) and the use of monitors who collaborated with physicians across centres. Some heterogeneity is, however, an intrinsic characteristic of all studies that include a high number of centres.

Second-generation DAAs offer pangenotypic efficacy, can be administered for a short time in patients without cirrhosis, have excellent tolerability profiles, and are available at reduced cost. These features should encourage health authorities to organize extensive therapy programmes[40] and, with the collaboration of the General Practitioners,[41] to attempt the eradication of HCV by 2030 as recommended by the World Health Organization.[42,43]

5 | CONCLUSION

In conclusion, our prospective observational study confirms that patients with SVR to DAA regimens have improved liver and cardiovascular outcomes, and the effects of HCV eradication are most evident in patients with chronic hepatitis and compensated cirrhosis. These findings could justify wide access to DAA therapy to all infected individuals, regardless of liver disease stage, and confirm the goal of SVR as a clinically relevant end point.

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CONFLICTS OF INTEREST

Vincenza Calvaruso served on the advisory board of Abbvie and Intercept, and served on the speaker's bureau of Gilead, Salvatore Petta served on the advisory board of Abbvie and Gilead, and served on the speaker's bureau of Gilead and Abbvie, Marco Distefano, Gaetano Scifo, Maurizio Russello served on the advisory board of Abbvie and served on the speaker's bureau of Gilead and Abbvie, Giuseppe Cabibbo served on the advisory board of Bayer. Vito Di Marco received research support from Abbvie, Gilead, Intercept and Merck/MSD and served on the advisory boards of Abbvie, Gilead and MSD/Merck. Antonio Craxì received research support from Abbvie, Gilead, Merck/MSD and Intercept and consulted for and served on the speaker's bureau and advisory boards of Abbvie, Intercept, Gilead, and MSD/Merck. Giovanni Raimondo served on the advisory boards of Abbvie, Gilead, and MSD/Merck. Calogero Cammà served on the advisory board of Bayer and MSD/Merck. The other authors have no disclosures to declare.

AUTHORS CONTRIBUTIONS

Guarantor of the article: VDM. V.C. contributed to analysis and interpretation of data, drafting of the manuscript, statistical analysis and critical revision of the manuscript for important intellectual content. S.P., I.C., G.C. and F.C. contributed to acquisition of data and critical revision of the manuscript for important intellectual content. M.D, G.S, M.DR., M. R., T. P., S. M., G. M., A. M., A. D., A. L., B. C. and G.B. contributed to acquisition of data. M.E. and S.B. contributed to statistical analysis. G.R. contributed to study concept and design and critical revision of the manuscript for important intellectual content. C.C. contributed to study concept and design, analysis and interpretation of data, statistical analysis and critical revision of the manuscript for important intellectual content. A.C. contributed to study concept and design, analysis and interpretation of data and critical revision of the manuscript for important intellectual content. V.DM. contributed to study concept and design, analysis and interpretation of data, drafting of the manuscript and study supervision. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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