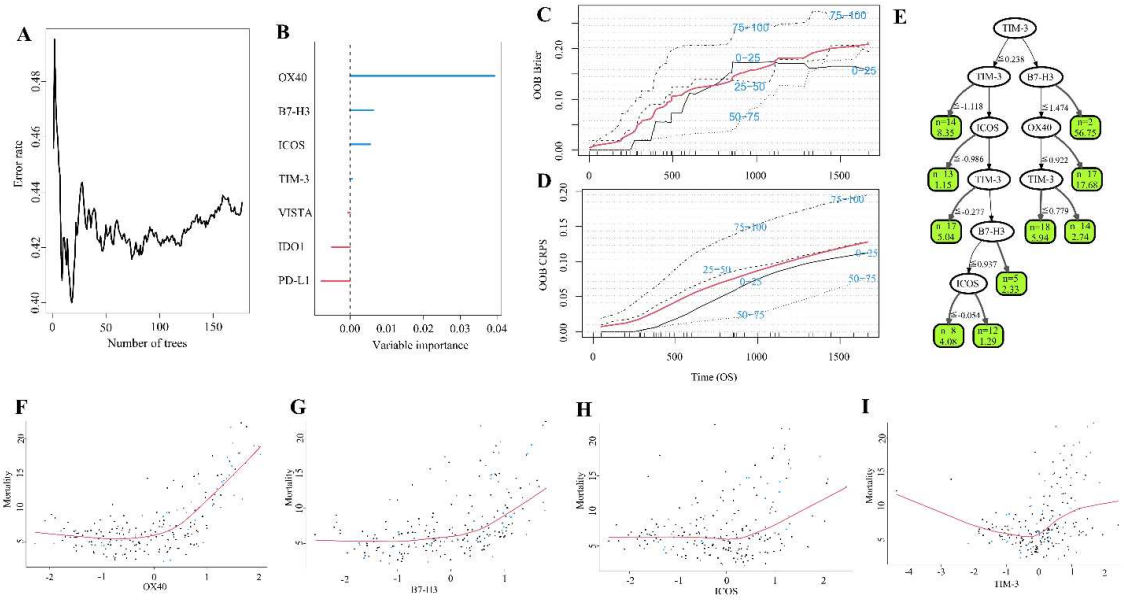

Supplementary Figure S2: Variable selection and construction of the ICS, a classifier comprising four immune checkpoints, using a random forest model in the discovery set (n = 212).

(A) Seven variables were included in the random forest model, and as the number of trees increased, the error rate gradually stabilized between 0.42-0.44. When the parameter "ntree" was set to 177, we calculated the Gini index of these seven variables. Plot (B) shows the importance of seven variables when predicting OS. According to the importance ranking (variable importance > 0), OX40, B7-H3, ICOS and TIM-3 were selected for the model. Since the random forest model cannot be visualized directly, the decision tree was used to indirectly reflect the prediction process of the model. The out-of-bag (OOB) Brier and OOB continuous rank probability score (CRPS) were consistently used to evaluate the prediction accuracy of the model. Plots (C and D) show that the OOB Brier and OOB CRPS gradually increase as the OS time increased. Brier score (0 = perfect, 1 = poor, and 0.25 = guessing) stratified by ensemble mortality. Stratification was performed into 4 groups corresponding to the 0-25, 25-50, 50-75 and 75-100 percentile values of mortality. The red line is the overall (nonstratified) Brier score. CRPS equals the integrated Brier score divided by

time. Plot (E) shows a decision tree in the random forest. A nonlinear relationship exists between the four selected genes, OX40 (F), B7-H3 (G), ICOS (H) and TIM-3 (I), and mortality. Overall, TIM-3 was a protective factor, whereas OX40, B7-H3 and ICOS were risk factors.

Abbreviations: ICS, immune checkpoint-based signature; OOB, out-of-bag; CRPS, continuous rank probability score; TIM-3, T cell immunoglobulin and mucin domain containing-3; ICOS, inducible costimulatory molecule; OX40, costimulatory molecule 40.