Peripheral immune markers can detect hepatocellular carcinoma in blood in a Latin American cohort

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Abstract

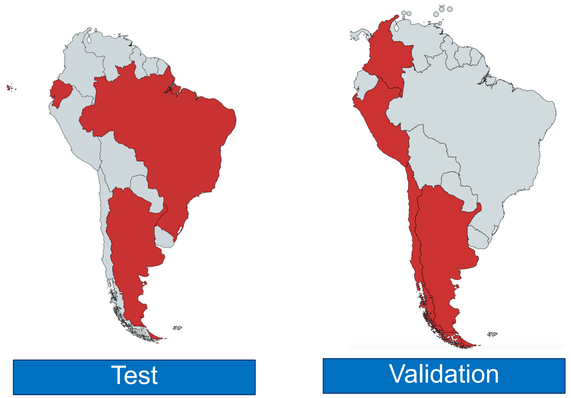
Background: Late detection of hepatocellular carcinoma (HCC) due to suboptimal surveillance with ultrasound is a major problem worldwide but with further importance in resource-limited settings. Blood biomarkers are urgently needed and currently alpha-fetoprotein (AFP) is the only accepted biomarker. However, AFP has poor accuracy for early HCC detection and has mainly been studied in resource-rich settings. We prospectively investigated circulating immune markers to detect HCC in 2 different groups of Latin American patients acting as discovery and validation cohorts.

Methods: Through the ESCALON network we prospectively evaluated a discovery cohort of 127 individuals with HCC and 113 cirrhotic controls from 3 countries in Latin America (Argentina, Brazil and Ecuador) as well as a validation cohort of 145 HCCs and 75 cirrhotic individuals from a different set of institutions in Latin America (Chile, Peru, Argentina, Ecuador, Colombia). Blood samples were analyzed for 37 unique immune markers using the multiplex Bio-Rad platform. Differences between HCC and cirrhosis were analyzed via t-test and ANOVA, and tuned with lasso coefficient-bootstrap computing. We used leave-one-out cross-validation (LOOCV) to compute an ROC curve.

Results: In the discovery cohort 22 markers showed a significant difference between cases and controls for all size tumors and 15 for those tumors <5cm. A set of 5 markers which were highly differential in HCC vs cirrhosis controls identified via Lasso and bootstrap: HGF, MIP-3a, MIG, CCL-25, and MDC. The AUROC for this top-5 set in detecting HCC was 0.83 (CI 0.78-0.88) for all tumors and 0.75 (CI 0.66-0.83) for tumors <5cm. In this same cohort, the AUROC for AFP was only 0.69 for all tumors and 0.66 for tumors <5cm. The addition of AFP to the top-5 markers did not significantly increase the AUROC (0.83 to 0.85). We investigated the set of top-5 markers in the validation cohort and found that they could detect HCC with an AUROC of 0.73 (CI 0.642-0.810). The main differences between both cohorts were in the underlying liver diseases in HCC, with viral hepatitis being the most common in the validation cohort (42%) and non-alcoholic fatty liver disease in the validation cohort (56%).

Conclusions: Our study identified a set of 5 cytokines that can detect HCC by means of blood measurement in a discovery and validation cohort in Latin America. To our knowledge this is the first study assessing immune markers with a high degree of accuracy in a unique Latin American cohort.

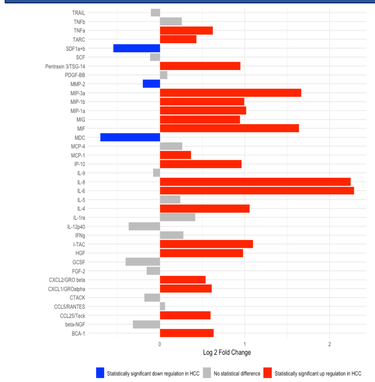
Countries



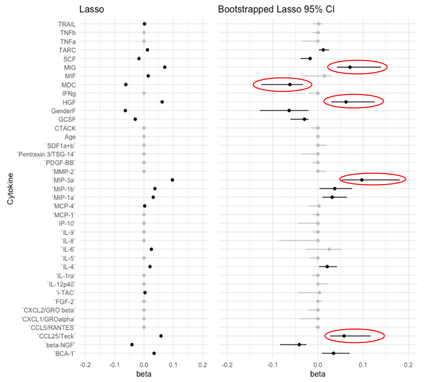
Test | Validation

Results

T-test

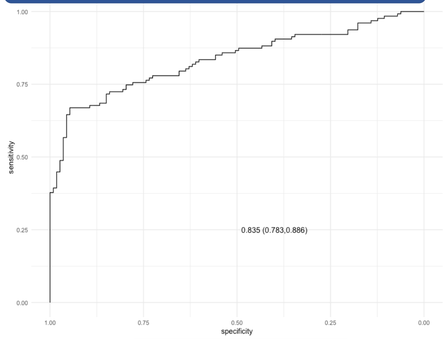


Lasso/Bootstrapped Lasso



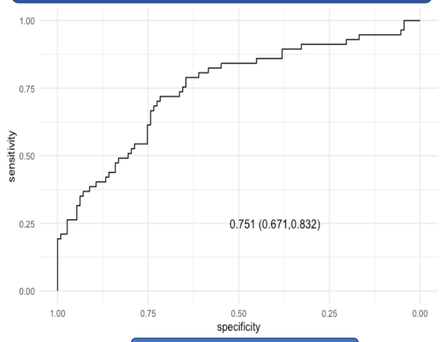
MIP3A, MIG, CCL-25, MDC, HGF

All HCC



AUROC 0.83 (CI 0.78-0.88)

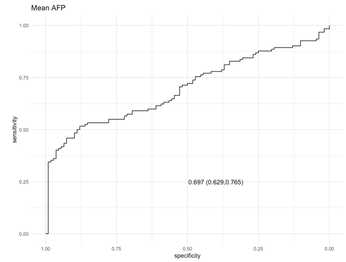
HCC <5cm



AUROC 0.75 (CI 0.66-0.83)

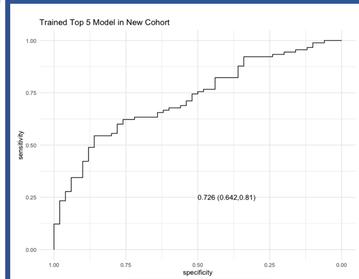
Results

AFP



AUROC: 0.697

Top 5 markers-Validation cohort



AUROC: 0.726

Conclusions

- Our study identified a set of 5 cytokines that can detect HCC with a high degree of confidence in a South American cohort
- The 5 cytokines showed a superior AUC than AFP and were reliable in tumors <5cm
- The AUC decreased in the validation cohort likely owing to the difference sin underlying liver disease
- A larger study is underway to confirm these findings