MicroRNAs have been proposed to regulate metastasis and serve as important clinical biomarkers. In the current study, Sun et al studied a miRNA i.e. miR-1246, which the authors identified as a highly upregulated miRNA between Hep11 and Hep12, two cell lines isolated from primary and recurrent HCC tumors, respectively. Using in vitro migration and invasion assays, authors found that change in levels of miR-1246 impaired cells migratory and invasive properties by suppressing CADM1 expression. In addition, the authors further found a negative correlation between miR-1246 and CADM1 expression in Stage1 HCC patients. Thus, their results suggest that miR-1246 could be potentially used as biomarkers in HCC patients. Their experiments are well performed; however, several things need to be further explained or need clarifications.

Major revisions:

1. The authors showed in the Supplementary Fig S1 and S2 that miR-1246 level is higher in Hep12, and four other HCC cell lines including HepG2, SMMC-7712, Hep3b and BEL-7402, than Hep11. However, nothing is stated about the metastatic properties of these cell lines. For example, does the miR-1246 endogenous levels in those cell lines correlates with high migratory and invasive behavior of the cells? Please provide the data. Also, what is the effect of miR-1246 knockdown in Hep12 cells on migration and invasion?

2. For figure 3, please compare CADM1 protein levels between different HCC lines. This information would substantiate the finding that miR-1246 suppresses CADM1 in HCC. Also, did authors observe suppression of CADM1 expression with miR-1246 overexpression in Hep11 cells? Please provide the data. It was mentioned in the discussion that CADM1 gets methylated or lost its expression by LOH, so it would be interesting to know whether miR-1246 targets CADM1 in these HCC cell lines directly. Please perform Luciferase assay.

3. In Figure 4, the authors perform knockdown of CADM1 only in one cell line i.e. SMMC, yet concluded in the discussion that CADM1 knockdown results in increase in migration and invasion of HCC cell lines. This conclusion is incorrect. To strengthen this statement, please perform CADM1 knockdown in Hep11 and HepG2 cells and perform migration and invasion assays.

4. It is shown in figure 6C and 6D that miR1246 and CADM1 levels can stratify
HCC stage 1 patients for disease free survival. However it is unclear whether these two parameters are exclusive from each other or can be used together on those samples. Please clarify.

Minor revisions:
In Dual Luciferase assay method section, it was stated that “ an 66 bp fragment of CADM1 3’UTR containing the predicted site for miR-9 was synthesized”-please clarify.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.