Dear Editor,

We read with great interest the article by Aller et al. regarding the effect of sylimar in and Vitamin E in patients with non-alcoholic fatty liver disease (NAFLD). The authors reported the results of a pilot study of 36 patients randomized in two groups: the group I was treated with sylimarin plus Vitamin E (2 tablet/day), hypo caloric diet (1520 kcal, 52% of carbohydrates, 25% of lipids and 23% of proteins) and exercise for three months. The Group II was treated only with hypo caloric diet. The results obtained are interesting and have demonstrated that the treatments adopted ameliorated the hepatic functions. These conclusions have been measured by Fatty Liver Index (FLI), Liver Accumulation Product (LAP) and NAFLD-Fibrosis Score (FS). They have concluded that silymarin can be a valid alternative therapeutic option especially as a complementary treatment associated with other therapeutic programs.

Regarding the clinical aspects, the median age of the patients was 47.4 years; we are surprised that no elderly or frail patients (i.e., HCV, HBV, diabetics, etc.) were enrolled.

Recent progress regarding the biological features of new biomarkers either in NAFLD and hepatocellular carcinoma (HCC) could improve the clinical managements of these so called frail patients. Currently, a similar pilot study is ongoing in two Italian health institutions and the preliminary results are comparable to Aller et al data. Our study is designed with two randomized patient groups: the group I is treated with a combination of anti-oxidant molecules includes sylimarin 400 mg/day, Vitamin E 12 mg/day, N-acetyl cysteine 600 mg/day betaine 600 mg/day and selenium 81 µg/day (3 tablet/day of Epatil®), hypo caloric diet (1500 kcal, 50% of carbohydrates, 20% of lipids and 25% of proteins) and exercise for three months. The Group II is treated only with hypo caloric diet and exercise for three months.

The study includes patients with NAFLD (diagnosis confirmed by percutaneous liver biopsy) and with HCC. In addition, elderly patients (until 70 years old) and HIV-, HCV- and HBV-positive patients have been enrolled. The preliminary results show an encouraging amelioration in group I, especially evident in the frail patients (unpublished data). Furthermore, the clinical management of these frail patients has been currently improved in the last decade. In addition, comprehensive genomics assay have detected numerous genetic alterations to confirm the previously published data in NAFLD and HCC infected by HIV and HCV.

The patients genotyping NAFLD panel test (Ampli-NAFLD, Diachem, Naples, Italy) could be helpful for the clinicians to prevent fibrosis-related grade ≥ 3 toxicity and to preserve treatment compliance. In addition, the detection of the individual metabolic profile by genotyping the cytochrome P450 status, is a highly supportive tool in the clinical practice, especially in frail patients treated with polytherapy.

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Instead, the clinical utility of the polymorphisms involved in NAFLD and HCC based-therapy is in part limited by: (1) low diffusion of genotyping methods in the routine clinical diagnostics\textsuperscript{10}; (2) the evidence that Pharmacogenomic testing improves clinical outcomes and its cost-effectiveness is still an open question\textsuperscript{11}; and (3) the need to find clinical expertise to interpret laboratory data results\textsuperscript{12,13}.

The cost of a genetic testing for the detection of individual metabolic profile, includes more than just the cost of the test itself. However, additional costs are genetic counseling, laboratory equipment, time-labor and further diagnostics are potentially of greater magnitude and should be evaluated\textsuperscript{14}.

Finally, waiting for the conclusion of our study, we think that the use of anti-oxidant poly-therapy could improve the regressions of hepatic disease like NAFLD and fibrosis in the so called frail patients previously genotyped for individualized treatments. Based on these purposes the clinician should evaluate advantages and limitations, in terms of costs and applicability of the most appropriate multidisciplinary approach to hepatocellular disease in according to new health challenges in the 3rd Millennia\textsuperscript{15}.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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