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A Novel Clinical Five-Risk Factor Panel for Individualized Recurrence Risk Assessment of Patients With Acute Anterior Uveitis

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Purpose: Detecting and managing relapses of acute anterior uveitis (AAU) is necessary for improving follow-up planning to minimize recurrences and further complications. However, reliable clinical and laboratory risk factors are lacking, as is a predictive model for use in clinical practice that is capable of identifying patients at high risk for recurrence after remission.

Methods: We analyzed 38 laboratory parameters and clinical data from a large longitudinal retrospective cohort of 233 patients with AAU. Association of laboratory parameters with recurrence-free survival (RFS) was evaluated using univariate Cox proportional hazards regression. A clinically applicable predictive model was developed using a logistic regression model.

Results: Of the 38 laboratory parameters studied, we identified 5 parameters (HDL, ankylosing spondylitis, HLA-B27, MO, and LDL) to be associated with RFS. We developed a clinical five-risk factor panel (5RF-panel), which was capable of effectively distinguishing recurrent patients from nonrelapsed patients (area under the curve [AUC] = 0.837), as well as between patients with high and low risks of AAU recurrence (hazard ratio [HR] = 45.874, 95% confidence interval [CI] = 5.232-402.2, $P < 0.001$). The robust performance of the 5RF-panel was further validated in the testing cohort (AUC = 0.725, and HR = 51.982, 95% CI = 4.438-608.9, $P = 0.024$). Furthermore, the 5RF-panel demonstrated superior performance in stratifying recurrence risk based on known risk factors.

Conclusions: We identified and validated a novel clinical 5RF-panel to predict individualized risk of AAU recurrence and improved patient classification for clinical management.

Translational Relevance: The present study identified and validated a 5RF-panel that is a promising individualized predictive tool to monitor recurrence risk and guide personalized management of patients with AAU.

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Introduction

Uveitis, an intraocular inflammation involving the middle layer of the eye, the uvea, and the surrounding tissues, is the fifth leading cause of blindness in the United States, where it is estimated to account for approximately 10% to 15% of blindness cases. The incidence of uveitis is estimated to be 17 to 52 cases per 100,000 person-years, and the prevalence rate of uveitis is 38 to 714 per 100,000 person-years.[1] Uveitis can be broadly classified into four anatomic subtypes: anterior, intermediate, posterior, and panuveitis. A clinico-epidemiological survey of patients with uveitis in a Chinese tertiary center indicated that acute anterior uveitis (AAU), which account for more than 45% of diagnosed cases, is the most frequent type of uveitis.[2]

The primary ocular symptoms of AAU are pain, redness, and photophobia. In severe cases, it may also lead to posterior synechia, secondary glaucoma, and complicated cataracts, among other complications. Although the prognosis is generally good for patients with AAU, many individuals with remitted primary anterior uveitis will experience relapse in the form of repetitive episodes of intraocular inflammation, which can ultimately lead to tissue damage, increased complications, and even blindness.[3,4] Therefore, detecting and managing relapses of AAU will improve personalized treatment and allow effective follow-up planning to minimize recurrences and further complications.

Previous studies have identified a number of indicators associated with AAU recurrence. For example, young adults and men are more prone to recurrence. HLA-B27 and ankylosing spondylitis (AS) are both important risk factors in the onset and recurrence of AAU. The number of previous episodes a patient has experienced is an additional predisposing factor for AAU recurrence.[3,5–9] However, despite the fact that several risk factors associated with AAU recurrence have been proposed, reliable clinical and laboratory risk factors and predictive models for use in clinical practice to identify patients at high risk for recurrence after remission remain lacking.

In this study, we performed a systematic analysis of pathological relevant laboratory parameters and clinical data from a large retrospective cohort of 233 patients diagnosed with AAU, with the goal of identifying high-risk factors for AAU recurrence and developing a clinically applicable predictive model for individualized recurrence risk assessment and management of patients with AAU.

Materials and Methods

Study Population

Data from 233 patients diagnosed with AAU between January 2015 and February 2020 according to the criteria established by the International Uveitis Study Group were retrospectively retrieved from an eye hospital affiliated with Wenzhou Medical University.[10] All patients diagnosed with AAU were followed up for at least 11 months, with a follow-up rate of 85.35% (233/273). The most recent follow-up time was January 2021. All included patients were in the active state (i.e. presented with ocular inflammation). We focused solely on acute uveitis, so we only included patients with an onset time below 3 months. Exclusion criteria were: (1) the presence of intermediate and/or posterior uveitis and/or other concomitant ocular inflammatory diseases; (2) the presence of other systemic autoimmune diseases beyond ankylosing spondylitis; (3) the presence of malignant tumors or ongoing treatment for malignant tumors; (4) pregnancy or breastfeeding; (5) presence of infectious disease; and (6) confirmation of two recurrences where the time of the second recurrence was unknown during follow-up. Three (1.09%) patients were excluded because the second recurrence time was not accurate. Thirty-seven (13.55%) patients were lost to follow-up. The study was approved by the Ethic Committee of the Eye Hospital of Wenzhou Medical University.

Data Collection

All patient laboratory and clinical data were recorded in the medical record system during the initial visit. We included all recorded laboratory parameters in the medical record system, including routine blood test, lipid profiles, liver and kidney function test, and rheumatism-related indicators. These parameters are often used to exhibit the circulating inflammation and evaluate the status of body. Dates of recurrences were obtained when patients returned for follow-up after their first episode and were observed to present signs of ocular inflammation. Patients for whom no recurrence records were found in the medical record system were contacted by telephone for follow-up. If the date of recurrence was unknown, the patient was excluded from our study. All ophthalmic specialists responsible for patient evaluation had completed internal medicine residency.

Statistical Analysis

Data are presented as mean ± standard deviation (SD) when normally distributed, as median and interquartile range (IQR) when non-normally distributed, and as percentages when categorical. Statistical significance for baseline characteristics in two-group comparisons was performed using the Wilcoxon signed-rank test (for non-normally distributed variables), Student's *t*-test (for normally distributed variables), and chi-square test (for categorical or binary variables), unless otherwise specified in the figure legend. All baseline characteristics were stratified by the number of episodes. Potential recurrence-associated risk factors were evaluated using univariate Cox proportional hazards regression. Hazard ratios (HRs) and 95% confidence intervals (CIs) were generated. A risk factor panel for individualized recurrence risk stratification was established using a logistic regression model with the R package "stats." Patients were equally distributed to the training cohort and testing cohort in the recurrent group and nonrecurrent group, randomly. The Kaplan-Meier method was used to estimate recurrence-free survival (RFS), and the log rank test was used to compare survival distributions between groups. The predictive performance levels of individual variables and of the full risk factor panel were assessed by area under the receiver operating characteristic (AUROC) curve analysis and were compared using Delong's test. Statistical significance was determined using a cutoff value of 0.05, and all tests were two-sided unless stated otherwise. All statistical analysis was performed using R software (version 4.0.3) and Bioconductor (version 3.13).

Results

Baseline Characteristics of the Study Population

The clinical characteristics and laboratory indicators of 233 patients categorized by number of episodes are summarized in the Table and Figure 1A.

Of 233 patients with AAU, 73 (31.33%) patients experienced a recurrence during the follow-up process. The median age (+IQR) of all patients was 39.70 (32.12–49.16) years old. One hundred fifty (64.38%) of all patients were men; this finding is consistent with the age and gender characteristics of patients with AAU. A total of 94 (40.34%) patients suffered from AS, with 55 (34.38%) patients in the group with one disease episode reporting AS and 39 (53.42%) patients in the group with two or more disease episodes reporting AS ($P = 0.006$). A total of 129 (70.88%) patients were HLA-B27 positive, 80 (65.57%) patients were HLA-B27 positive in the one-disease-episode group, and 49 (81.67%) patients were HLA-B27 positive in the two-or-more-disease-episodes group ($P = 0.025$). These results indicate that patients with positive HLA-B27 and AS are more likely to relapse. The average number of monocytes MO (±SD) 10ˆ9/L was 0.53 ± 0.19 in the one-disease-episode group and 0.45 ± 0.20 in the two-or-more-disease-episodes group ($P = 0.007$). Median triglyceride (TG; +IQR) levels (mmol/L) in the one-disease-episode group were 1.47 (0.94–2.1), and the median of the group with two or more disease episodes was 1.01 (0.74–1.53; $P = 0.023$). Average high-density lipoprotein (HDL; ±SD; mmol/L) in the one-disease-episode group was 1.29 ± 0.28, and average HDL in the group with two or more disease episodes was 1.47 ± 0.34 ($P = 0.004$). Average low-density lipoprotein (LDL; ±SD) (mmol/L) in the one-disease-episode group was 3.02 ± 0.80, and the average level for participants with two or more disease episodes was 2.63 ± 0.77 ($P = 0.004$).

Identification of Potential Clinical Risk Factors Associated With AAU Recurrence

To identify potential clinical risk factors for AAU recurrence, we performed univariate Cox proportional hazards regression analysis for 38 clinical features with RFS. As shown in Figure 1B, high HDL (HR = 4.985, 95% CI = 1.845 to 13.471, $P = 0.002$), AS (HR = 1.668, 95% CI = 1.049 to 2.654, $P = 0.031$) and HLA-B27 positive status (HR = 1.94, 95% CI = 1.004 to 3.747, $P = 0.049$) were significantly associated with increased relapse risk, whereas MO (HR = 0.074, 95% CI = 0.01 to 0.541, $P = 0.01$) and LDL (HR = 0.583, 95% CI = 0.36 to 0.945, $P = 0.029$) tended to be protective factors and were significantly associated with improved RFS.

Establishment and Performance Evaluation of a Five-Risk Factor Panel for Recurrence Risk Prediction

We integrated the five risk factors identified by univariate analysis to develop a 5-risk factor panel (5RF-panel) for individualized recurrence risk assessment of AAU in the training cohort using the following logistic regression model: $5RF\text{-}panel_{score}$ = AS*0.09230 + HLA-B27*0.19863 + MO*(−0.59456) + HDL*0.36348 + LDL*(−0.12934) + 0.3287.

We estimated a 5RF-panel score for each patient with AAU in the training cohort. The distribution of

Table. Baseline Characteristics of Patients With Acute Anterior Uveitis Included in the Study

Characteristics	One Disease Episode ($n = 160$)	Two or More Disease Episodes ($n = 73$)	Total ($n = 233$)	*P* Value
Male	105 (65.63)	45 (61.64)	150 (64.38)	0.556[c]
Age (years)	40.03 (31.61–50.09)	39.07 (33.55–48.47)	39.70 (32.12–49.16)	0.508[b]
Ankylosing spondylitis	55 (34.38)	39 (53.42)	94 (40.34)	0.006[c]
Diabetes	17 (10.63)	8 (10.96)	25 (10.73)	0.939[c]
Hypertension	15 (9.38)	3 (4.11)	18 (7.73)	0.163[c]
HLA-B27	80 (65.57)	49 (81.67)	129 (70.88)	0.025[c]
Anterior chamber cell number	2.18 ± 1.25	2.20 ± 1.21	2.19 ± 1.23	0.950[a]
Intraocular pressure (mm Hg)	10.5 (7.9–13.6)	9.7 (7.9–13)	10.1 (7.9–13.2)	0.806[b]
NEU (10^9/L)	5.32 ± 1.97	5.39 ± 2.56	5.34 ± 2.13	0.779[a]
LYM (10^9/L)	2.01 ± 0.74	1.89 ± 0.77	1.98 ± 0.75	0.339[a]
NLR	2.59 (1.87–3.70)	2.44 (1.91–3.69)	2.51 (1.89–3.70)	0.866[b]
MO (10^9/L)	0.53 ± 0.19	0.45 ± 0.20	0.51 ± 0.20	0.007[a]
EO (10^9/L)	0.10 ± 0.10	0.08 ± 0.08	0.09 ± 0.10	0.664[a]
BASO (10^9/L)	0.02 (0.01–0.03)	0.02 (0.01–0.03)	0.02 (0.01–0.03)	0.128[b]
CRP (mg/L)				
CRP <5	66 (59.46)	25 (64.10)	91 (60.67)	0.610[c]
CRP > = 5	45 (40.54)	14 (35.90)	59 (39.33)	0.610[c]
SAA (mg/L)	11.71 (5.09–28.89)	8.64 (2.97–39.02)	11.38 (4.21–30.35)	0.577[b]
AST (U/L)	17 (15–22)	17 (15–19)	17 (15–20.5)	0.467[b]
ALT (U/L)	23.86 ± 16.45	19.38 ± 10.04	22.72 ± 15.17	0.221[a]
AST/ALT	1.00 ± 0.43	1.03 ± 0.32	1.01 ± 0.41	0.406[a]
GGT (U/L)	26 (18–50)	22 (19–33)	25 (18–44)	0.240[b]
ALP (U/L)	85.41 ± 23.11	78.94 ± 24.91	83.80 ± 23.64	0.174[a]
TP (g/L)	77.6 (74.6–80.6)	78.8 (74.7–80.15)	77.95 (74.6–80.55)	0.916[b]
ALB (g/L)	47.3 (44.9–50)	47.05 (45.05–49)	47.2 (45–49.8)	0.677[b]
GLB (g/L)	30.24 ± 3.73	30.39 ± 3.56	30.28 ± 3.68	0.836[a]
A/G	1.61 ± 0.26	1.57 ± 0.21	1.60 ± 0.25	0.564[a]
TBIL (μmol/L)	11.04 ± 4.76	10.81 ± 4.77	10.99 ± 4.75	0.770[a]
DBIL (μmol/L)	4.2 (3.3–5.5)	3.9 (3.4–4.8)	4.2 (3.3–5.4)	0.393[b]
IBIL (μmol/L)	5.9 (4.5–7.8)	6.1 (4.3–7.7)	5.95 (4.5–7.75)	0.866[b]
GLU (mmol/L)	5.78 (5.32–6.81)	5.7 (5.31–6.31)	5.76 (5.32–6.73)	0.664[b]
UA (μmol/L)	330.96 ± 71.28	322.53 ± 77.82	328.81 ± 72.82	0.551[a]
Crea (μmol/L)	68 (57–76)	66 (57–78.5)	66 (57–76)	0.913[b]
Urea (mmol/L)	5.09 ± 1.26	5.00 ± 1.27	5.07 ± 1.26	0.655[a]
TG (mmol/L)	1.47 (0.94–2.1)	1.01 (0.74–1.53)	1.42 (0.88–2.00)	0.023[b]
TCH (mmol/L)	4.93 (4.13–5.63)	4.5 (3.72–5.4)	4.84 (4–5.52)	0.149[b]
HDL (mmol/L)	1.29 ± 0.28	1.47 ± 0.34	1.34 ± 0.30	0.004[a]
LDL (mmol/L)	3.02 ± 0.80	2.63 ± 0.77	2.92 ± 0.81	0.012[a]
RF (IU/mL)	8 (5–10)	7 (5–9.5)	7 (5–10)	0.439[b]
VD (25-OH) (ng/mL)	23.89 ± 9.05	25.38 ± 8.38	24.25 ± 8.86	0.530[a]
ESR (mm/h)	17.79 ± 16.48	17.90 ± 13.38	17.82 ± 15.66	0.645[a]

[a]Data are presented as mean ± standard deviation (SD) when characteristics are normally distributed. Characteristics were compared using the Student's *t*-test.

[b]Data are presented as median and interquartile range (IQR) when characteristics are non-normally distributed. Characteristics were compared using the Wilcoxon signed-rank test.

[c]Data are presented as number and percentage when characteristics are categorical. Characteristics were compared using the chi-square test.

NEU, neutrophil count; LYM, lymphocyte count; NLR, neutrophil to lymphocyte ratio; MO, monocyte count; EO, eosinophil count; BASO, basophil count; CRP,C reactive protein; SAA, serum amyloid A; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AST/ALT, aspartate aminotransferase to alanine aminotransferase; GGT, glutamyl transpeptidase; ALP, alkaline phosphatase; TP, total protein; ALB, albumin; GLB, globulin; A/G, albumin to globulin; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; GLU, glucose; UA, uric acid; Crea, creatinine; TG, triglycerides; TCH, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; RF, rheumatoid factor; VD (25-OH), 25-hydroxyvitamin D; ESR, erythrocyte sedimentation rate.

5RF-panel scores and other clinical features are shown in Figure 2A. The 5RF-panel score exhibited significantly negative associations with MO (Pearson r = −0.47, $P < 0.001$) and LDL (Pearson r = −0.59, $P < 0.001$), but a significantly positive association with HDL (Pearson r = 0.55, $P < 0.001$). Patients with recurrence showed significantly higher 5RF-panel scores compared to those without recurrence (median

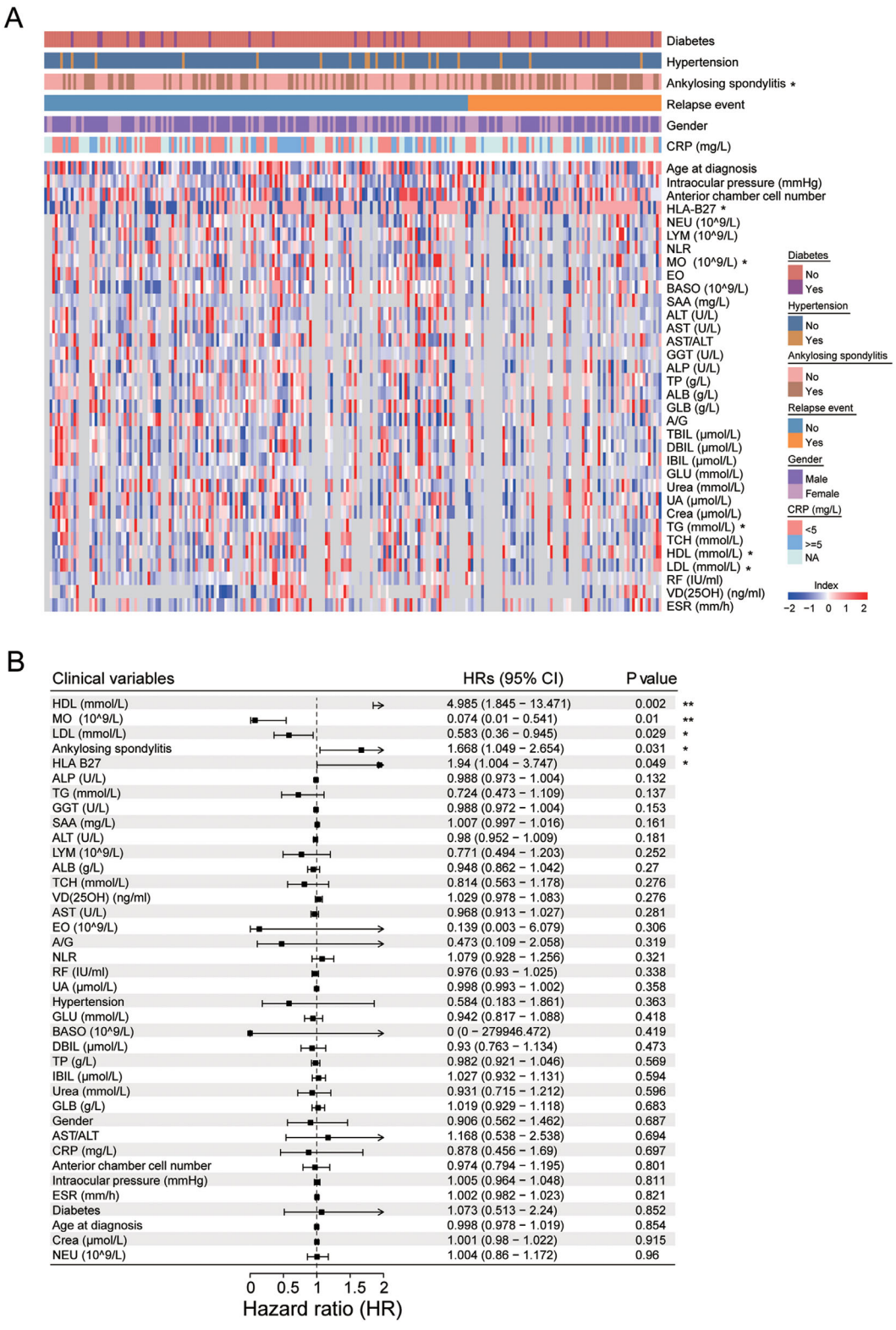

Figure 1. **Overview of baseline characteristics of the study population.** (**A**) Heat map showing characteristics of patients with AAU. (**B**) Forest plot showing the HRs and 95% confidential interval of each laboratory parameter calculated by univariate Cox model. Wilcoxon signed-rank test and Student's t-test were used for statistical analysis: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

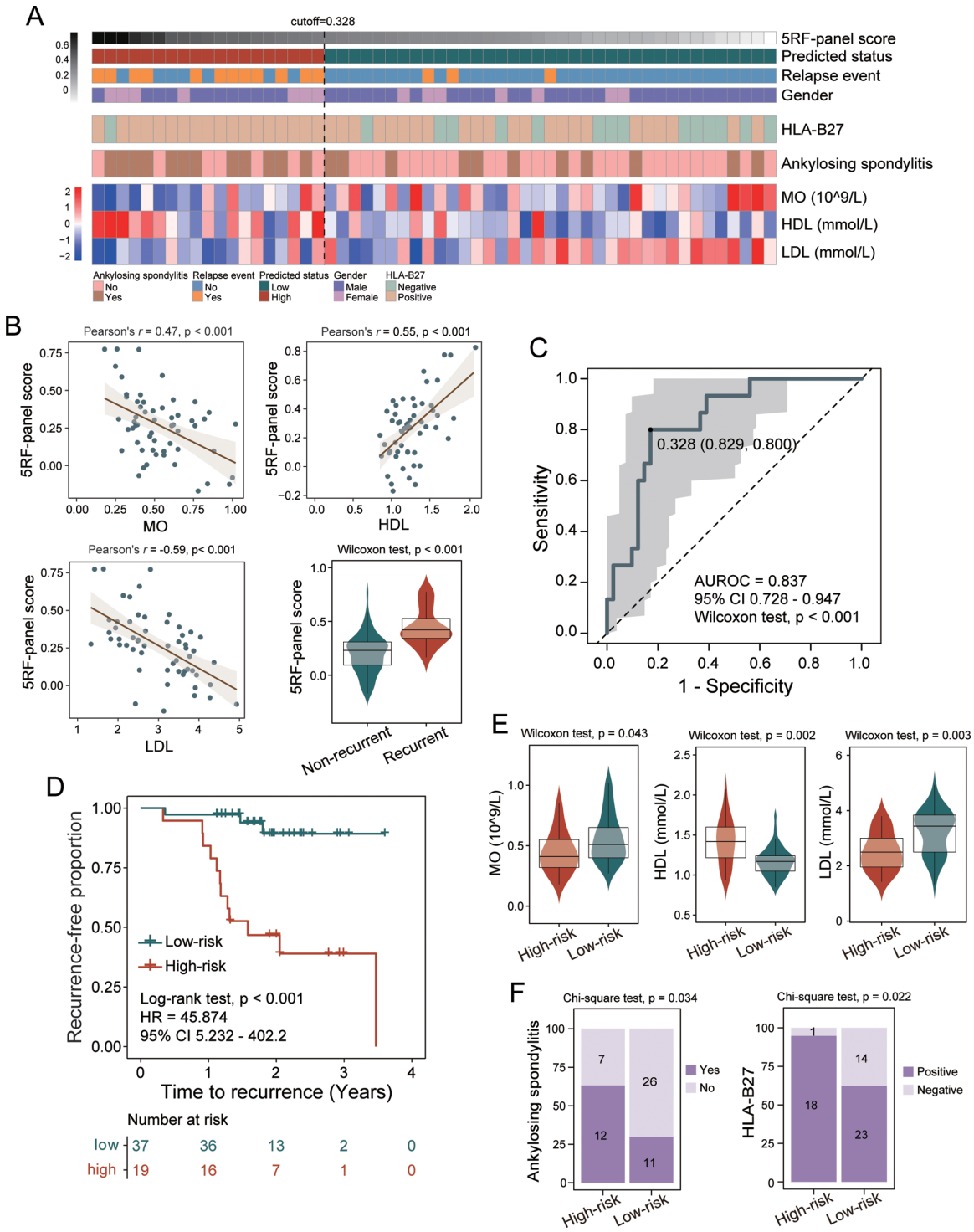

Figure 2. **Development and performance evaluation of the five-risk factor panel in the training cohort.** (**A**) Heat map visualizing the distribution of 5RF-panel scores and laboratory parameters. (**B**) Correlation between 5RF-panel score and four risk laboratory parameters. (**C**) Receiver operating characteristic (ROC) curve for the 5RF-panel score in in discriminating patients who had disease recurrence from non-relapsed patients. The *P* value was calculated using the Wilcoxon test. (**D**) Kaplan-Meier survival analysis of recurrence-free time in the training cohort with 5RF-panel scores between high-risk and low-risk groups. The *P* value was calculated using the log-rank test. (**E**) Box plot displaying differences in MO, HDL, and LDL between high-risk and low-risk groups predicted by the 5RF-panel. The Wilcoxon signed-rank test was used for statistical analysis. (**F**) Bar plot displaying the distribution of patients with AS or HLA-B27 between high-risk and low-risk groups predicted by the 5RF-panel. The chi-squared test was used for statistical analysis.

0.421 vs. 0.234, Wilcoxon test $P < 0.001$; Fig. 2B). The receiver operating curve (ROC) analysis revealed that the 5RF-panel demonstrated superior predictive capability, with an AUC of 0.837 (95% CI = 0.728 to 0.947, Wilcoxon test $P < 0.001$) for the discrimination of patients with disease recurrence from non-relapsed patients (Fig. 2C). Next, we obtained an optimal risk cutoff of 0.328, with a sensitivity of 80% and specificity of 82.9%. This optimal risk cutoff reclassified patients into high-risk ($n = 19$) and low-risk ($n = 37$) groups. RFS was significantly different between the two predicted risk groups (log-rank test $P < 0.001$; Fig. 2D). The proportions of relapse-free patients in the low- and high-risk groups were 89.2% and 39.0%, respectively, after 3 years. As shown in Figure 2E, MO (Wilcoxon test $P = 0.043$) and LDL (Wilcoxon test $P = 0.003$) tended to be higher in the low-risk group than the high-risk group, whereas HDL (Wilcoxon test $P = 0.002$) was higher in the high-risk group. Furthermore, the two risk groups varied substantially in the prevalence of the AS index (chi-square test $P = 0.034$) and HLA-B27 (chi-square test $P = 0.022$; Fig. 2F).

Validation of 5RF-Panel in the Testing Cohort

To evaluate the reproducibility and robustness of the 5RF-panel, we next calculated 5RF-panel scores for each patient in the testing cohort. The distribution of 5RF-panel scores and the standard clinical features of patients in the testing cohort is shown in Figure 3A. As observed in the training cohort, the 5RF-panel had similar negative associations with MO (Pearson r = −0.55, $P < 0.001$) and LDL (Pearson r = −0.43, $P < 0.001$), in addition to a similar significantly positive association with HDL (Pearson r = 0.65, $P < 0.001$; Fig. 3B). Furthermore, patients with recurrence showed significantly higher 5RF-panel scores than those without recurrence (median 0.535 vs. 0.316, Wilcoxon test $P < 0.001$; see Fig. 3B). The 5RF-panel effectively discriminated patients with recurrence from individuals without recurrence with an AUC of 0.725 (95% CI = 0.561 to 0.889, Wilcoxon test $P = 0.005$; Fig. 3C). Meanwhile, the risk cutoff derived from the training cohort was sufficient to divide patients into low-risk ($n = 24$) and high-risk ($n = 31$) groups with significantly different recurrence-free survival (log-rank test $P = 0.024$; Fig. 3D). In the high-risk group, RFS was significantly lower than that in the low-risk group (HR = 51.982, 95% CI = 4.438 to 608.9; see Fig. 3D). The 3-year RFS rate of the low-risk group was 85.1%, whereas the corresponding rate of the high-risk group was 55.7%. Furthermore, compared to those in the low-risk groups, patients in the predicted high-risk group had lower MO and LDL and higher HDL, prevalence of AS and HLA-B27 positive status (Figs. 3E, 3F).

Performance Comparison of the 5RF-Panel With Known Risk Factors

To compare the predictive performance of the 5RF-panel with known risk factors (HLA-B27 and AS), we first performed ROC curve analysis to assess discriminatory power across all patients with AAU. As shown in Figure 4A, the 5RF-panel exhibited the best AUC of 0.766 (95% CI = 0.668 to 0.863), significantly higher than those of HLA-B27 (AUC = 0.596, 95% CI = 0.51 to 0.681, DeLong's test $P = 0.003$) and AS (AUC = 0.581, 95% CI = 0.476 to 0.687, DeLong's test $P = 0.003$). Furthermore, Kaplan-Meier curves also showed that patients separated by HLA-B27 or AS did not have significantly different RFS rates (log rank test $P = 0.07$ for HLA-B27 and $P = 0.2$ for AS; Fig. 4B).

We next carried out a stratified analysis to evaluate whether the 5RF-panel could identify patients at high risk of relapse based on the same clinical features. Using the same risk cutoff, we found that the 5RF-panel was still able to effectively divide patients into high and low-risk groups for the same AS (Yes) group log rank test $P = 0.002$, HR = 32.963, 95% CI = 2.658 to 408.9) and AS (No) group (log rank test $P = 0.008$, HR = 72.089, 95% CI = 6.801 to 746.1), revealing respective 3-year RFS rates of 94.4% and 49.7% for patients with low- and high-risk scores in the ankylosing spondylitis (Yes) group and of 83.1% and 39.8% for patients in in the AS (No) group (Figs. 4C, 4D). In addition, the distribution of 5RF-panel scores was significantly different between high-risk and low-risk groups for the ankylosing spondylitis (Yes; Wilcoxon test $P = 0.006$) and AS (No) subgroups (Wilcoxon test $P = 0.005$), and the median 5RF-panel score for the high-risk group was significantly higher than those of the low-risk group for both AS subgroups (Yes: 0.506 vs. 0.316 and No: 0.385 vs. 0.24; see Figs. 4C, 4D). Similar predictive values were also shown for HLA-B27 subgroups. The 5RF-panel was able to define high- and low-risk groups for HLA-B27 positive patients (log rank test $P = 0.002$, HR = 29.825, 95% CI = 4.104 to 216.8) and HLA-B27 negative patients (log rank test $P = 0.007$, HR = 136.175, 95% CI = 4.1 to 4523). The 3-year RFS rates for low-risk and high-risk subgroups of HLA-B27 positive patients were 81.6% and 51.1%, respectively, whereas the corresponding rates for HLA-B27 negative patients were 92.9% and 33.3%. Meanwhile, the distribution of 5RF-panel scores significantly differed between high-risk and

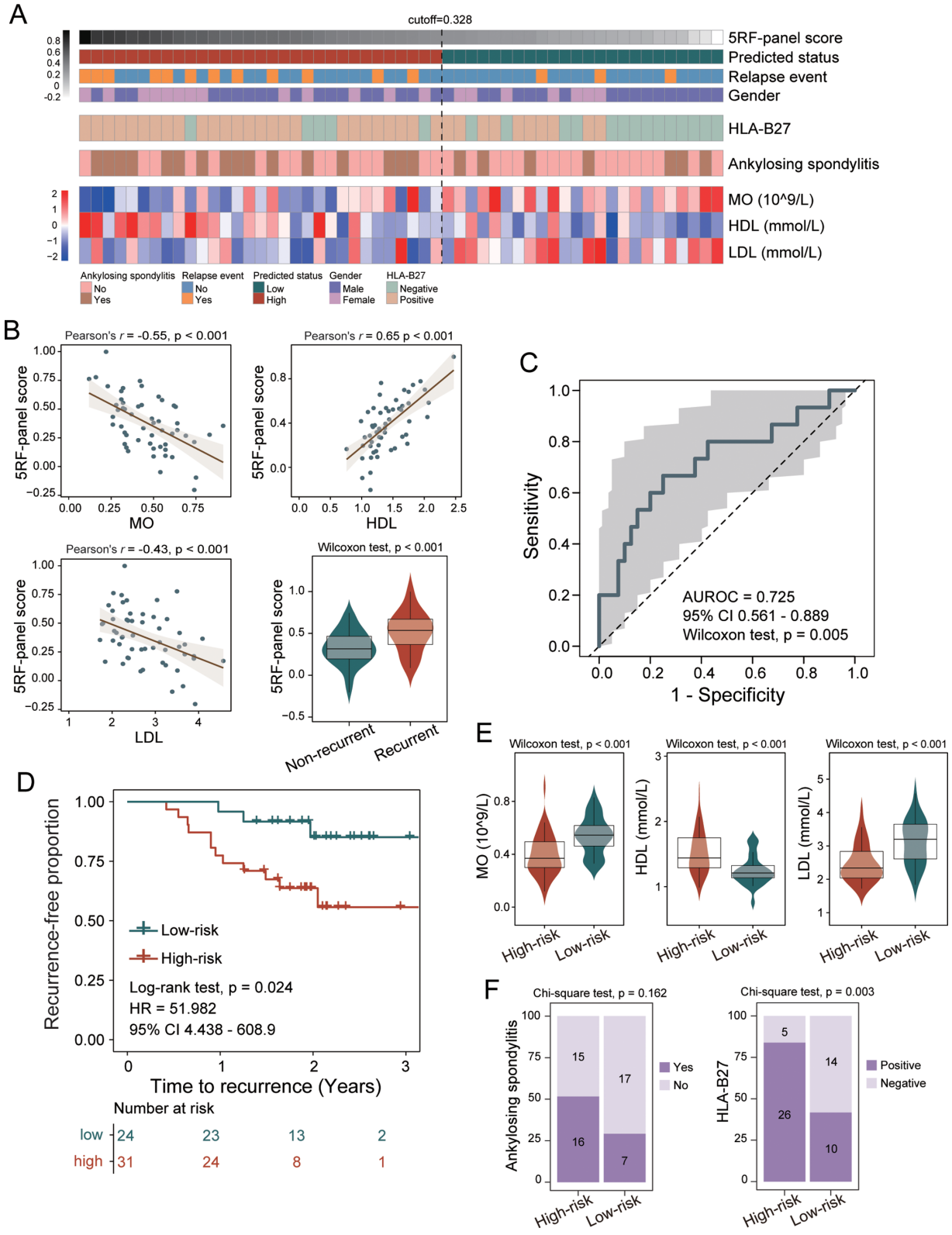

Figure 3. **Independent validation of the five-risk factor panel in the testing cohort.** (**A**) Heat map visualizing the distribution of 5RF-panel scores and laboratory parameters. (**B**) Correlation between 5RF-panel score and four risk laboratory parameters. (**C**) Receiver operating characteristic (ROC) curve for the 5RF-panel score in discriminating patients who had disease recurrence from nonrelapsed patients. The *P* value was calculated using the Wilcoxon test. (**D**) Kaplan-Meier survival analysis of recurrence-free time in the training cohort with 5RF-panel score between high-risk and low-risk groups. The *P* value was calculated using the log-rank test. (**E**) Box plot displaying differences in MO, →

←

HDL, and LDL between high-risk and low-risk groups predicted by the 5RF-panel. The Wilcoxon signed-rank test was used for statistical analysis. (**F**) Bar plot displaying the distribution of patients with AS or HLA-B27 between high-risk and low-risk groups predicted by the 5RF-panel. The chi-squared test was used for statistical analysis.

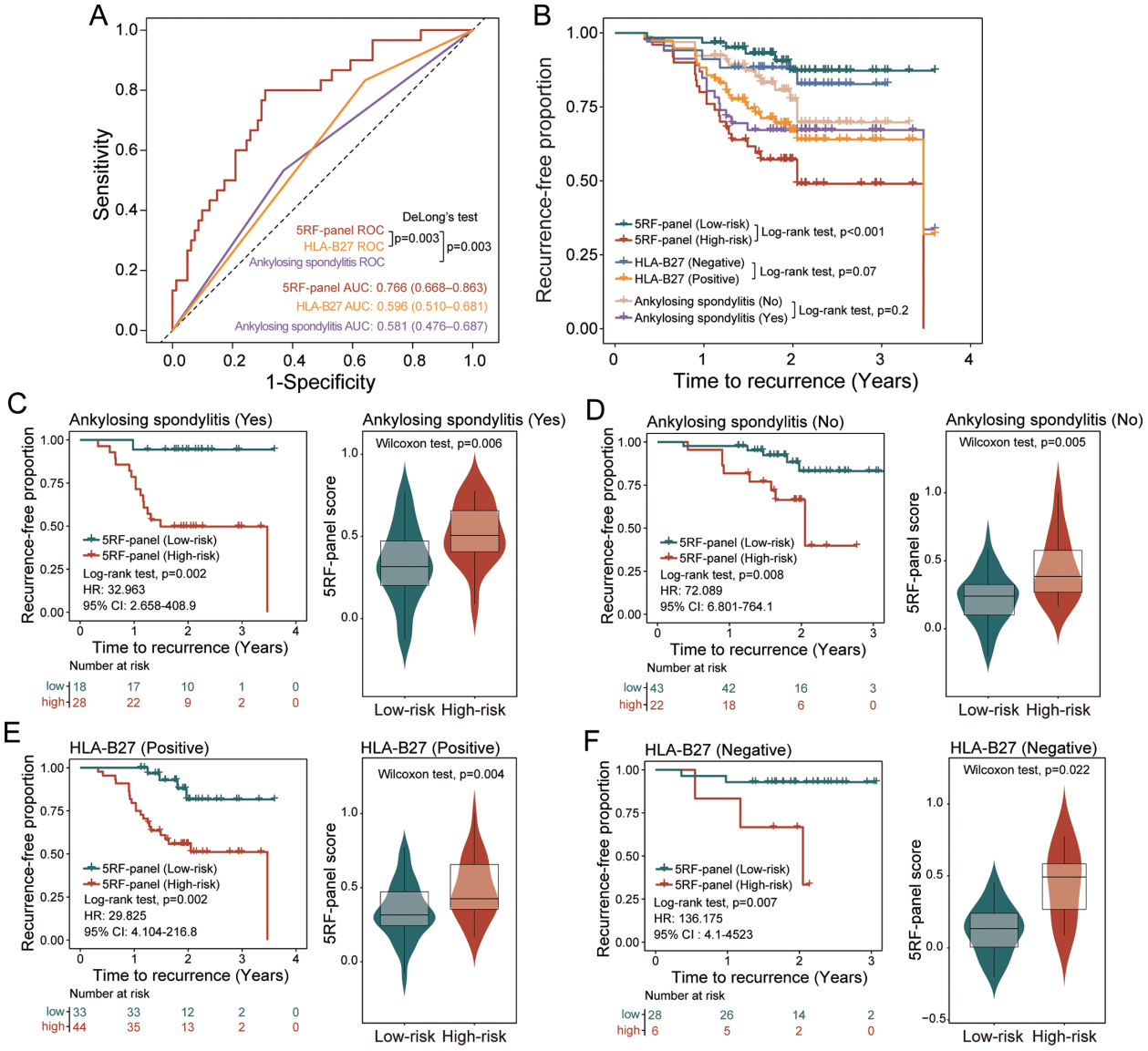

Figure 4. **Comparison of predicative performance of the five-risk factor panel and other known risk factors.** (**A**) Receiver operating characteristic (ROC) curve analysis for the 5RF-panel and other known risk factors in discriminating patients who had disease recurrence from nonrelapsed patients. Delong's test was used for statistical analysis. (**B**) Kaplan-Meier curve analysis of recurrence-free time in high- and low-risk groups predicted by the five-risk factor panel and other risk factors. (**C, D**) Risk prediction by the five-risk factor panel for patients with AAU stratified by ankylosing spondylitis. (**E, F**) Risk prediction by the five-risk factor panel for patients with AAU stratified by HLA-B27. The Wilcoxon signed-rank test and log rank test were used for statistical analysis.

low-risk groups for both HLA-B27 positive (median 0.425 vs. 0.316, Wilcoxon test $P = 0.022$) and HLA-B27 negative (median 0.492 vs. 0.134, Wilcoxon test $P = 0.004$) patients (Figs. 4E, 4F). These results indicate that the 5RF-panel is highly predictive, independent of both HLA-B27 and ankylosing spondylitis.

Discussion

With high numbers of episodes, AAU can lead to severe complications. Moreover, the risk of recurrence is different for each patient with AAU. Therefore, there

is a critical and urgent need to identify patients at high risk for recurrence in order to guide personalized clinical management. In this study, we analyzed associations among 38 laboratory parameters and RFS in a large retrospective cohort of 233 patients diagnosed with AAU and identified 5 risk factors (HLA-B27, AS, HDL, LDL, and MO) significantly associated with recurrence time of AAU. Of the five risk factors, AS and HLA-B27 have been reportedly associated with AAU's pathological mechanism.[11–14] Although previous clinical studies have explored the correlation between HLA-B27 and AAU recurrence,[3,8,9] these results have been inconsistent. Pedroza-Seres et al. found that HLA-B27 positive patients had a higher frequency of recurrences than HLA-B27 negative patients.[9] However, two other studies reported that HLA-B27 positive patients have the same frequency of recurrences as HLA-B27 negative patients.[3,8] Our study provided further evidence supporting the correlation between HLA-B27 and recurrence in patients with AAU. In addition to these two well-known risk factors (HLA-B27 and AS), HDL, LDL, and MO were also found to play important roles in the prediction of AAU recurrence. HDL is positively correlated with recurrence risk, whereas both LDL and MO are negatively correlated with recurrence risk. Previous studies showed that all these factors are subject to inflammatory signal pathway, which is related to cardiovascular disease (CVD)[15] and cancer.[16] HDL is a protective factor in CVD, nonetheless LDL is a risk factor.[17–21] MO is correlated with poor prognosis in some types of cancers.[22,23] These diseases are characterized by a chronic course, which means the impact of these factors is persistent. AAU is characterized by sudden onset with limited duration, different from CVD or cancer. Chronic inflammation is harmful to the human body, whereas acute inflammation for the body means beneficial response.[24] The impact of prognostic factors in the chronic inflammatory process may be opposite to an acute inflammatory process. MO is derived from bone marrow granulocyte-macrophage progenitor cells, which account for 4% to 5% of the total number of white blood cells in peripheral blood.[25] MO plays an important part in human immunity responses by serving as antigen-presenting immune cells, as has been reported for many autoimmune diseases.[26–28] When the human body is in an inflammatory or other unstable state, the plasma monocyte pool increases.[29,30] MO plays an important role in the pathogenesis of AAU, related to the disease activity.[31,32] Dysbiotic microbiota, possible etiology of AAU, will increase the number of MO in peripheral blood and lymph node.[11,33] Meanwhile, MO gobbles up the microbiota and presents the antigen to T cells, which is a crucial procedure in immune response. The biological properties of HDL and LDL in the human body are primarily related to cholesterol metabolism.[34] LDL accumulates cholesterol in peripheral cells, whereas HDL brings cholesterol from peripheral cells back to the liver, after which cholesterol can be excreted in the form of bile acid. Oxidized LDL promotes inflammation by activating phagocytosis.[35] HDL suppresses LDL oxidation and decreases the generation of secreted adherence factor, which has anti-inflammatory effects.[36] HDL also can compete with monocyte macrophages and bind to activated T-cell surface stimulating factors, thereby inhibiting monocyte macrophages from producing inflammatory factors.[37] However, some studies have also shown that HDL is not always associated with positive disease outcome.[38–41] In certain physical conditions, HDL may increase monocyte chemotaxis and phospholipid oxidation.[38] Apolipoprotein A-I, an important component of HDL, may be replaced by serum amyloid A, and changes, such as decreased enzymatic activity, can transform HDL into a pro-inflammatory factor.[42] There is no previous study reporting the correlation among HDL, LDL, and AAU, but studies have shown that HDL decreases during the active phase of Behcet's disease, which is another kind of uveitis.[43] HDL and LDL are probably involved in the pathogenesis of AAU.

Previous studies have overlooked the importance of laboratory indicators, and most have been based on a single index, leading to poor AAU recurrence risk predictability. Therefore, in order to accelerate clinical application and improve prediction accuracy, five risk factors were integrated to form a predictive panel (designated the 5RF-panel) using a logistic regression model. The 5RF-panel can not only effectively discriminate patients with disease recurrence from nonrelapsed patients but could also distinguish between patients with high and low risk of AAU recurrence in the training cohort. The robust performance of the 5RF-panel was further validated in the testing cohort. Furthermore, the 5RF-panel demonstrated superior performance for recurrence risk stratification with respect to known risk factors.

The discriminatory ability of the 5RF-panel was also tested based on the patients' AS and HLA-B27 status. For each subgroup, we identified the significant difference between recurrence rates in low- and high-risk groups. Stratified analysis showed that the 5RF-panel is suitable for the assessment of patients with various types of AAU. The 5RF-panel is a robust tool that allows individualized prediction and identification of patients at high risk for recurrence after remission. The 5RF-panel could also be used in tertiary ocular inflammation centers. When patients with primary AAU come to the hospital, clinicians can use the

5RF-panel to score patients' risk of recurrence. Patients with scores above the designated threshold can be identified as high-risk patients. Once these patients have been identified, attention should be paid to encourage strict adherence to follow-up plans. Doctors also can appropriately extend the use cycle of hormone drugs or immunosuppressive agents.

Our study is longitudinal and retrospective, with some associated limitations. We only included patients presenting with an initial episode of AAU; the number and frequency of previous episodes were not included in this study, although this can be explored further in future research. Blood collection was performed while in the active phase, so this panel can only be applied to patients in the active phase. Our study is a retrospective single-center study. We hope these results can be validated in a multicenter study in the future.

In conclusion, this study identified and validated a novel clinical 5RF-panel, including HDL, AS, HLA-B27, MO, and LDL, capable of predicting individualized risk of AAU recurrence. With further prospective validation, the universality and simplicity of the 5RF-panel make it a promising individualized predictive tool to monitor recurrence risk and guide personalized management of patients with AAU.

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