## Appendix 1

## Methods

### *Formulas for serum models of liver fibrosis or prognostic scores*

Two serum models of liver fibrosis were calculated according to the following (15,16):

$$\text{APRI} = [\text{AST (U/L)}/\text{upper limit of normal AST} \times 100]/\text{platelet count } (10^9/\text{L}) \quad [2]$$

$$\text{Fibrosis-4 index} = [\text{age (year)}] \times [\text{AST (U/L)}]/[\text{platelet count } (10^9/\text{L}) \times \text{ALT level (U/L)}^{1/2}] \quad [3]$$

Three serum parameters of prognostic scores were calculated according to the following:

$$\text{MELD} = [0.957 \times \ln(\text{serum Cr}) + 0.378 \times \ln(\text{serum bilirubin}) + 1.120 \times \ln(\text{international normalized ratio}) + 0.643] \times 10 \quad [4]$$

(if hemodialysis, value for creatinine is automatically set to 4.0)

Note: if any score is <1, the MELD assumes the score is equal to 1 (32);

$$\text{MELD-Na} = \text{MELD score} - \text{Na} - 0.025 \times \text{MELD} \times (140 - \text{Na}) + 140 \quad [5]$$

Note: sodium is limited in a range of 125–140, and if outside of these bounds, is set to the nearest limit (33);

Child-Pugh (34):

| Factors | Levels | Points |
|---|---|---|
| Bilirubin (total) | <2 mg/dL (<34.2 μmol/L) | 1 |
| | 2–3 mg/dL (34.2–51.3 μmol/L) | 2 |
| | >3 mg/dL (>51.3 μmol/L) | 3 |
| Albumin | >3.5 g/dL (>35 g/L) | 1 |
| | 2.8–3.5 g/dL (28–35 g/L) | 2 |
| | <2.8 g/dL (<28 g/L) | 3 |
| International normalized ratio | <1.7 | 1 |
| | 1.7–2.2 | 2 |
| | >2.2 | 3 |
| Ascites | Absent | 1 |
| | Slight | 2 |
| | Moderate | 3 |
| Encephalopathy | No encephalopathy | 1 |
| | Grade 1–2 | 2 |
| | Grade 3–4 | 3 |

## References


32. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-70.
33. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau TM. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008;359:1018-26.
34. Child CG, Turcotte JG. Surgery and portal hypertension. Major Probl Clin Surg 1964;1:1-85.



https://dx.doi.org/10.21037/qims-21-871

**Table S1** Packages of R software used in this study

| Functions | R package |
|---|---|
| Harrell's C-index, log-rank | survival |
| PH-CR model | cmprsk |
| AUC | pROC |
| Bar diagrams and ROC | ggplot2 |
| IDI | survIDINRI |
| Hosmer-Lemeshow test | ResourceSelection |
| VIF | car |
| Kaplan-Meier | survminer |
| Calibration curves | rms |

C-index, concordance index; PH-CR, proportional-hazards competing risk; AUC, area under the receiver operating characteristic curve; ROC, receiver operating characteristic; IDI, Integrated Discriminating Improvement; VIF, variance inflation factor.

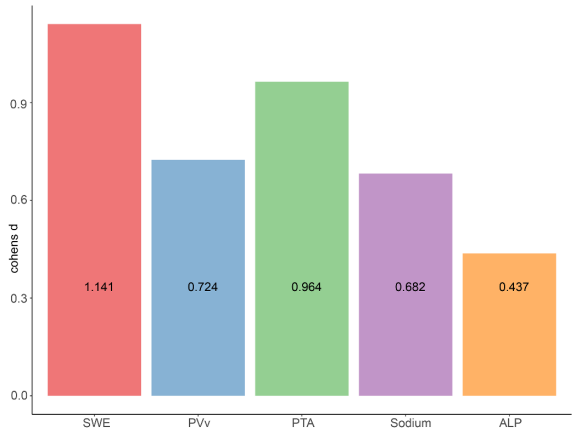


**Figure S1** Percentage effect size (mean the difference between alive and dead patients/standard deviation) for the main predictors of 90-day ACLF development in univariate analysis. ACLF, acute-on-chronic liver failure; SWE, shear wave elastography; PVv, peak velocity of portal vein; PTA, prothrombin activity; ALP, alkaline phosphatase.

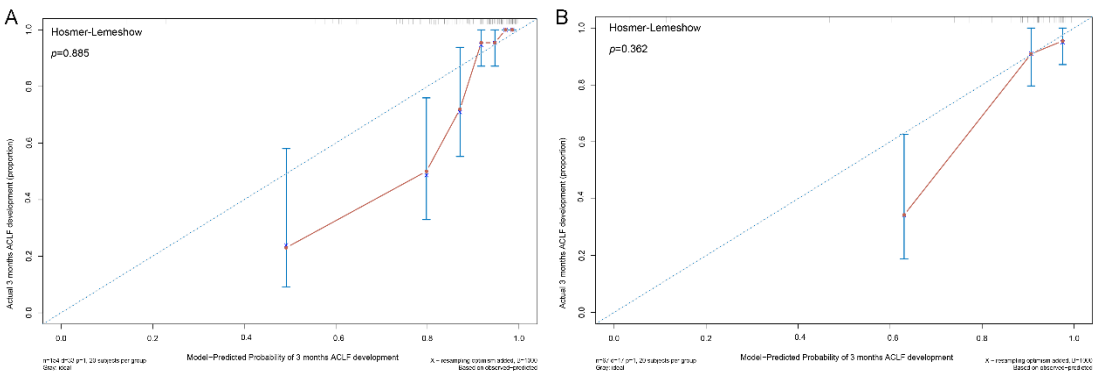


**Figure S2** Calibration curves for estimation of 90-day ACLF development predicted by the SWE model in the derivation (A) and validation cohorts (B). ACLF, acute-on-chronic liver failure; SWE, shear wave elastography.


https://dx.doi.org/10.21037/qims-21-871

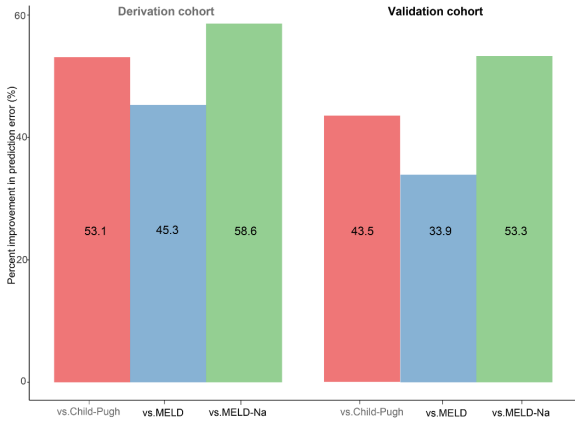


**Figure S3** Relative (percentage) reduction in prediction error rates of the SWE model score compared to Child-Pugh, MELD, and MELD-Na scores. SWE, shear wave elastography; MELD, model for end-stage liver disease.

**Table S2** Summary of baseline patient characteristics in the derivation and validation cohorts by 90-day ACLF development

| Characteristics | Derivation cohort | | | Validation cohort | | |
|---|---|---|---|---|---|---|
| | ACLF developed (n=33) | ACLF absent (n=121) | P value | ACLF development (n=17) | ACLF absent (n=50) | P value |
| Clinical data | | | | | | |
| Age | 47.24±11.02 | 52.03±12.33 | 0.045 | 50.29±9.22 | 55.92±12.25 | 0.088 |
| Female sex | 5 (15.2) | 36 (29.8) | 0.120 | 6 (35.3) | 12 (24.0) | 0.364 |
| Body mass index, kg/m$^2$ | 23.8 (20.3–27.0) | 21.8 (19.5–24.6) | 0.027 | 23.1 (20.8–28.1) | 21.3 (20.3–24.0) | 0.068 |
| MBP | 88.80±12.66 | 87.31±13.02 | 0.558 | 81.45±10.20 | 88.68±11.86 | 0.028 |
| Ascites | 29 (87.9) | 104 (86.0) | 1.000 | 16 (94.1) | 43 (86.0) | 0.448 |
| Splenomegaly* | 24 (75.0) | 90 (76.9) | 0.820 | 15 (88.2) | 38 (80.9) | 0.712 |
| Infections | 27 (81.8) | 84 (69.4) | 0.159 | 13 (76.5) | 30 (60.0) | 0.257 |
| Gastrointestinal bleeding | 5 (15.2) | 17 (14.0) | 0.873 | 2 (11.8) | 6 (88.2) | 1.000 |
| Hepatic encephalopathy | 2 (6.1) | 10 (8.3) | 0.742 | 0 | 0 | – |
| Laboratory data | | | | | | |
| HBeAg: positive | 14 (42.4) | 38 (31.4) | 0.235 | 5 (29.4) | 15 (30.0) | 0.963 |
| Log HBV DNA, copies/mL | 5.62 (4.26–7.29) | 5.06 (2.93–6.48) | 0.193 | 5.76 (4.71–7.16) | 4.54 (2.93–5.76) | 0.149 |
| White-cell count, ×10$^9$/L | 5.56 (4.43–7.27) | 4.35 (2.97–5.92) | 0.016 | 5.55 (1.96–6.76) | 4.61 (3.44–7.42) | 0.795 |
| PLT, 10$^9$/L | 85.0 (59.0–112.0) | 91.0 (49.0–132.0) | 0.814 | 67.0 (44.0–122.0) | 93.0 (53.5–163.0) | 0.252 |
| Serum albumin, g/dL | 2.82±0.52 | 2.91±0.54 | 0.392 | 3.00±0.63 | 2.95±0.52 | 0.718 |
| Serum bilirubin, mg/dL | 12.54 (10.14–17.29) | 4.49 (3.08–11.85) | <0.001 | 10.97 (3.82–18.65) | 4.45 (2.84–15.17) | 0.103 |
| Serum creatinine, mg/dL | 0.72 (0.61–0.79) | 0.74 (0.64–0.89) | 0.123 | 0.77 (0.67–1.04) | 0.78 (0.65–0.97) | 0.564 |

**Table S2** (*continued*)


https://dx.doi.org/10.21037/qims-21-871

**Table S2** (*continued*)

| Characteristics | Derivation cohort | | | Validation cohort | | |
|---|---|---|---|---|---|---|
| | ACLF developed (n=33) | ACLF absent (n=121) | P value | ACLF development (n=17) | ACLF absent (n=50) | P value |
| Plasma sodium, mEq/L | 135.9 (132.7–138.1) | 139.1 (137.0–140.7) | <0.001 | 132.7 (130.9–136.4) | 138.2 (135.4–40.1) | 0.003 |
| ALT, IU/L | 97.0 (57.0–385.8) | 44.0 (24.0–258.0) | 0.036 | 43.0 (28.0–104.0) | 34.5 (23.5–134.9) | 0.521 |
| AST, IU/L | 137.0 (88.0–285.2) | 62.0 (44.4–193.0) | 0.013 | 98.0 (66.0–204.0) | 51.5 (40.6–162.7) | 0.113 |
| GGT, IU/L | 84.0 (51.0–124.0) | 63.0 (27.0–127.0) | 0.152 | 48.0 (29.0–128.0) | 41.5 (20.3–101.5) | 0.436 |
| ALP, IU/L | 150.0 (130.3–213.9) | 125.0 (101.0–170.0) | 0.015 | 133.0 (107.0–183.0) | 114.5 (87.0–170.2) | 0.138 |
| LDH, IU/L | 248.0 (211.6–333.0) | 259.0 (210.0–325.0) | 0.718 | 292.2 (216.0–328.0) | 270.1 (223.8–329.8) | 0.851 |
| PT, s | 19.8 (18.0–23.9) | 16.9 (16.2–19.2) | <0.001 | 22.4 (20.4–24.5) | 16.8 (16.2–18.3) | <0.001 |
| INR | 1.76 (1.57–2.10) | 1.48 (1.40–1.62) | <0.001 | 1.94 (1.81–2.25) | 1.50 (1.41–1.60) | <0.001 |
| PTA, % | 40.6 (33.6–47.9) | 51.5 (45.7–57.2) | <0.001 | 34.4 (30.6–38.3) | 51.8 (44.9–56.5) | <0.001 |
| Ultrasounic data | | | | | | |
| Spleen longitudinal diameter, mm | 14.2 (13.2–16.2) | 13.6 (11.6–15.2) | 0.138 | 14.5 (12.4–15.8) | 13.9 (12.0–15.3) | 0.589 |
| portal vein diameter, mm | 13.2 (12.6–14.8) | 12.5 (11.4–13.4) | 0.005 | 12.5 (11.1–13.7) | 12.6 (11.4–13.8) | 0.634 |
| HAv, cm/s | 59.88 (49.42–74.62) | 59.92 (48.22–71.34) | 0.444 | 58.80 (45.82–61.90) | 53.62 (47.10–60.20) | 0.948 |
| PVv, cm/s | 13.80 (10.40–15.25) | 15.75 (12.12–18.30) | 0.001 | 12.50 (10.90–16.96) | 15.76 (10.30–19.49) | 0.258 |
| HARI | 0.73 (0.70–0.77) | 0.72 (0.69–0.77) | 0.984 | 0.74 (0.71–0.79) | 0.73 (0.70–0.77) | 0.638 |
| Fibrosis tests | | | | | | |
| 2D SWE, kPa | 44.8 (35.7–54.2) | 26.2 (18.2–36.3) | <0.001 | 42.8 (33.3–52.8) | 24.15 (18.73–34.25) | 0.001 |
| SWE results | | | | | | |
| "Very reliable"[#] | 10 (27.0) | 33 (26.4) | 0.153 | 4 (22.2) | 14 (26.9) | 0.898 |
| "Reliable"[#] | 23 (62.2) | 88 (70.4) | | 13 (72.2) | 36 (69.2) | |
| "Poorly reliable"[#] | 4 (10.8) | 4 (3.2) | | 1 (5.6) | 2 (3.8) | |
| APRI | 3.75 (2.21–7.47) | 2.85 (1.80–5.42) | 0.044 | 2.34 (1.88–9.51) | 2.52 (1.15–4.13) | 0.098 |
| Fibrosis-4 index | 7.59 (5.18–15.77) | 7.43 (4.36–10.77) | 0.374 | 7.19 (6.41–14.58) | 6.30 (4.16–11.54) | 0.086 |
| Severity scores | | | | | | |
| Child-Pugh | 13.0 (12.0–14.0) | 12.0 (11.0–13.0) | 0.002 | 13.0 (12.0–14.0) | 12.0 (10.0–13.0) | 0.017 |
| MELD | 23.79 (20.83–25.32) | 16.80 (14.89–20.29) | <0.001 | 24.72 (19.69–26.94) | 17.00 (14.76–22.32) | 0.003 |
| MELD-Na | 25.18 (22.56–27.64) | 18.30 (15.88–21.81) | <0.001 | 26.10 (22.00–29.49) | 18.96 (16.00–23.44) | 0.001 |
| Outcome | | | | | | |
| 90-day mortality rate[†] | 16 (48.5) | 5 (4.1) | | 8 (47.1) | 2 (4.0) | |

Continuous data were expressed as mean ± standard deviation or median (25–75% quantiles); categorical data were expressed as n (%). *, 1 patients ACLF developed and 4 patients ACLF absent of the derivation cohort and 3 patients ACLF absent of the validation cohort underwent splenectomy; [#], 2D SWE reliability by IQR/M: "very reliable" (IQR/M ≤0.10), "reliable" (0.10< IQR/M ≤0.3), and "poorly reliable" (IQR/M >0.30); [†], the start date of the follow-up period was the date of hospital admitted. ACLF, acute-on-chronic liver failure; MBP, mean arterial pressure; HBeAg, hepatitis B e antigen; HBV, hepatitis B viral; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, g-glutamyl transferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; PT, prothrombin time; INR, international normalized ratio; PTA, prothrombin activity; HAv, hepatic arterial velocity; PVv, peak velocity of portal vein; HARI, hepatic arterial resistive index; 2D, two-dimensional; SWE, shear wave elastography; APRI, aspartate aminotransferase-to-platelet ratio index; MELD, model for end-stage liver disease; IQR/M, interquartile range/median ratio.


https://dx.doi.org/10.21037/qims-21-871