Response letter

Reviewer 1 (code 02728252)

We'd like to thank the reviewer for her/his thoughtful comments. Here there is our point-by-point response to reviewer concerns. All changes are made in red in the revised manuscript.

R1. It is well performed retrospective-prospective observational study as the authors reported that direct-acting antiviral agents are effective in inducing sustained virologic response and protecting against hepatocellular carcinoma or death. The introduction section is well written and the rational of the study is sound. The study design and the sample size are appropriate and the results and conclusion are indicative and consistent with the aim.

AU. We thank the reviewer.

Reviewer 2 (code 03021264)

We'd like to thank the reviewer for her/his thoughtful comments. Here there is our point-by-point response to reviewer concerns. All changes are made in red in the revised manuscript.

R2: This is a well-written article investigating the outcomes of HCV-infected patients with the treatment of DDA drugs by focusing on HCC and death. The evaluation of HCV-infected patient's outcome in the era of DDA is a hot topic, the author of the manuscript illuminated a new perspective on this topic and drew convincing conclusions. In addition to the positive aspect of the study, several questions should be answered by the authors: **1. It was mentioned in the manuscript that some patients had been previously treated with interferon-based regimens without achieving SVR. Did this group of patients show different outcomes compared with the other patients?. And did they successfully achieve SVR with DDA treatment?.**

AU: In our population of 380 HCV-infected patients, 36% had been previously treated with interferon unsuccessfully. DAAs treatment induced SVR in 94.8% of these patients and in 95.5% of those who had never used interferon before. HCC developed in 5.8% of patients previously treated with interferon-based regimens and in 3.7% of those not. We didn't find any differences between these groups. This point has been specified in the revised manuscript.

R2: **2. Please specify the name of DDAs.**

AU: The name of DAAs has been specified in Table S2 of the supplemental material. This has been indicated in the revised manuscript.

R2: **3. Regarding the HCC patients who underwent surgical resection and liver transplantation, how about the recurrence rate. What is the treatment for preventing HCV re-infection after liver transplantation?**

AU: In our population, 8 patients had a previous diagnosis of HCC that was cured by orthotopic liver transplantation or surgical resection. Of these patients, 5 achieved SVR after DAAs treatment and did not develop HCC, 3 did not achieve SVR and developed a new HCC. These patients were treated with DAAs for HCV infection

after liver transplantation or surgical resection according to the Italian guidelines. This has been specified in the revised manuscript.

R2: **4. Are there any experience about the interactions between DDAs and immunosuppressive agents?**

AU: We did not observe any significant interaction between DAAs and immunosuppressive agents that led us to modify the dose or type of drug. This has been pointed out in the revised manuscript.

Reviewer 3 (code 02861305)

We'd like to thank the reviewer for her/his thoughtful comments. Here there is our point-by-point response to reviewer concerns. All changes are made in red in the revised manuscript.

R3: **1. Whether DAAs treatment can be a risk factor for HCC development could not be found in the study. Because there was not a control group.**

AU: We agree with the reviewer that the lack of a control group did not permit to explore the hypothesis of DAAs as a potential risk factor for HCC development. However, this investigation was not among the aims of our study. This has been pointed out in the revised manuscript as a limit of the study.

R3: **2. Table 1 should be slightly simplified**

AU: We tried to simplify the readability of Table 1.

Reviewer 4 (code 00006518)

We'd like to thank the reviewer for her/his thoughtful comments. Here there is our point-by-point response to reviewer concerns. All changes are made in red in the revised manuscript.

R4: **1. Give full term before abbreviation, such as hepatitis C virus (HCV), in its first appearance.**

AU: We checked that the full term is given before each abbreviation according to reviewer suggestion.

R4: **2. Do not put any medical abbreviation in the keywords.**

AU: We modified medical keywords according to reviewer suggestions.

R4: **3. Make sure that 'multi-state' is a keyword.**

AU: We have changed the word "multi-state" with "survival analysis".

R4: **4. Polish the language, such as 'lost at follow-up' might be replaced by 'lost to follow-up' in Patients and Methods.**

AU: We submitted the manuscript to an English editing service (AJE) for improving language.

R4: **5. Explain or address 'restrictive inferential methods' in the Statistical methods.**

AU We have addressed "restrictive inferential methods" in the revised manuscript as suggested by the reviewer.

R4: **6. I suggest the authors give a percentage unit in all tables to second decimal place (or at least first decimal place) since the case number was small in this study.**

AU: The percentages have been given to the first decimal position as suggested.

R4: **7. Please explain the reason for a low incidence of mixed cryoglobulinemia (9.21%) in the study cohort.**

AU: This is the prevalence of type II/III cryoglobulinemia diagnosed in our population by a cryocrit greater than 1%. This cut-off point can have led us to underestimate low-grade cryoglobulinemia. This important point has been discussed in the revised manuscript.

R4: **8. Further address or modification for the conclusion '…or with extra-hepatic HCV-related complications' might be needed because only mixed cryoglobulinemia & eGFR were taking into account in extra-hepatic manifestations in this study.**

AU: We modified the conclusion as suggested by the reviewer.

Reviewer 5 (code 02959077)

We'd like to thank the reviewer for her/his thoughtful comments. Here there is our point-by-point response to reviewer concerns. All changes are made in red in the revised manuscript.

R5: Colussi et al. wrote an interesting retrospective study about outcomes in HCV patients according to SVR: they pointed an actual subject (DAA, HCV and HCC occurrence.), used a pertinent statistical method (Markov Model.). According to my advice, this paper can be accepted. **Some little corrections are needed nevertheless: precise MDRD equation (MDRD4? MDRD6?), replace Fibroscan by FibroScan.**

AU: We made the corrections in the revised manuscript as suggested by the reviewer.

Reviewer 6 (code 03020633)

We'd like to thank the reviewer for her/his thoughtful comments. Here there is our point-by-point response to reviewer concerns. All changes are made in red in the revised manuscript.

R6: **1. I think that the interval of follow-up is relatively short for HCC development.**

AU: We agree with the reviewer that the median follow up interval is relatively short for HCC development in a general population of HCV-infected patients. However, because of the national guidelines limit DAAs prescription to patients with advanced liver disease, we necessarily treated HCV-infected patients with a high risk of developing HCC in a shorter period. This important point has been discussed in the revised manuscript.

R6: **2. The high incidence of HCC in without SVR patients was mainly due to the advanced state of disease. The comparison of HCC incidence should be done in the patients with comparable state of liver disease (such as liver cirrhosis) that with and without SVR to DAAs.**

AU: Cirrhosis has been included as a cofactor in all multivariate analyses performed and the protective effect of SVR on HCC or mortality was independent of its presence. To remark this point, we added the Kaplan-Meir curves of the probability of HCC or mortality free event by SVR response and presence of cirrhosis in the supplemental material (Figure S1).