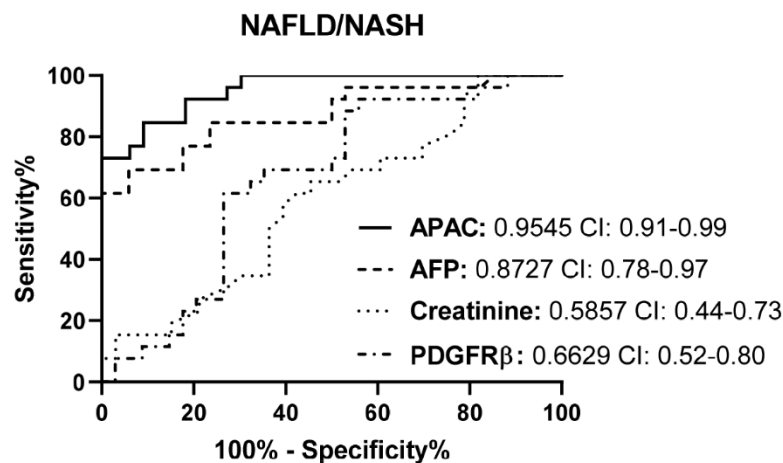
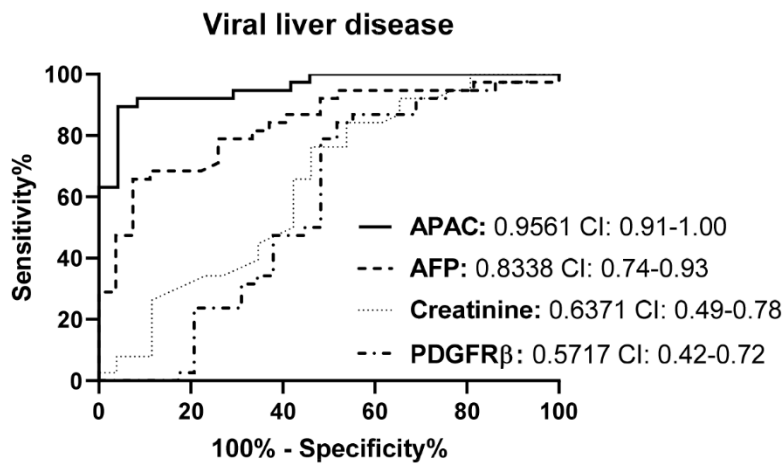
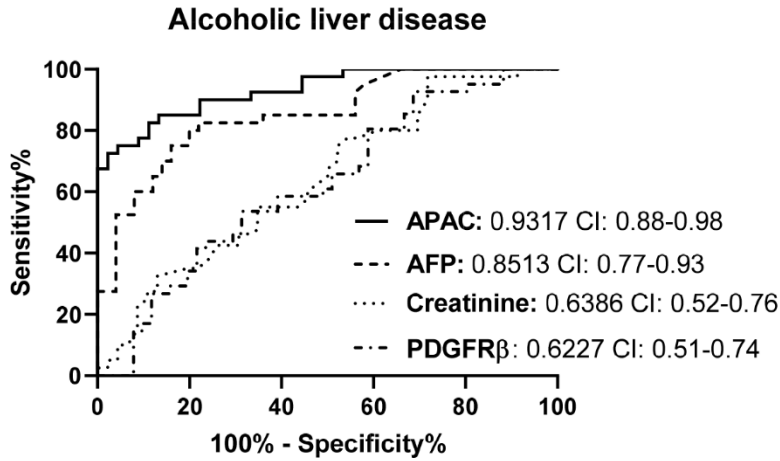
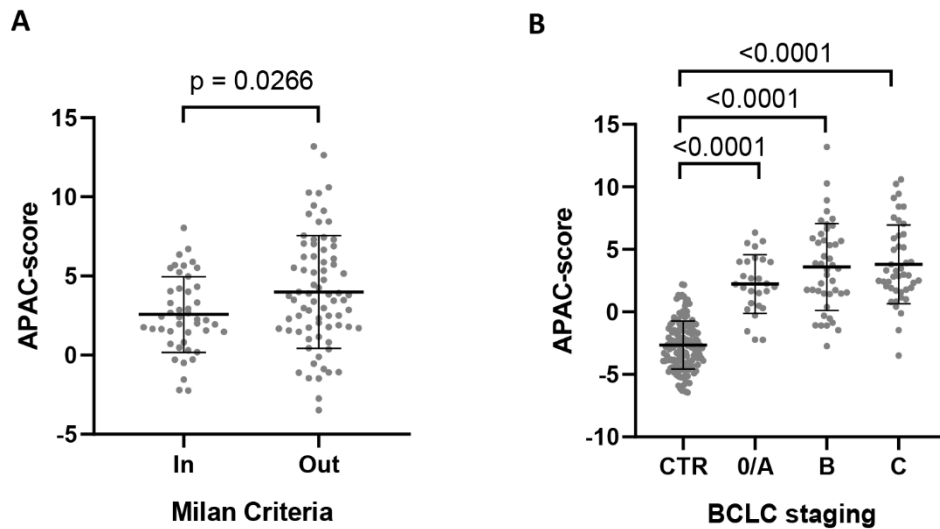


**Supplementary Figure S1.** The diagnostic accuracy of the APAC-score is not influenced by the extent of cirrhosis. The comparison of APAC-scores between HCC patients and cirrhotic controls, with all individuals categorized into Child-Pugh stage A, identified the high and superior diagnostic accuracy of the APAC-score, as compared to the GALAD-score. The area under the ROC-curve (AUC) values and their confidence interval (CI) are given.

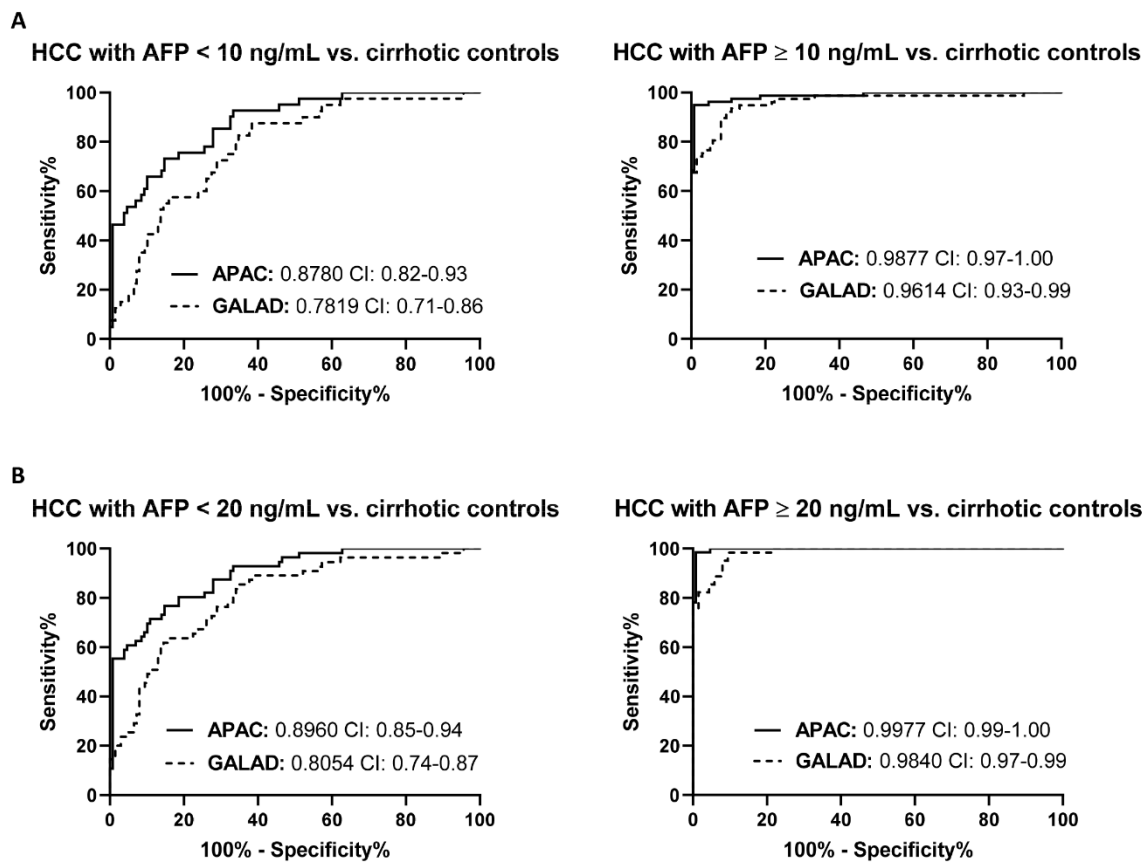


**Supplementary Figure S2.** Etiology-independence of the APAC-score, compared to its constituents, for diagnosis of HCC. Receiver operating characteristic curves identified constant, and superior, diagnostic accuracy of the APAC-score for the diagnosis of HCC in each

etiology-specific HCC patient cohort. The area under the ROC-curve (AUC) values and their confidence interval (CI) are given.



**Supplementary Figure S3.** Relationship of the APAC-score with the stage of HCC, as measured through (A) Milan criteria and (B) BCLC-staging.



**Supplementary Figure S4.** Diagnostic utility of the APAC-score in HCC patients with low levels of AFP. HCC patients were divided into those with low and high levels of circulating AFP, based on the cut-offs of (A) 10 ng/mL and (B) 20 ng/mL. Receiver operating characteristic curves identified the APAC-score to be superior for HCC diagnosis, independent of the circulating AFP levels. The area under the ROC-curve (AUC) values and their confidence interval (CI) are given.

**Supplementary Table S1.** Accuracy of soluble PDGFR $\beta$ -levels for the diagnosis of hepatocellular carcinoma, in comparison to clinical-used serological HCC scoring tools.

|                        | Cut-off value | AUC (95% CI)           | p-value AUC (vs. sPDGFR $\beta$ ) | Sensitivity, % | Specificity, % | PPV, % | NPV, % |
|------------------------|---------------|------------------------|-----------------------------------|----------------|----------------|--------|--------|
| sPDGFR $\beta$ , pg/mL | 8106          | 0.6421 (0.5758-0.7084) | -                                 | 69.67          | 56.64          | 57.48  | 68.94  |
| AFP, ng/mL             | 6.350         | 0.8571 (0.8113-0.9028) | < 0.0001                          | 79.17          | 78.17          | 75.31  | 81.69  |
| MELD                   | 11.06         | 0.7956 (0.7390-0.8521) | 0.0075                            | 72.73          | 76.03          | 71.85  | 76.82  |
| ALBI                   | -1.999        | 0.6896 (0.6195-0.7598) | ns                                | 70.25          | 65.71          | 63.28  | 72.42  |
| GALAD                  | -0.6373       | 0.8995 (0.5612-0.9379) | < 0.0001                          | 81.20          | 85.51          | 82.50  | 84.39  |

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin score; APAC, age, PDGFR $\beta$ , AFP, creatinine-score; AUC, area under the ROC curve; GALAD, gender, age, AFP-L3, and DCP-score; MELD, model for end-stage liver disease; NPV, negative predictive value; PDGFR $\beta$ , platelet derived growth factor receptor beta, PPV, positive predictive value;.

**Supplementary Table S2.** Comparison of the performance of the APAC-score with its constituents and the GALAD score for diagnosis of hepatocellular carcinoma in etiology-specific cohorts.

|                                | Cut-off value | AUC (95% CI)           | p-value AUC (vs. APAC) | Sensitivity, % | Specificity, % | PPV, % | NPV, % |
|--------------------------------|---------------|------------------------|------------------------|----------------|----------------|--------|--------|
| <b>Alcoholic liver disease</b> |               |                        |                        |                |                |        |        |
| APAC                           | 0.6419        | 0.9317 (0.8811-0.9822) | -                      | 75.00          | 95.56          | 93.14  | 82.63  |
| sPDGFR $\beta$ , pg/mL         | 11228         | 0.6227 (0.5084-0.7370) | < 0.0001               | 92.68          | 31.37          | 52.05  | 84.21  |
| Creatinine, mg/dL              | 1.450         | 0.6386 (0.5222-0.7550) | < 0.0001               | 97.50          | 28.26          | 52.21  | 52.21  |
| AFP, ng/mL                     | 6.050         | 0.8513 (0.7723-0.9302) | 0.0500                 | 82.50          | 78.00          | 75.09  | 75.09  |
| GALAD                          | -0.4254       | 0.8520 (0.7704-0.9336) | 0.0499                 | 80.00          | 84.00          | 80.07  | 83.94  |
| <b>Viral liver disease</b>     |               |                        |                        |                |                |        |        |
| APAC                           | 0.7731        | 0.9561 (0.9096-1.0000) | -                      | 92.11          | 91.67          | 93.54  | 93.54  |
| sPDGFR $\beta$ , pg/mL         | 8907          | 0.5717 (0.4201-0.7233) | 0.0002                 | 84.21          | 48.28          | 68.08  | 70.01  |
| Creatinine, mg/dL              | 0.9150        | 0.6371 (0.4922-0.7821) | 0.0001                 | 84.21          | 46.15          | 67.19  | 69.05  |
| AFP, ng/mL                     | 23.45         | 0.8338 (0.7351-0.9325) | 0.0005                 | 65.79          | 92.59          | 92.08  | 67.38  |
| GALAD                          | -1.018        | 0.9027 (0.8242-0.9812) | 0.0683 (ns)            | 86.49          | 88.00          | 90.42  | 83.26  |
| <b>NAFLD</b>                   |               |                        |                        |                |                |        |        |
| APAC                           | -0.1217       | 0.9545 (0.9094-0.9997) | -                      | 84.62          | 90.91          | 87.68  | 88.55  |
| sPDGFR $\beta$ , pg/mL         | 9731          | 0.6629 (0.5236-0.8021) | 0.0001                 | 92.31          | 44.12          | 55.81  | 88.24  |
| Creatinine, mg/dL              | 1.090         | 0.5857 (0.4392-0.7321) | < 0.0001               | 65.38          | 54.55          | 52.38  | 67.33  |
| AFP, ng/mL                     | 9.750         | 0.8727 (0.7788-0.9666) | 0.0286                 | 69.23          | 94.12          | 90.00  | 80.00  |
| GALAD                          | -0.8344       | 0.9095 (0.8322-0.9796) | 0.1531 (ns)            | 76.00          | 88.24          | 83.17  | 82.78  |

AFP, alpha-fetoprotein; APAC, age, PDGFR $\beta$ , AFP, creatinine-score; AUC, area under the ROC curve; GALAD, gender, age, AFP-L3, and DCP-score; NPV, negative predictive value; ns, non-significant; PDGFR $\beta$ , platelet derived growth factor receptor beta; PPV, positive predictive value.

**Supplementary Table S3.** Comparison of the performance of the APAC-score with the GALAD score for diagnosis of early or late stage hepatocellular carcinoma.

|                               | Cut-off value | AUC (95% CI)           | p-value AUC (vs. APAC) | Sensitivity, % | Specificity, % | PPV, % | NPV, % |
|-------------------------------|---------------|------------------------|------------------------|----------------|----------------|--------|--------|
| <b>Inside Milan criteria</b>  |               |                        |                        |                |                |        |        |
| APAC                          | -0.3225       | 0.9488 (0.9133-0.9844) | -                      | 91.11          | 85.27          | 64.71  | 97.00  |
| GALAD                         | -0.4405       | 0.8583 (0.7961-0.9205) | 0.0006                 | 71.11          | 86.96          | 61.79  | 91.03  |
| <b>Outside Milan criteria</b> |               |                        |                        |                |                |        |        |
| APAC                          | 0.7969        | 0.9505 (0.9205-0.9804) | -                      | 83.78          | 95.35          | 90.31  | 91.91  |
| GALAD                         | 0.0972        | 0.9261 (0.8857-0.9666) | 0.1899 (ns)            | 80.56          | 92.03          | 83.94  | 90.15  |
| <b>BCLC 0/A</b>               |               |                        |                        |                |                |        |        |
| APAC                          | 0.1839        | 0.9317 (0.8787-0.9846) | -                      | 85.19          | 89.15          | 59.37  | 97.00  |
| GALAD                         | -2.2860       | 0.8081 (0.7195-0.8967) | 0.0006                 | 88.89          | 61.59          | 30.10  | 96.75  |
| <b>BCLC B</b>                 |               |                        |                        |                |                |        |        |
| APAC                          | 1.3970        | 0.9430 (0.9047-0.9813) | -                      | 79.07          | 99.22          | 96.85  | 93.98  |
| GALAD                         | -0.4405       | 0.9060 (0.8550-0.9570) | 0.0754 (ns)            | 80.95          | 86.96          | 65.32  | 93.77  |
| <b>BCLC C</b>                 |               |                        |                        |                |                |        |        |
| APAC                          | 0.7969        | 0.9662 (0.9332-0.9991) | -                      | 90.91          | 95.35          | 85.58  | 97.19  |
| GALAD                         | -0.6373       | 0.9389 (0.8900-0.9879) | 0.2570 (ns)            | 92.86          | 85.51          | 66.03  | 97.53  |

APAC, age, PDGFR $\beta$ , AFP, creatinine-score; AUC, area under the ROC curve; BCLC, Barcelona clinic liver cancer-score; GALAD, gender, age, AFP-L3, and DCP-score; ns, non-significant; NPV, negative predictive value; PPV, positive predictive value.

**Supplementary Table S4.** Performance of the APAC-score, in comparison to the GALAD-score, for diagnosis of hepatocellular carcinoma in patients with high or low levels of AFP.

|                          | AUC (95% CI)           | p-value AUC (vs. APAC) |
|--------------------------|------------------------|------------------------|
| <b>AFP &lt; 10 ng/mL</b> |                        |                        |
| APAC                     | 0.8780 (0.8212-0.9349) | -                      |
| GALAD                    | 0.7819 (0.7052-0.8586) | 0.0146                 |
| <b>AFP ≥ 10 ng/mL</b>    |                        |                        |
| APAC                     | 0.9877 (0.9741-1.0000) | -                      |
| GALAD                    | 0.9614 (0.9336-0.9893) | 0.0126                 |
| <b>AFP &lt; 20 ng/mL</b> |                        |                        |
| APAC                     | 0.8960 (0.8487-0.9434) | -                      |
| GALAD                    | 0.8054 (0.7375-0.8733) | 0.0045                 |
| <b>AFP ≥ 20 ng/mL</b>    |                        |                        |
| APAC                     | 0.9977 (0.9939-1.0000) | -                      |
| GALAD                    | 0.9840 (0.9716-0.9964) | 0.0367                 |

AFP, alpha-fetoprotein; APAC, age, PDGFR $\beta$ , AFP, creatinine-score; AUC, area under the ROC curve; GALAD, gender, age, AFP-L3, and DCP-score; ns, non-significant; NPV, negative predictive value; PPV, positive predictive value.