Authors' contributions

All authors contributed to the conception of the study and the final manuscript. FK carried out the formal analyses and wrote the original draft.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.04.027.

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Freiburg index of post-TIPS survival: The first score for individual prediction and a complementary tool for risk stratification

To the Editor:

We have read with great interest the impressive study conducted by Bettinger *et al.* about the development of the Freiburg index of post-TIPS survival (FIPS) score.[1] The authors established a prognostic model to achieve both individual outcome prediction (with the formula and the online calculator) and risk stratification (with a cut-off point), which had superior performance compared to previous prognostic models. Moreover, its ability to stratify patients at high and low risk remained robust in subgroups with different indications for transjugular intrahepatic portosystemic shunt (TIPS), different types of TIPS stents, well-preserved liver function, and impaired renal function.

Since the FIPS score is developed on the basis of a training cohort which consisted of German patients, we hoped to externally validate it and to assess its prognostic value within a Chinese TIPS cohort of 536 patients. In this cohort, the indication of TIPS included secondary prophylaxis of variceal rebleeding (n = 468, 87.3%), refractory ascites (n = 60, 11.2%) and early TIPS (n = 8, 1.5%). Among these patients, 109 (20.3%), 350 (65.3%), and 77 (14.4%) patients were graded as Child-Pugh A, B, and C, respectively, and the median model for end-stage liver disease (MELD) score was 11.5 (IQR 9.7–141). Major etiologies of chronic liver disease included HBV infection (292, 54.5%), autoimmune liver disease (53, 9.9%), and HCV infection (7.8%). Median follow-up was 23.7 (IQR 16.8–36.2) months.

We first tested the performance of FIPS score, Child-Pugh score,[2] MELD score,[3] and CLIF C-AD score.[4] Regarding the time-dependent AUROC for 3-month, 6-month, 1-year, 2-year, and 3-year death, Child-Pugh score had the best performance at all time points, whereas corresponding AUROCs of FIPS score were slightly lower (Fig. 1A, Table S1). Similarly, the C-indices for Child-Pugh score and FIPS score were 0.68 and 0.66, respectively (Table S1).

Subsequently, we validated the discriminative ability of FIPS score and Child-Pugh score. According to the original cut-off point of the FIPS score (0.92), only 7 patients were identified as high-risk patients, with significantly higher mortality than those with low risk (log-rank p <0.01, Fig. S1). Given the extremely low number of high-risk patients, we replaced the original cut-off with -0.006, the 85th percentile in the current cohort. For ease of use, we further modified it to 0 since only 1 patient had a FIPS score falling between -0.006 and 0, and the capability of risk stratification remained robust (log-rank p <0.01, Fig. 1B). Similarly, Child-Pugh score could also achieve adequate risk stratification with its grading system (log-rank p <0.01, Fig. 1C).

Finally, we investigated the risk stratification effect of the FIPS score in different Child-Pugh grades and *vice versa*. The FIPS score could significantly discriminate patients with high and low risk in Child-Pugh A and B subgroups (both with log-rank p <0.01, Fig. 1D, E), but not in the Child-Pugh C subgroup (log-rank p = 0.10, Fig. 1F). Inversely, in the low-risk subgroup defined by FIPS score, Child-Pugh score could stratify patients into grades A, B, and C (log-rank p <0.01, Fig. 1G). While in high-risk subgroup, Child-Pugh score did not reach statistical significance for risk stratification (log-rank p = 0.56, Fig. 1H).

In the original study, Bettinger *et al.* focused on the performance of FIPS score in predicting 3-month and 6-month survival, which proved satisfactory. Accordingly, we confirmed that FIPS score has similar AUROC for predicting 3-month and 6-month survival in this external validation cohort, and that patients with high and low risk

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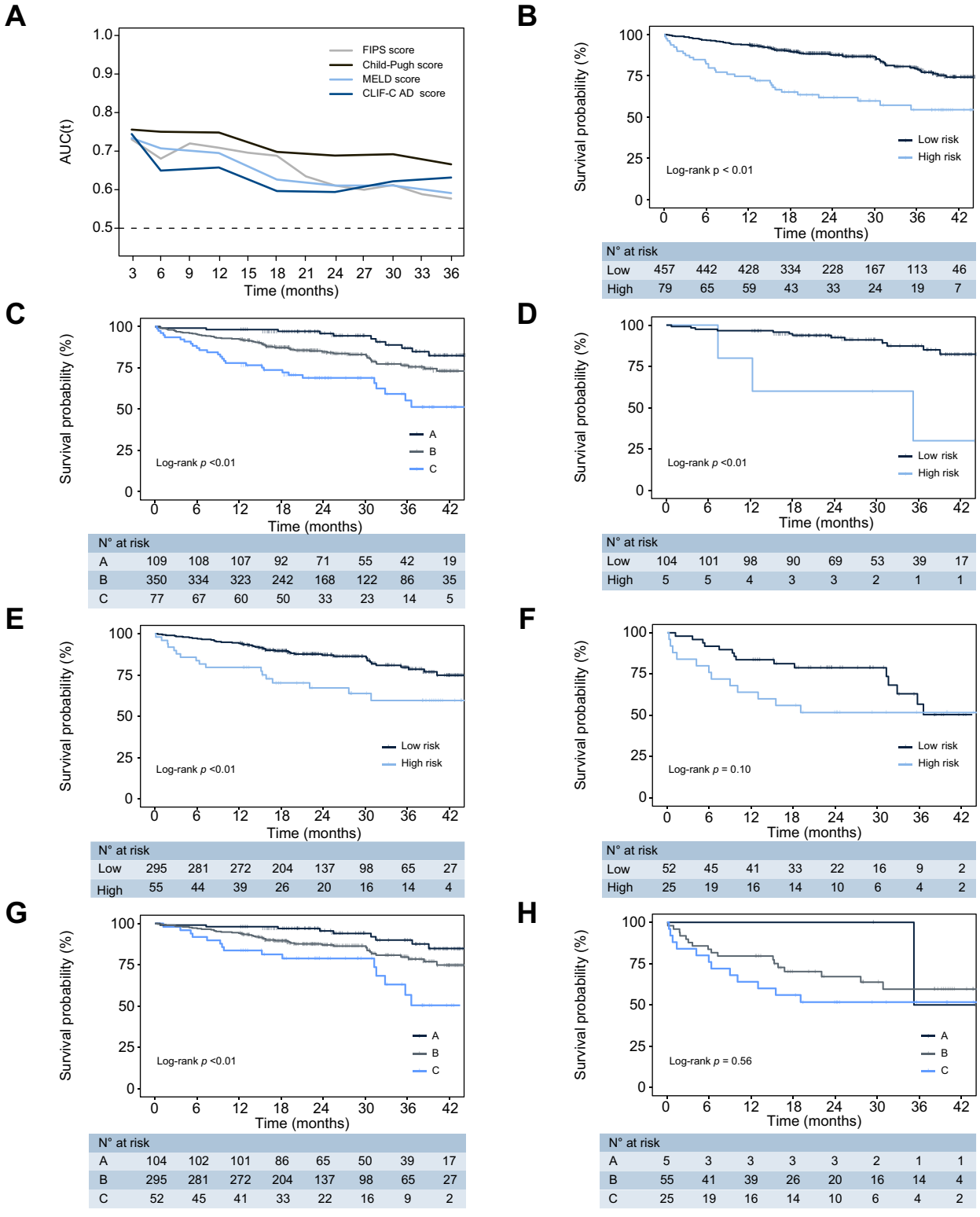

Fig. 1. Performance and risk stratification of prognostic models. (A) Time-dependent AUROC of the FIPS score, Child-Pugh score, MELD score, and CLIF C-AD score. (B) Risk stratification of the FIPS score with 0 point being the cut-off. Survival was significantly different between the 2 strata with log-rank p <0.01. (C) Risk stratification of Child-Pugh score. Survival was significantly different between grades A, B, and C with log-rank p <0.01. (D) Risk stratification of the FIPS score in patients with Child-Pugh A. Survival was significantly different between the 2 strata with log-rank p <0.01. (E) Risk stratification of the FIPS score in patients with Child-Pugh B. Survival was significantly different between the 2 strata with log-rank p <0.01. (F) Risk stratification of the FIPS score in patients with Child-Pugh C. There was no statistical difference between the 2 strata with log-rank p = 0.10. (G) Risk stratification of Child-Pugh score in low-risk patients defined by FIPS score. Survival was significantly different between different grades with log-rank p <0.01. (H) Risk stratification of Child-Pugh score in high-risk patients defined by FIPS score. There was no statistical difference between the 3 grades with log-rank p = 0.56. FIPS, Freiburg index of post-TIPS survival; MELD, model for end-stage liver disease; TIPS, transjugular intrahepatic portosystemic shunt.

of death could be well-stratified. Indeed, FIPS score might be a landmark since it is the first model to achieve individual outcome prediction for patients receiving TIPS. However, in our cohort, Child-Pugh score appeared to be a more favourable choice with better performance (Fig. 1A, Table S1) if a single prognostic model is to be independently used for risk stratification, since it had the best performance. Interestingly, in subgroup analyses, FIPS score could further stratify risk levels in patients even if they were classified as low and intermediate risk groups according to Child-Pugh score (*i.e.*, grade A and B), and Child-Pugh score could also stratify low-risk patients defined by FIPS score. These results might be caused by the different variables used in these 2 scoring systems, and consequently indicated that FIPS score and Child-Pugh score are to some degree complementary in identifying high-risk patients. Therefore, when a more accurate and detailed risk stratification is required, the FIPS risk stratification based on Child-Pugh grading system could be a new solution.

In summary, for individual outcome prediction of survival after TIPS, FIPS score is the best option; whereas for risk stratification, Child-Pugh score appeared to be more favorable for Chinese patients, while FIPS score could provide a more detailed and accurate "secondary" risk stratification on the basis of Child-Pugh grade.

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Conflict of interest
Prof. Han is listed as a co-author in the FIPS study by Bettinger *et al.* due to his role of data acquisition.

Authors' contributions
Study concept and study design: Qiuhe Wang, and Guohong Han. Follow-up and data collection: Wei Bai. Statistical analyses: Qiuhe Wang. Drafting and revision of the manuscript: Qiuhe Wang, Wei Bai, and Guohong Han.

Data availability statement
The deidentified data can be made available upon request for non-commercial purposes and after approval of a study proposal through a signed data access agreement. Proposals should be directed to the corresponding author (hangh@fmmu.edu.cn).

Supplementary data
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Reply to: Correspondence on "Refining prediction of survival after TIPS with the novel Freiburg index of post-TIPS survival"

To the Editor:
With great interest, we have read the letters from Kraglund *et al.*[1] and Wang *et al.*[2] who provided external validation of the FIPS score[3] and also proposed a detailed risk stratification combining the Child-Pugh score and the FIPS score.

Kraglund *et al.* analyzed 104 patients who received transjugular intrahepatic portosystemic shunt (TIPS) implantation. In their cohort, only 5 patients presented with a FIPS score ≥0.92 and were therefore classified as high-risk patients. Due to the low number of high-risk patients the FIPS score did not show superior prognostic accuracy compared to the model for end-stage liver disease (MELD) and Child-Pugh score.[1]

Importantly, the authors mention that their cohort was similar to our FIPS cohort.[3] However, after reviewing the detailed description of the baseline characteristics of their study cohort,[4] it has to be mentioned that there are important differences compared to the FIPS cohort. Indeed, Kraglund *et al.* included 18 patients with emergency TIPS and 3 patients with urgent TIPS implantation (20.2% of the included 104 patients).[4] These patients with preemptive or urgent TIPS implantation were not included for development of the FIPS score as these patients are clinically

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