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EFNA3 is a prognostic biomarker for the overall survival of patients with hepatocellular carcinoma

To the Editor:

We read with great interest the article by Husain *et al.*,[1] showing that the expression of *EFNA3* was upregulated in hepatocellular carcinoma (HCC) and related to poorer survival rates. Husain *et al.* found that the expression level of *EFNA3* was regulated by HIF-1α in a hypoxic microenvironment. Hypoxia-induced Ephrin-A3/EphA2 forward signaling played a vital role in initiation and progression of HCC. The authors identified the clinical significance and molecular mechanisms of *EFNA3* in HCC. However, the relationship between the HCC patients' overall survival (OS) and *EFNA3* was explored only based on The Cancer Genome Atlas (TCGA) database in their study. Without independent validation, evidence of the prognostic role of *EFNA3* in HCC is not solid. Hence, the clinical observations regarding the beneficial effects of *EFNA3* on OS in patients with HCC need to be confirmed in other independent cohorts.

Previous studies showed that *EFNA3* was a prognostic indicator of some types of tumors. For example, Zheng *et al.* demonstrated that upregulation of *EFNA3* was correlated with worse survival rates in gastric cancer.[2] Dent *et al.* showed that

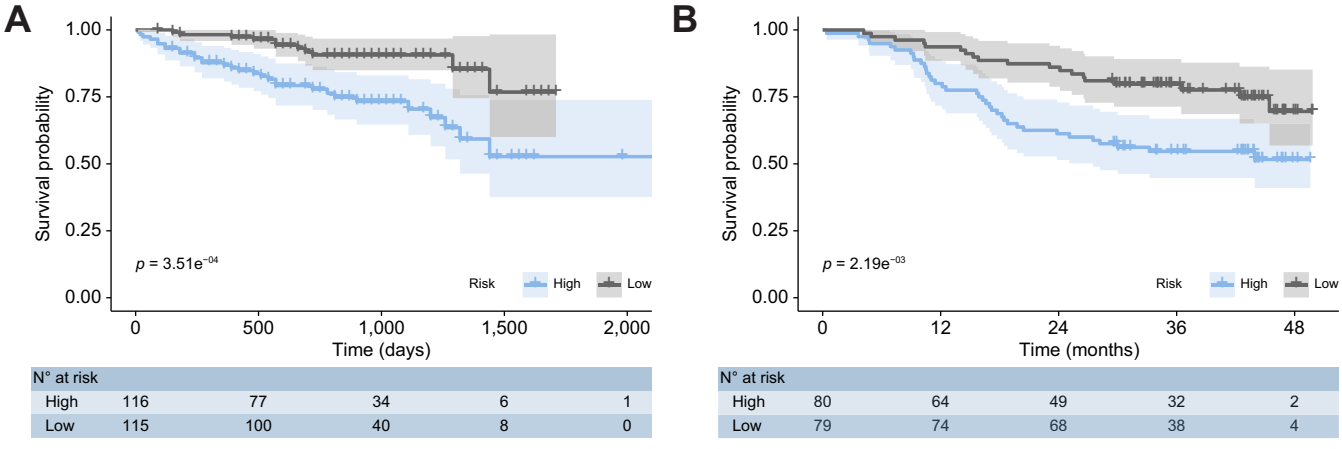

Fig. 1. Kaplan-Meier curves for overall survival based on gene expression of *EFNA3*. Log-rank test in (A) LIRI-JP and (B) CHCC cohorts.

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high *EFNA3* expression was significantly correlated with inferior survival in patients with lung adenocarcinoma.[3] It is imperative to identify the relationships between *EFNA3* and OS in patients with HCC based on multi-cohort data. Here, we collected two datasets that contain RNA sequencing (RNA-seq) profiles and follow-up survival information to validate the relationship between *EFNA3* and OS in HCC. The first dataset liver cancer-RIKEN, JP (LIRI-JP) project, containing the RNA-seq and clinical follow-up data of 231 patients with HCC, was downloaded from the International Cancer Genome Consortium (ICGC) portal (https://dcc.icgc.org/).[4] The median age of these patients was 69, with 170 males and 61 females. Sixty-one patients had HBV infection. In total, 141 patients with HCC were classified as TNM stage 1 to 2. Another RNA-seq dataset that included 159 Chinese HCC(CHCC) patients was also retrieved from the literature.[5] In the CHCC cohort, all patients had HBV infection and the median age was 54, with 128 males and 31 females. The majority (105 out of 159, 66.0%) of patients with HCC were classified as TNM stage 1 to 2. Patients with HCC were stratified into 2 groups, a high-*EFNA3* and a low-*EFNA3* group, based on the median expression of *EFNA3* in each cohort. The Kaplan–Meier plots showed that patients with HCC in the high-*EFNA3* group had inferior survival in the LIRI-JP cohort (hazard ratio [HR] 3.25, 95% CI 1.77–5.96; p <0.001; Fig. 1A) and CHCC cohort (HR 2.31, 95% CI 1.37–3.91, p = 0.002; Fig. 1B).

The article by Husain *et al.* provided novel insights into HCC clinical biomarker identification and molecular mechanisms.[1] We validated the prognostic value of *EFNA3* in two HCC cohorts, which could further validate the findings from the TCGA database. In summary, we show that elevated *EFNA3* expression represents an important OS predictor in patients with HCC. We are now carrying out immunochemical tests to further assess the clinical value of *EFNA3*.

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Conflicts of interest
The authors declare no conflicts of interest in this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
Peng Lin and Hong Yang participated to data acquisition, statistical analysis, data interpretation, and writing of the manuscript. All authors approved the final version of the manuscript.

Data availability statement
Data analyzed during the current study are available from the ICGC (https://icgc.org/, dataset ID: LIRI-JP,) and NODE (https://www.biosino.org/node, dataset ID: OEP000321).

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We greatly appreciate the corresponding medical project for providing the public data (ICGC database and CHCC).

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.03.008.

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Author names in bold designate shared co-first authorship

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Reply to: 'EFNA3 is a prognostic biomarker for the overall survival of patients with hepatocellular carcinoma'

EFNAs are functional predictors of overall survival in patients with hepatocellular carcinoma

To the Editor:

We take delight in reading the report from Lin *et al.*[1] They refer to our study describing the functional and mechanistic roles of the Ephrin-A3/EphA2 axis in hypoxic hepatocellular carcinoma

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