Editorial Commentary

May an aspirin a day truly take hepatocellular carcinoma away?

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The relationship between platelets and hepatic carcinogenesis is complex and involves several interplays among hepatic inflammation, cytokine *milieu*, and interactions between platelet and hepatic vessels (1,2). Thrombocytopenia, *per se*, has been used to identify patients at risk of developing hepatocellular carcinoma (HCC) to insert them into surveillance programs for the early detection of primary liver cancer with the ultimate goal of improving their prognosis. Thrombocytopenia has also been used to identify patients at higher risk of developing HCC (3-5). The pathophysiological basis underlying the increased risk of HCC in patients with cirrhosis and thrombocytopenia can be found in the determinants of decreased platelet count in patients with chronic liver disease, such as portal hypertension and decreased hepatic production of thrombopoietin, findings more evident in patients with advanced liver disease (6,7). Also, thrombocytosis has been associated with HCC, a result more frequent in patients with larger tumors and better liver function (8).

Indeed, platelets have always been represented as a double-edged sword in patients with chronic liver disease since both low and high platelet counts have been associated with a dismal prognosis in patients with HCC (8,9). Furthermore, the platelet count is frequently identified as a crucial parameter in prognostic scores used to assess the outcome of these patients (10-12). As a fact, platelets produce a vast array of cytokines that may lead to decreased hepatocellular apoptosis and increased neo-angiogenesis, promote HCC proliferation by down-regulating tumor suppressor genes, and induce growth, migration, and invasion of HCC cells (13-15).

In this complex scenario, anti-platelets therapy is an appealing therapeutic option. Initial evidence in this regard was provided several years ago by a seminal study showing that—in a mouse model of chronic hepatitis B-aspirin treatment was able to reduce HCC development and increase survival, a finding likely mediated by decreased platelet-mediated adherence and extravasation of lymphocytes in the hepatic parenchyma (16,17). Since the publication of these basic science studies, several human studies have contributed to the wealth of evidence supporting a positive role of anti-platelet therapy—and in particular aspirin—on HCC development both in patients with chronic liver disease and in the general population, while more recent studies also showed a positive effect of anti-platelet therapy on HCC recurrence following curative resection (18-21).

The study by Jang *et al.*, recently published in *Hepatology*, provides another relevant piece of evidence supporting the chemo-preventive effect of regular aspirin use on the development of HCC in patients with chronic hepatitis B with or without cirrhosis (22). This study included a large population (n=329,635) of Korean patients with chronic

hepatitis B infection who received aspirin treatment for more than 90 consecutive days (n=20,200) or who never received antiplatelet therapy (n=309,435). One of the most relevant characteristics of the study is that, due to the sample numerosity, it was possible to perform an adequately large propensity score matching of the two subgroups, aspirin users and non-users, and aimed at assessing the liver-related mortality in these patients. This study showed that regular aspirin use was associated with a decreased 10-year risk of developing HCC [adjusted sub-distribution hazard ratio =0.85; 95% confidence interval (CI): 0.78–0.92]. This finding was not confirmed in the sub-group of matched patients with cirrhosis (2,479 pairs), an association of aspirin use with HCC risk was not evident (adjusted sub-distribution hazard ratio =1.00; 95% CI: 0.85–1.18). The fact that the risk of development of HCC was not influenced by the use of aspirin in patients with cirrhosis may reside in the potential inability of aspirin to counteract carcinogenetic pathways that may already be at play in patients with advanced disease, and that cannot be disrupted by the modulation exerted by aspirin.

This study also showed that regular aspirin use was associated with a decrease in liver-related deaths, a finding again significant in patients without cirrhosis. This result may be of interest as the majority of patients with chronic hepatitis B virus infection is currently virus-suppressed, and the risk of liver-related death in these patients is almost abolished by antiviral therapy. Although this study did not allow to perform more in-depth speculations on this finding, it is a result worth being explored in other cohorts, for example, patients with non-alcoholic steatohepatitis, where the absence of efficacious treatment for the underlying liver disease and the almost universal presence of metabolic and cardiovascular comorbidities renders the potential positive effect of aspirin use more appealing.

This study also addressed another relevant "elephant in the room" often overlooked in these studies, namely the risk of bleeding during aspirin treatment. Indeed, some previous studies already addressed this issue, finding that the risk of bleeding in nucleos(t)ide analogs-suppressed patients with chronic hepatitis B virus infection on aspirin was similar to the one of non-users of aspirin and lower than the risk of patients on other anti-platelet therapies such as clopidogrel (18). In the study by Jang *et al.*, this effect was not confirmed in patients without cirrhosis, where the risk of bleeding at ten years was 15% higher in aspirin users compared to non-users of aspirin, a finding not confirmed in patients with cirrhosis (22). This finding, which is at odds with previous results, may be explained by the subsequent stratification of patients showing that the increase in bleeding risk was confined to elderly patients. At the same time, it was not observed in younger patients and therefore seemed to limit this adverse treatment event to a more fragile population. Moreover, the study did not report whether patients were on proton pump inhibitors to reduce the likelihood of upper gastrointestinal bleeding—a side event of anti-platelet therapy that is more common among elderly patients—as recommended by current guidelines. Therefore, this drawback precludes a definite and meaningful conclusion on this relevant issue (23,24).

To conclude, we feel that the results of the study by Jang *et al.* further enhance the suggestion that regular use of aspirin in patients with chronic liver disease and without cirrhosis may be beneficial on the risk of developing HCC: it is likely that, based on the results of this study and of similar studies with consistent results published in the past, aspirin may positively enter the therapeutic armamentarium of liver disease specialists as a pleiotropic drug.

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Footnote

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