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ORIGINAL RESEARCH

# The Aggregate Index of Systemic Inflammation (AISI) is a Novel IgA Nephropathy Prognosis Predictor

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**Purpose:** Inflammation and immune factors are closely related to the development of IgA nephropathy (IgAN), and the aggregate index of systemic inflammation (AISI) has been identified as a prognostic indicator for various diseases lately. We aimed to evaluate its predictive value in IgAN.

**Patients and Methods:** This retrospective single-center study included 1792 biopsy-confirmed IgAN patients from October 2019 to September 2023 with>12-month follow-up. The optimal cut-off value of AISI for renal poor outcome was identified by receiver operating characteristic curves (ROC). Cox regression analyses, Kaplan-Meier curves and restricted cubic splines were performed to determine the relationship between AISI and IgAN prognosis. The predictive value of AISI on IgAN prognosis was conducted by the area under the receiver operating characteristic curve (AUC).

**Results:** A total of 1792 IgAN patients were included in the study and were divided into three groups (tertial 1-3) according to the baseline AISI. The higher AISI groups had worse clinicopathological features and renal survival showed by Kaplan-Meier analysis (Log-Rank=17.38, P<0.001). Multivariate Cox regression identified elevated AISI as an independent risk factor for renal prognosis in IgAN (adjusted HR:2.359,95% CI:1.365–4.078, P=0.002). Subgroup analysis highlighted significance in male, uric acid>420μmol/L, 24h proteinuria>3.5g, eGFR>30mL/min/1.73m², and the Oxford classification of renal pathology (MEST-C) T0-T1. The best cut-off AISI for renal survival was 198.78, sensitivity 70.0%, and specificity 51.4% (AUC:0.626). Patients were divided into a low AISI group (AISI≤198.78, n=894) and a high AISI group (AISI>198.78, n=898) according to AISI cut-off value and propensity matched. Multivariate Cox regression analysis revealed that a higher AISI was significantly associated with a poorer renal outcome of IgAN patients (HR:1.568,95% CI:1.007–2.442, P=0.046). Multivariate adjusted restricted cubic splines demonstrated a linear correlation between AISI and a poor renal prognosis (P for overall=0.0135, P for nonlinearity=0.773).

**Conclusion:** AISI is a novel independent predictor of renal progression in IgAN patients.

**Keywords:** the aggregate index of systemic inflammation, IgA nephropathy, renal survival, prognosis

## Introduction

IgA nephropathy(IgAN), which is characterised by the deposition of IgA1 in the mesangium of the glomerulus, is currently the most common primary glomerulonephritis worldwide, accounting for approximately 40–50% of primary glomerular diseases.[1] IgAN is the leading cause of end-stage renal disease (ESRD), perhaps 25% to 50% of patients with primary IgAN will develop into ESKD if they are followed for 20 to 30 years of diagnosis,[2] at the moment, IgAN has transformed into a critical public health issue that threatens people's physical health. Therefore, early evaluation of renal prognosis and adoption of active intervention measures are of vital importance to decelerate the progression to ESRD in IgAN. Although the pathogenic mechanism of IgAN has not been completely clarified yet, Studies have indicated that

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inflammation play an important role in the development and progression of IgAN.[3] It is predicted that for IgAN patients, inflammatory biomarkers will contribute to the prediction of mortality and renal outcomes.

The aggregate index of systemic inflammation(AISI) computed as neutrophils(/L)×monocytes ×platelets(/L)/lymphocytes(/L), was first studied in 2018 in relation to post-procedure prognosis for surgical patients which has been receiving increasing attention recently.[4] Previous researches have confirmed that AISI was an independent predictor of various diseases, including coronavirus disease (COVID-19),[5] stroke,[6] retinopathy,[7] breast cancer,[8] idiopathic pulmonary fibrosis,[9] hypertension[10] and chronic renal failure(CRF),[11] however, the association of AISI and the prognosis of IgAN patients is limited. Therefore, our research sought to investigate this problem.

## Materials and Methods

This retrospective single centre study included 2154 patients with IgAN diagnosed by renal biopsy at Hangzhou Hospital of Traditional Chinese Medicine from October 2019 to September 2023. Among them, 362 individuals were excluded for the following reasons: 67 patients less than 18 years old, 209 patients had potential secondary causes of IgAN, such as diabetes mellitus, anaphylactoid purpura, and autoimmune disorders, 75 patients follow-up of less than 12 months, 5 patients had acute active infection, pregnancy and malignant tumours, and 6 patients did not have sufficient clinical or pathologic data. All patients were followed up for at least 12 months (Figure 1). The study was approved by the Ethics Committee of Hangzhou Hospital of Traditional Chinese Medicine and All subjects have signed informed consent. (NO. 2024KLL230)

### Clinical Data

By looking through electronic medical records, we collected the data including demographics (age, sex, hypertension and diabetic history), clinical data (hemoglobin (Hb), albumin (ALB), total cholesterol (TCH), triglyceride (TG), low-density lipoprotein (LDL), uric acid (UA), serum creatinine (Scr), Serum C3, Serum C4, 24 hour urine protein (24h Upro) and estimated glomerular filtration rate (eGFR)) and treatment plan at the time of renal biopsy. Renal biopsy samples were evaluated by light microscopy, immunofluorescence and electron microscopy by two experienced pathologists and nephrologists according to the Oxford classification (MEST-C) of IgAN: mesangial hypercellularity (M0/M1), endocapillary hypercellularity (E0/E1), segmental glomerulosclerosis (S0/S1), tubular atrophy/interstitial fibrosis (T0/T1/T2), and cellular or fibro-cellular crescents (C0/C1/C2).

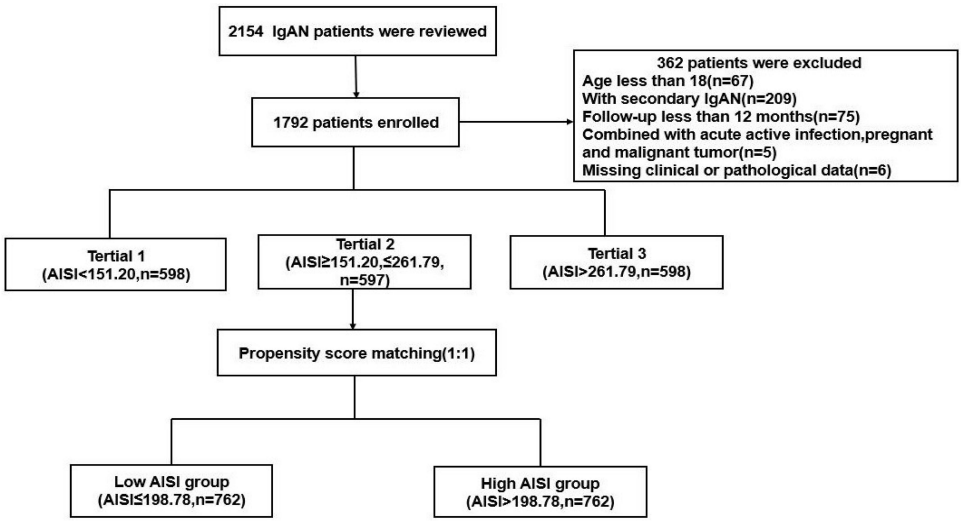



**Figure 1** Flowchart of excluded patients.

## Definition of AISI, PLR and PAR

The computational equation of AISI values was as follows: neutrophils(/L)×monocytes ×platelets(/L)/lymphocytes(/L).

Platelet-to-lymphocyte ratio (PLR)=platelets(/L)/lymphocytes(/L).

Platelets/Albumin (PAR)=platelets(/L)/albumin(g/L).

## Prognosis Definition

The primary renal endpoint event was defined as a composite event of either a 50% decline in the eGFR or ESRD (defined as eGFR<15 mL/min/1.73 m2 or need for kidney replacement therapy).

## Statistical Analysis

IBM SPSS software, version 26.0, was used for all statistical analyses. Continuous distributions are displayed as the mean±standard deviation, while skewed distributions are expressed as the median with interquartile range and were analysed by an unpaired *t* test, the Kruskal–Wallis *H*-test or the nonparametric Mann–Whitney *U*-test. Categorical data are presented as frequencies and were analysed by $\chi^2$ or Fisher's exact tests. The Correlation analyses were conducted to examine the association between the AISI and clinicopathological variables, the Spearman correlation analysis was employed for continuous variables, whereas logistic regression analysis was utilized for categorical variables. Survival curves of the kidney endpoint were analysed by the Kaplan-Meier method and the Log rank test. Cox regression were performed to analyse independent factors for IgAN prognosis. Subgroup analyses were performed by Cox regression models. The cut-off and predictive values of AISI, PLR and PAR for renal prognosis were assessed by receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC) as the primary metric. A 1:1 propensity score(PS)match was carried out to eliminate important differences at baseline. According to the greedy matching algorithm, Kaplan-Meier survival analysis and Cox regression were then used on the new matched cohort. We also used the restricted cubic splines to study the potential nonlinear relationship between AISI and the hazard renal endpoint after matching. In addition, multivariable ROC curve analysis using logistic regression was conducted to explores the risk factors of IgAN renal prognosis. Significance was defined at a P value<0.05.

# Results

## Baseline Characteristics of All Patients

A total of 2154 patients with IgAN were involved while 362 individuals were excluded for the following reasons: age less than 18, secondary IgAN, less than 12 months follow-up before reaching endpoints, combined with active infection, pregnancy and malignant tumours, or insufficient pathological data. After strict inclusion and exclusion criteria, 1792 patients were finally included in this study, as shown in Figure 1. This cohort study comprised 760 (42.4%) males and 1032 (57.6%) females, and the mean age was 43.0(36.0–53.0) years old. Based on the baseline AISI level, all the patients were divided into three groups: Tertial 1 (<151.20, n=598, account for 33.4%), Tertial 2 (≥151.20, ≤261.79, n=597, account for 33.3%), and Tertial 3 (>261.79, n=597, account for 33.3%). Analysis of baseline data of patients in each group showed that except for age, gender, presence of hypertension, and hemoglobin, there were significant differences in other clinical indicators among the groups. As the AISI level increases, patients exhibit gradual increases in TCH, TG, LDL, Scr, UA, C3, C4, H-CRP, and 24-hour urine protein levels, while the eGFR level gradually decreases. The MEST-C score of renal pathology showed that the E, T, and C scores in all groups were significantly different. Along with the elevation of AISI level, the proportion of patients received Steroid with/without Immunosuppressants treatment were gradually increased, as shown in Table 1.

## Correlation of AISI with Clinical Parameters and Pathologic Lesions

The correlation analyses were conducted to clarify the relationship between the AISI and important clinicopathological variables. According to Table 2, Our findings revealed that there was a significantly positive correlation between AISI and total cholesterol (r=0.089, P<0.001), triglyceride (r=0.112, P<0.001), low-density lipoprotein (r=0.122, P<0.001), serum creatinine (r=0.142, P<0.001), uric acid (r=0.079, P<0.001), 24hUpro (r=0.220, P<0.001), meanwhile, there was

**Table 1** Demographic and Clinicopathological Characteristics of 1792 IgAN Patients

| Variables | Total (n=1792) | Tertile 1 (n=598) <151.20 | Tertile 2 (n=598) ≥151.20 ≤261.79 | Tertile 3 (n=598) >261.79 | P value |
|---|---|---|---|---|---|
| Age, years | 43.0(36.0–53.0) | 42.5(36.0–53.0) | 43.0(35.0–53.0) | 43.0(36.0–52.0) | 0.860 |
| Male, n(%) | 760(42.4) | 233(38.9) | 263(44.1) | 264(44.2) | 0.112 |
| Hypertension, n(%) | 195(10.9) | 61(10.2) | 61(10.2) | 75(12.6) | 0.267 |
| Hb, g/L | 126.00±19.20 | 125.19±17.55 | 126.38±19.87 | 126.41±20.10 | 0.457 |
| ALB, g/L | 38.50(35.70–41.00) | 39.05(36.50–41.50) | 38.35(35.63–41.1) | 38.20(34.75–40.55) | **<0.001** |
| TCH, mmol/L | 4.65(4.07–5.37) | 4.56(4.02–5.21) | 4.63(4.08–5.27) | 4.80(4.15–5.74) | **<0.001** |
| TG, mmol/L | 1.30(0.90–1.99) | 1.17(0.82–1.80) | 1.31(0.91–2.03) | 1.42(0.98–2.13) | **<0.001** |
| LDL, mmol/L | 2.84(2.35–3.42) | 2.71(2.24–3.29) | 2.81(2.36–3.35) | 2.99(2.47–3.61) | **<0.001** |
| Scr, μmol/L | 80(62–109) | 76(60–99) | 81(62–110) | 84(64–127) | **<0.001** |
| UA, μmol/L | 365(300–438) | 353(291–422) | 369(302–454) | 371(308–440) | **<0.001** |
| Serum C3, mg/dl | 97(86–110) | 92(80–104) | 96(86–108) | 103(90–116) | **<0.001** |
| Serum C4, mg/dl | 23(19–28) | 21(17–25) | 23(19–27) | 26(21–30) | **<0.001** |
| H-CRP, mg/L | 1.03(0.51–2.38) | 0.74(0.40–1.54) | 0.96(0.53–2.02) | 1.73(0.71–0.29) | **<0.001** |
| 24h Upro, g/L | 0.91(0.46–1.81) | 0.67(0.36–1.34) | 0.95(0.48–1.70) | 1.17(0.59–2.37) | **<0.001** |
| eGFR, mL/min/1.73m$^2$ | 85.20(61.00–106.60) | 89.10(69.40–108.10) | 85.55(61.08–106.33) | 78.85(51.48–105.60) | **<0.001** |
| PLR | 116.04(92.04–144.90) | 95.79(78.23–117.38) | 116.82(94.36–136.85) | 139.82(114.18–178.97) | **<0.001** |
| PAR | 5.81(4.81–7.05) | 4.99(4.10–5.89) | 5.87(5.06–6.99) | 6.64(5.69–8.33) | **<0.001** |
| Mesangial cellularity, n (%) | | | | | |
| M0 | 22(1.2) | 7(1.2) | 8(1.3) | 7(1.2) | 0.954 |
| M1 | 1770(98.8) | 591(98.8) | 589(98.7) | 590(98.8) | |
| Endocapillary hypercellularity, n (%) | | | | | |
| E0 | 1232(68.8) | 432(72.2) | 419(70.2) | 381(63.8) | **0.005** |
| E1 | 560(31.2) | 166(27.8) | 178(29.8) | 216(36.2) | |
| Segmental sclerosis, n (%) | | | | | |
| S0 | 345(19.3) | 123(20.6) | 107(17.9) | 115(19.3) | 0.510 |
| S1 | 1447(80.7) | 475(79.4) | 490(82.1) | 482(80.7) | |
| Tubular atrophy/interstitial fibrosis, n (%) | | | | | |
| T0 | 1255(70.0) | 450(75.3) | 420(70.4) | 385(64.5) | **<0.001** |
| T1 | 414(23.1) | 130(21.7) | 127(21.3) | 157(26.3) | |
| T2 | 123(6.9) | 18(3.0) | 50(8.3) | 55(9.2) | |
| Crescents, n (%) | | | | | |
| C0 | 643(35.9) | 232(38.8) | 217(36.3) | 194(32.5) | **0.005** |
| C1 | 1004(56.0) | 331(55.4) | 337(56.4) | 336(56.3) | |

(*Continued*)

**Table 1** (Continued).

| Variables | Total (n=1792) | Tertile 1 (n=598) <151.20 | Tertile 2 (n=598) ≥151.20 ≤261.79 | Tertile 3 (n=598) >261.79 | P value |
|---|---|---|---|---|---|
| C2 | 145(8.1) | 35(5.8) | 43(7.3) | 67(11.2) | |
| Steroid with/without immunosuppressants treatment, n(%) | 513(28.6) | 155(25.9) | 168(28.1) | 190(31.8) | **<0.001** |
| Composite event, n(%) | 130(7.3) | 21(3.5) | 49(8.2) | 60(10.1) | **<0.001** |

**Notes**: Continuous variables are expressed as mean±standard deviation or as median (interquartile range); Categorical variables are expressed as frequency (%); Bold values was that the differences were significant (P<0.05).
**Abbreviations**: Hb, hemoglobin; ALB, albumin; TCH, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; UA, uric acid; Scr, serum creatinine; 24h Upro, 24-hour urine protein; eGFR, estimated glomerular filtration rate; PLR, Platelets/Lymphocytes; PAR, Platelets/Albumin.

**Table 2** Correlation Between AISI and Related Clinicopathological Variables

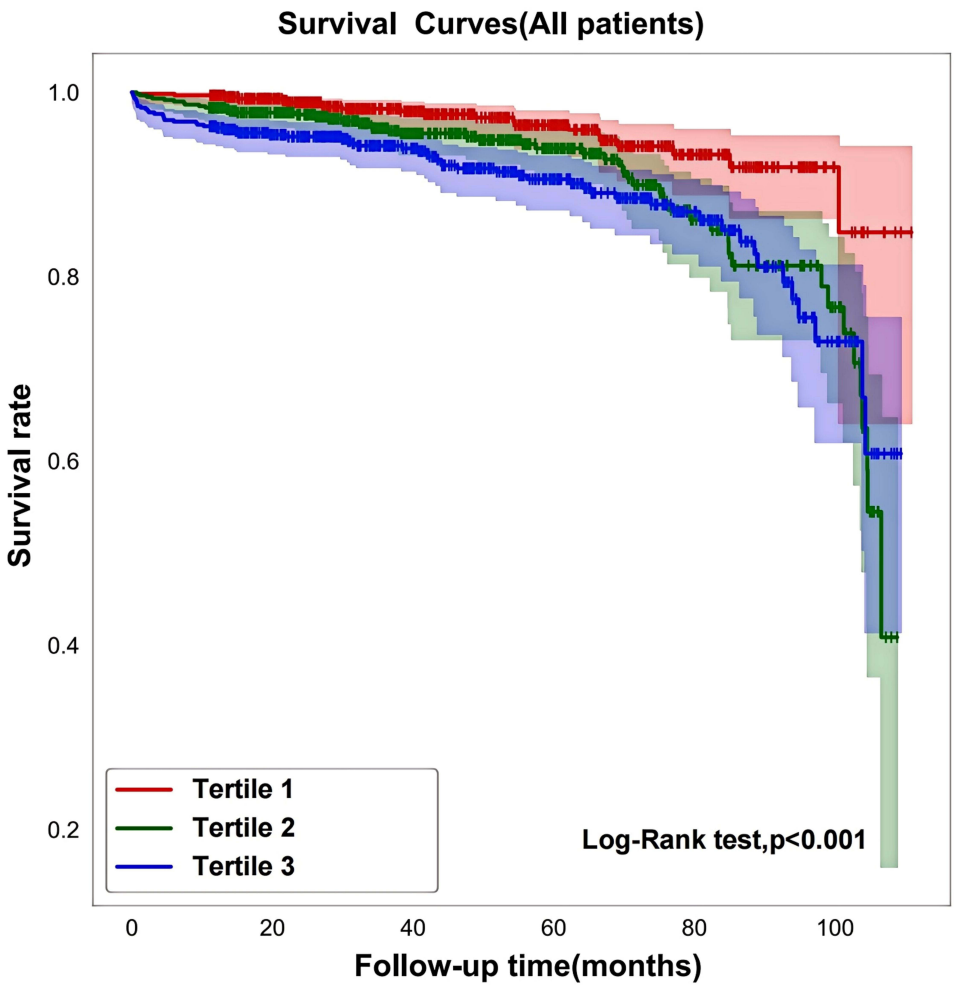
| | Variables | Correlation Coefficient (r) | P value |
|---|---|---|---|
| AISI | Sex | 0.053 | **0.025** |
| | Age | 0.012 | 0.609 |
| | Hb | 0.042 | 0.072 |
| | ALB | −0.018 | **<0.001** |
| | TCH | 0.089 | **<0.001** |
| | TG | 0.112 | **<0.001** |
| | LDL | 0.122 | **<0.001** |
| | Scr | 0.142 | **<0.001** |
| | UA | 0.079 | **<0.001** |
| | 24h Upro | 0.220 | **<0.001** |
| | eGFR | −0.132 | **<0.001** |

**Note**: Bold values was that the differences were significant (P<0.05).
**Abbreviations**: AISI, aggregate index of systemic inflammation; Hb, hemoglobin; ALB, albumin; TCH, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; UA, uric acid; Scr, serum creatinine; 24h Upro, 24-hour urine protein; eGFR, estimated glomerular filtration rate.

a significantly negative correlation between AISI and albumin (r=−0.018, P<0.001), eGFR (r=−0.132, p< 0.001). Additionally, the association between AISI and pathologic characteristics was examined using logistic regression analysis. The results indicated that patients with IgAN who had a higher AISI were prone to have pathologic lesions featuring of endocapillary hypercellularity (OR=1.475;95% CI:1.155–1.885; P=0.002), tubular atrophy/interstitial fibrosis (OR=1.674; 95% CI 1.304–2.150; P<0.001), and cellular or fibrocellular crescents (OR=1.317; 95% CI 1.038–1.670; P=0.023).

## Associations of AISI with Risk of Renal Survival Rate

Renal endpoint event was defined as a 50% decline in the eGFR or ESRD. Our results demonstrated that the incidence of endpoint events in the tertile 3 group was 10.1%, while in the other groups, fewer individuals had endpoint events, accounting for 8.2% and 3.5% respectively (P<0.001)(As shown in Table 1). Kaplan−Meier analysis suggested that participants in tertial 3 had a higher risk of developing kidney failure than the other groups (log-rank=17.38, P<0.001). Patients in the tertial 1 group had significantly longer mean kidney survival times (105.70 months, 95% CI: 103.35–108.04) than those in the other two groups (Figure 2).




| | Mean follow-up time (months) | 95%CI |
|---|---|---|
| Tertile 1 | 105.70 | 103.35-108.04 |
| Tertile 2 | 98.00 | 95.31-100.69 |
| Tertile 3 | 96.73 | 93.81-99.66 |
| Total | 100.47 | 98.81-102.14 |

**Figure 2** Kaplan–Meier curves of renal outcomes in different AISI groups.

In the Cox regression analysis, the AISI treated as a categorical variable. While in unadjusted Cox analysis, the hazard of poor renal prognosis in Tertial 1 was lower than that in Tertial 2 (HR=2.243, 95% CI:1.344–3.746, P=0.002) and Tertial 3 (HR=2.769, 95% CI: 1.684–4.554, P<0.001). To reduce the influence of other related factors, we built three models that incorporated relevant clinical, pathological and treatment data. As shown in Models 1,2 and 3, multivariate Cox regression analysis indicated that the high AISI was an independent risk factor for renal progression even after adjustment for clinical parameters (age, sex, Hb, ALB, TG, LDL, UA, 24h Upro and eGFR) (adjusted HR: 2.693, 95% CI: 1.563–4.638, P<0.001) and combined with pathologic lesions (Oxford MEST-C)(adjusted HR: 2.401, 95%

**Table 3** Multivariate Cox Regression Analysis AISI Group and Renal Outcomes

| | Crude Model | | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|---|---|
| **AISI group** | **HR(95% CI)** | **P value** | **HR(95% CI)** | **P value** | **HR(95% CI)** | **P value** | **HR(95% CI)** | **P value** |
| Tertile1 | 1 | | 1 | | 1 | | 1 | |
| Tertile2 | 2.243(1.344–3.746) | **0.002** | 2.106(1.215–3.653) | **0.008** | 1.432(0.813–2.521) | 0.214 | 1.391(0.784–2.466) | 0.259 |
| Tertile3 | 2.769(1.684–4.554) | **<0.001** | 2.693(1.563–4.638) | <0.001 | 2.401(1.391–4.142) | **0.002** | 2.359(1.365–4.078) | **0.002** |
| P for trend | | **<0.001** | | **0.002** | | **0.003** | | **0.003** |

**Notes**: Model 1: was adjusted for age, gender+clinic factors (hemoglobin, albumin, triglyceride, low-density lipoprotein, uric acid, 24h Upro and eGFR). Model 2: was adjusted for Model 1+Oxford (MEST-C). Model 3: was adjusted for Model 2+treatment. eGFR was transformed into a binary variable with a cutoff of 30. Tubulointerstitial atrophy/interstitial fibrosis(T)was transformed into a binary variable of T0+T1 and T2. Crescent(C) was transformed into a binary variable of C0+C1 and C2. Bold values was that the differences were significant (P<0.05).

**Abbreviations**: 24h Upro, 24-hour urine protein; eGFR, estimated glomerular filtration rate; CI, confidence intervals; HR, hazard ratios.

CI:1.391–4.142, P=0.002) and combined with treatment (adjusted HR: 2.359, 95% CI:1.365–4.078, P=0.002), as shown in Table 3.

## Subgroup Analysis

According to age (≤40/>50), gender (female/male), hemoglobin (Hb)(≤110/>110), albumin(ALB) (≤35/>35), uric acid (UA)(≤420/>420), triglyceride(TG)(≤1.7/>1.7), low-density lipoprotein(LDL) (≤3.6/>3.6), 24-hour urine protein (24h Upro)(≤3.5/>3.5), estimated glomerular filtration rate(eGFR)(≤30/>30) and renal pathological Oxford classification (MEST-C) of IgAN (E0/E1, S0/S1, T0-1/T2, C0-1/T2), we made various subgroup analysis to evaluate any potential heterogeneity between different groups. Our results showed that AISI tended to have great predictive power in patients younger than 40 years old, sex of male, with UA>420umol/l, 24hUPro>3.5g, and tubular atrophy/interstitial fibrosis T0-T1 (as shown in Figure 3). Kaplan−Meier analyses were used for subgroup analysis of sex, UA, 24h Upro and tubular atrophy/interstitial fibrosis. Our finding suggested that in individuals with IgAN, particularly the male patients (log-rank =15.795, P<0.001) and those with UA>420μmol/L (log-rank=12.272, P<0.001), 24hUpro>3.5g(log-rank=5.679, P=0.017), and tubular atrophy/interstitial fibrosis T0-T1 (log-rank=10.783, P<0.001), high AISI was a notable risk factor for progression to the renal endpoint (shown in Figure 4).

## Predictive Value of AISI for IgA Nephropathy Renal Outcomes

The ROC was used to determine the predictive value of AISI. Compared with the routine inflammatory and nutrient factors PLR and PAR, AISI had the highest AUC (0.626). The AUCs for PLR and PAR were 0.561 and 0.575 respectively, which were lower than those of AISI. The results indicated that AISI has a higher predictive value for renal outcomes in IgAN compared to the conventional inflammatory indices, and the cut-off value of AISI in IgAN patients was 198.78, with a sensitivity of 70.0% and a specificity of 51.4% (Figure 5).

## The Relationship Between AISI and Renal Prognosis in the Matched Cohort

According to the cut-off value of AISI, all people were distributed into two groups: the high group (AISI>198.78) and the low group (AISI≤198.78). To eliminate the differences in clinical and pathological indices between the two groups, 1:1 propensity score (PS) matching using the greedy matching algorithm obtained matched pairs of 762 patients with low AISI and 762 patients with high AISI. As shown in Table 4, in the propensity score matched cohort, there were no statistically significant differences in any of the covariates at baseline between the two groups. Kaplan−Meier analyses showed that patients in the high AISI group had a higher risk of developing kidney failure than those in the low AISI group in the matched cohort (log-rank=4.643, P=0.031, shown in Figure 6). In the low AISI group, the mean renal survival time was much longer than that in the high group. After PS, the unadjusted Cox analysis showed that a higher level of AISI which was treated as categorical variable was associated with an increased risk of developing kidney failure (HR=1.570, 95% CI:1.038–2.376, P=0.033). After adjusting for clinicopathological and treatment parameters, high AISI

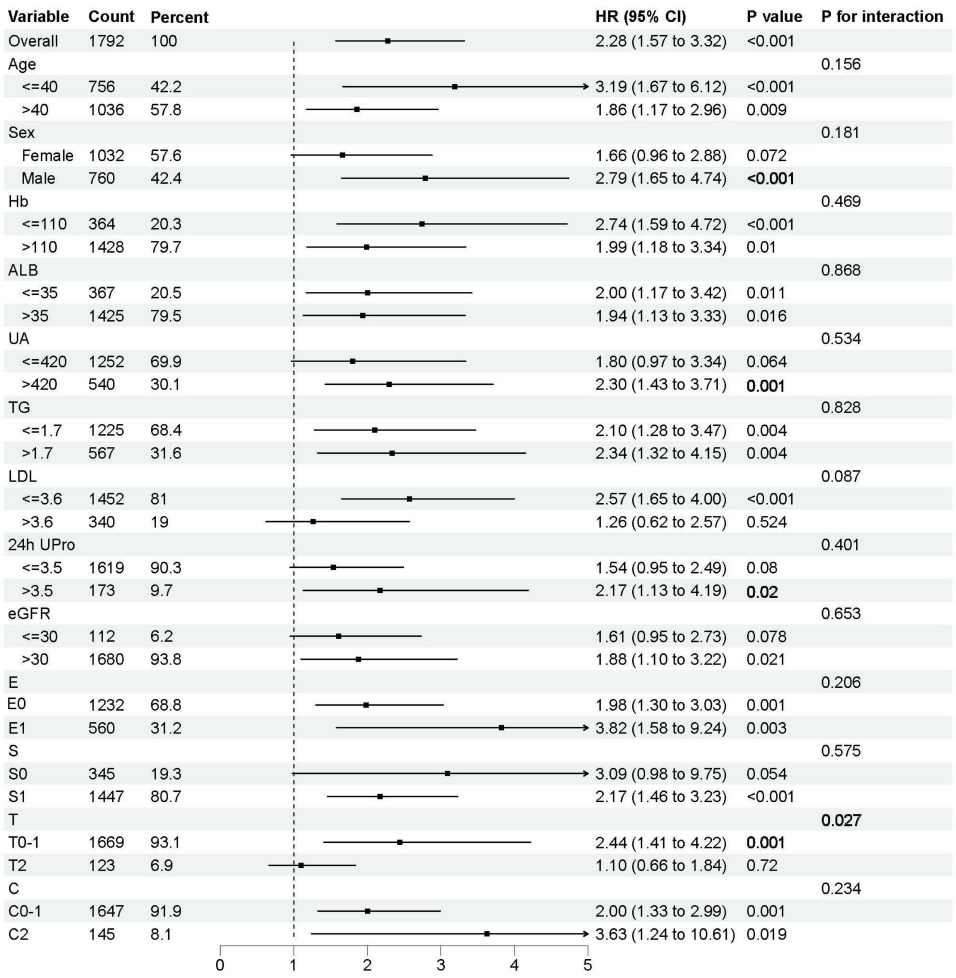



**Figure 3** Forest plot of subgroup and interaction effects analyses.
**Note**: Bold values was that the differences were significant (P<0.05).
**Abbreviations**: Hb, hemoglobin; ALB, albumin; UA, uric acid; TG, triglyceride; LDL, low-density lipoprotein; 24h Upro, 24h urine protein; eGFR, estimated glomerular filtration rate; E, Endocapillary hypercellularity; S, Segmental sclerosis; T, Tubular atrophy/interstitial fibrosis; C, Crescents.

remained an independent risk factor for poor renal prognosis in IgAN patients (HR=1.568, 95% CI: 1.007–2.442, P=0.046) (Table 5).

Moreover, through the multivariate adjusted restricted cubic splines for the matched cohort, we found out that that there was a linear correlation between AISI and poor renal prognosis (P for overall=0.0135, P for nonlinearity=0.773), showing a trend that as the AISI level rises, the risk of IgAN patients progressing to ESRD increases progressively (Figure 7).

These results indicated that baseline AISI is an important indicator of renal prognosis, and the probability of poor renal prognosis in patients with AISI>198.78 was much higher than that in patients with AISI≤198.78. Baseline AISI can effectively predict renal outcome of adult IgAN patients.

## Multivariate ROC Curve Associated with AISI and the IIgA-PRT Model

Multivariable logistic regression was performed on the original IIgAN-PRT model, incorporating relevant parameters both with and without AISI. ROC analysis demonstrated that the model with AISI (AUC:0.946) had a higher AUC compared to the original models (AUC:0.945) (Figure 8).

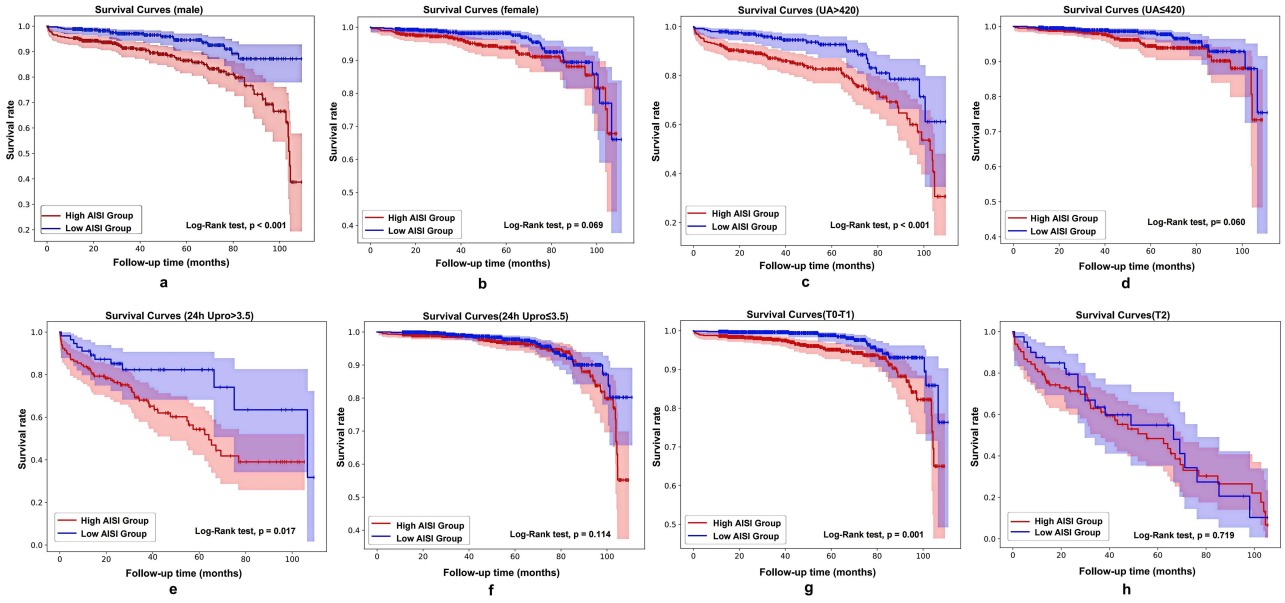



**Figure 4** Different types of Kaplan-Meier analysis for the renal endpoint. (**a** and **b**) Kaplan-Meier analysis for male and female patients. (**c** and **d**) Kaplan-Meier analysis for patients with different UA. (**e** and **f**) Kaplan-Meier analysis for patients with different 24h urine protein. (**g** and **h**) Kaplan-Meier analysis for patients with different tubulointerstitial atrophy/interstitial fibrosis(T).
**Abbreviations**: UA, uric acid; 24h Upro, 24h urine protein; T, Tubular atrophy/interstitial fibrosis.

## Discussion

IgAN is a kind of chronic immune-mediated inflammatory disorder, a considerable amount of researches indicate that the activation of inflammatory responses exerts a significant role in the occurrence and progression of IgAN,[12] therefore, accurate assessment of inflammation is crucial for preventing IgAN from progressing to ESRD. Previous studies have confirmed that a variety of inflammatory markers such as Platelets/Lymphocytes (PLR) and Platelets/Albumin (PAR) are related to the renal outcomes of IgAN.[13] The aggregate index of systemic inflammation (AISI), a novel inflammation marker which has received extensive attention recently, is calculated using four types of blood cells taking part in inflammation (neutrophils, monocytes, platelets and lymphocytes). As a comprehensive inflammation marker, AISI enables a more thorough assessment of the systemic inflammatory condition.[9] The study conducted by Wang et al affirmed that AISI has a close connection with the inflammatory status of patients with esophageal cancer.[14] Yan et al recently reported AISI as an indicator related to cardiovascular mortality and all-cause mortality in peritoneal dialysis patients.[15] While, there have been relatively few studies on the relationship between AISI and the prognosis of IgAN as so far.

In our retrospective study, among 1792 biopsy-confirmed IgAN patients, 130 individuals (7.3%) achieved the combined renal endpoint, and the incidence of endpoint events in the AISI 3 group was significantly higher than that in the other two groups. The patients with IgAN who had higher AISI levels also manifested more severe clinical features and pathological lesions. And we also disclosed that the AISI had a negative association with eGFR and a positive association with uric acid, serum creatinine and 24h urine protein. A higher AISI was also related to more severe renal pathological abnormalities, especially endocapillary hypercellularity, tubular atrophy/interstitial fibrosis and cellular or fibrocellular crescents in the individuals with IgAN. The K-M survival curves manifested that in the higher AISI group, the mean kidney survival time was considerably shorter than that in the other groups. Multivariate Cox regression further suggested that AISI was an independent risk factor for the renal prognosis of IgAN. And this is the only study known to us that assesses the relationship between AISI and the clinical and pathological characteristics of IgAN patients.

Although the pathogenic mechanism of IgAN remains to be fully clarified, several inflammatory cells are likely to be implicated, especially neutrophils, lymphocytes, monocytes and platelets. Neutrophils are indispensable constituents of the innate immune system due to the capability of coordinating host defensive processes and inflammation.[16] Neutrophils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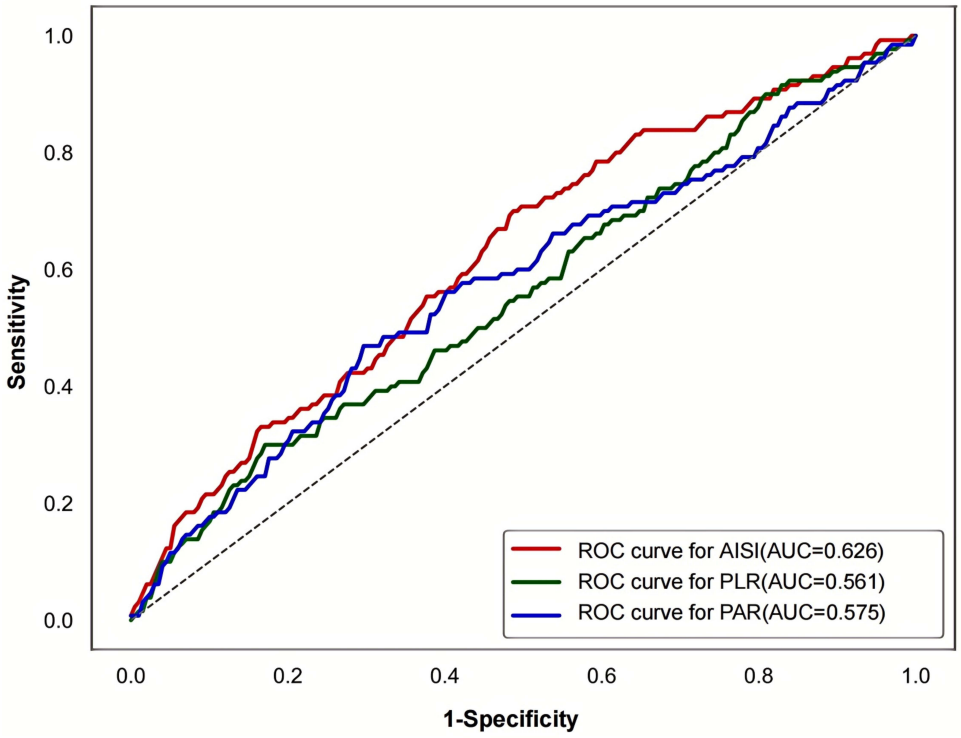



| Parameters | AUC(95% CI) | P value | Cut-off value | Sensitivity | Specificity |
|---|---|---|---|---|---|
| AISI | **0.626(0.576-0.675)** | **0.001** | **198.78** | **70.0%** | **51.4%** |
| PLR | 0.561(0.509-0.614) | 0.020 | 157.94 | 30.0% | 83.0% |
| PAR | 0.575(0.521-0.629) | 0.004 | 6.68 | 46.9% | 70.5% |

**Figure 5** The AUC of AISI, PLR, and PAR for IgAN renal outcomes.
**Abbreviations**: AUC, the area under the receiver operating characteristic curve; AISI, aggregate index of systemic inflammation=neutrophils(/L)×monocytes×platelets(/L)/lymphocytes(/L); PLR, Platelets/Lymphocytes=platelets(/L)/lymphocytes(/L); PAR, Platelets/Albumin=platelets(/L)/albumin(g/L).

play a significant role in the pathogenesis and pro gression of IgAN through a variety of complex pathways, such as the secretion of inflammatory mediators, engagement in inflammatory reactions, and participation in fibrotic healing processes.[1] Monocytes represent circulating phagocytic innate immune cells within the blood which can quickly mobilize to inflammatory sites and differentiate into macrophages or dendritic cells to exert pro-and anti-inflammatory effects.[17] Zheng et al have affirmed via single-cell RNA sequencing that the high expression of macrophages and monocytes in the kidney tissue of IgAN patients is correlated with inflammatory responses and disease progression.[18] Lymphocytes are essential for both innate and acquired immune responses and play an important role in Pathological process of IgAN.[19] Wang et al verified that high neutrophil-lymphocyte ratio is an independent risk factor for ESRD in IgA nephropathy.[20] By interacting with immune cells and secreting diverse proinflammatory cytokines, platelets are involved in initiating and exacerbating inflammation.[21] A single-center, retrospective study encompassing 124 IgAN patients demonstrated that PLT, PAR and PLR were closely associated with renal outcomes in IgAN patients.[22] AISI integrates these four inflammatory cells into a single measure, providing a more stable and comprehensive assessment of the inflammatory status for IgAN.

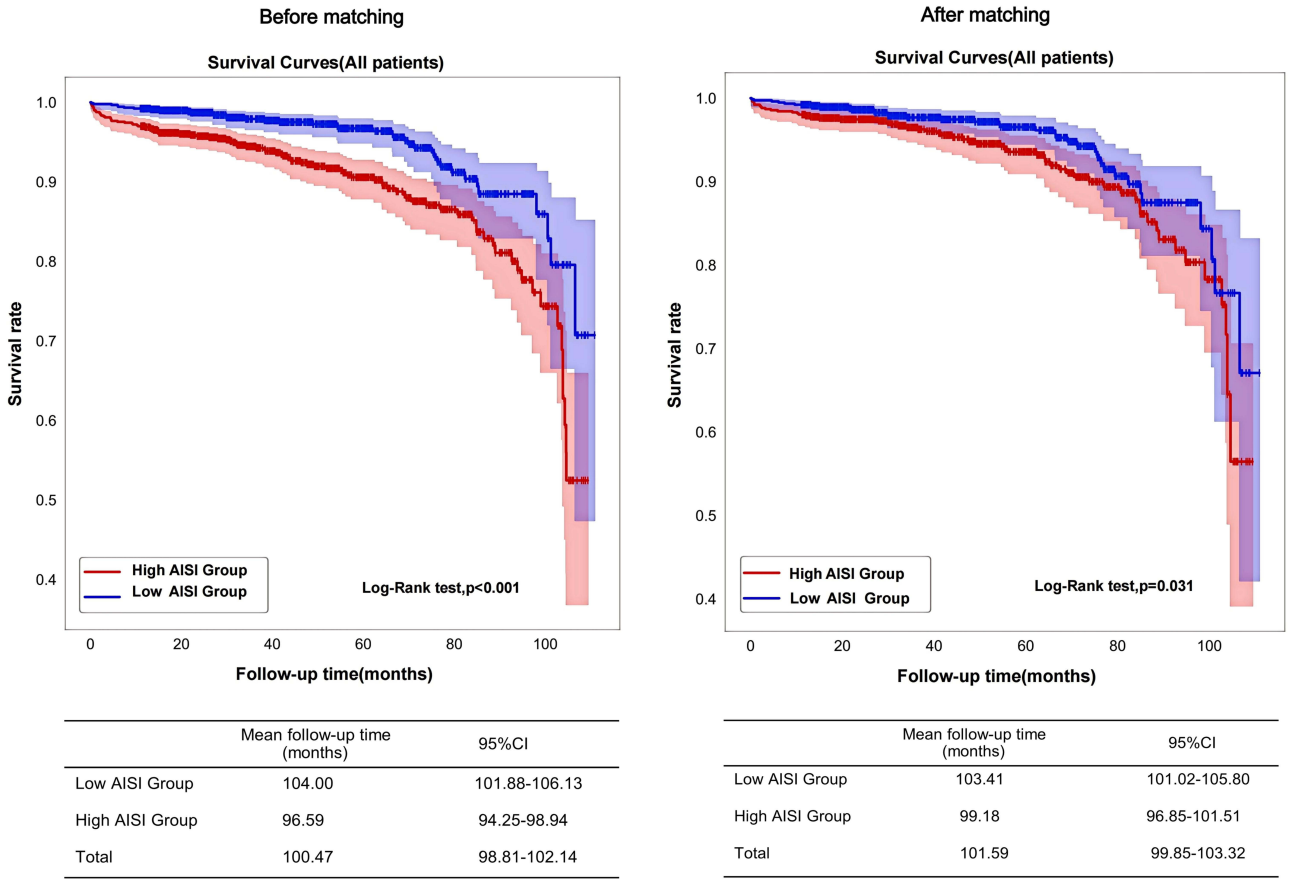
Our research indicates that AISI is an independent predictor for the progression to ESRD in IgAN patients. Furthermore, in order to more accurately assess the predictive power of AISI, we carried out subgroup analysis to analyse the predictive effect of AISI with different clinicopathological features in IgAN patients, the results showed that AISI has stronger predictive value in male patients, and the individuals with 24h urine protein levels more than 3.5g/24h

**Table 4** Baseline Characteristics of the Full Cohort of 1792 Patients with IgAN According to Cut-off Value of AISI and the Propensity Score Matched Cohort

| Variable | Total | Before Matching | | | After Matching | | |
|---|---|---|---|---|---|---|---|
| | | Low AISI Group (≤198.78) | High AISI Group (>198.78) | P value | Low AISI Group (≤198.78) | High AISI Group (>198.78) | P value |
| Participants, (n) | 1792 | 894 | 898 | | 762 | 762 | |
| Age, years | 43.0(36.0–53.0) | 42.0(35.0–53.0) | 43.0(36.0–52.0) | 0.479 | 43.0(35.0–53.0) | 43.0(36.0–52.0) | 0.974 |
| Male, n(%) | 760(42.4) | 354(39.6) | 406(45.2) | **0.016** | 337(44.2) | 312(40.9) | 0.195 |
| Hypertension, n(%) | 195(10.9) | 94(10.5) | 101(11.2) | 0.618 | 81(10.6) | 87(11.4) | 0.624 |
| Hb, g/L | 126.00±19.20 | 125.35±18.33 | 126.64±20.01 | 0.153 | 126.26±18.61 | 126.35±19.64 | 0.539 |
| ALB, g/L | 38.50(35.70–41.00) | 38.90(36.20–41.40) | 38.30(35.35–40.70) | **<0.001** | 38.80(36.00–41.30) | 38.60(35.90–40.90) | 0.530 |
| TCH, mmol/L | 4.65(4.07–5.37) | 4.58(4.04–5.53) | 4.77(4.10–5.56) | **<0.001** | 4.62(4.07–5.23) | 4.67(4.06–5.33) | 0.373 |
| TG, mmol/L | 1.30(0.90–1.99) | 1.21(0.85–1.87) | 1.40(0.96–2.07) | **<0.001** | 1.29(0.91–1.92) | 1.34(0.91–1.95) | 0.592 |
| LDL, mmol/L | 2.84(2.35–3.42) | 2.75(2.27–3.31) | 2.94(2.44–3.54) | **<0.001** | 2.81(2.33–3.28) | 2.90(2.41–3.35) | 0.051 |
| Scr, μmol/L | 80(62–109) | 77(66–100) | 84(64–120) | **<0.001** | 80(62–104) | 80(61–111) | 0.367 |
| UA, μmol/L | 365(300–438) | 359(296–428) | 374(308–449) | **0.003** | 367,301–437 | 364(297–436) | 0.878 |
| 24h Upro, g/L | 0.91(0.46–1.81) | 0.72(0.38–1.43) | 1.10(0.55–2.29) | **<0.001** | 0.84(0.46–1.54) | 0.94(0.50–1.61) | 0.137 |
| eGFR, mL/min/1.73m$^2$ | 85.20(61.00–106.60) | 88.60(68.10–107.80) | 84.45(53.90–105.60) | **<0.001** | 86.15(66.50–105.50) | 83.59(60.80–107.20) | 0.343 |
| Mesangial cellularity, n(%) | | | | | | | |
| M0 | 22(1.2) | 11(1.2) | 11(1.2) | 0.998 | 9(1.2) | 9(1.2) | 1.000 |
| M1 | 1770(98.8) | 883(98.8) | 887(98.8) | | 753(98.8) | 753(98.8) | |
| Endocapillary hypercellularity, n (%) | | | | | | | |
| E0 | 1232(68.8) | 641(71.7) | 591(65.8) | **0.007** | 535(79.6) | 510(66.9) | 0.168 |
| E1 | 560(31.2) | 253(28.3) | 307(34.2) | | 227(20.4) | 252(33.1) | |
| Segmental sclerosis, n (%) | | | | | | | |
| S0 | 345(19.3) | 174(19.5) | 171(19.0) | 0.821 | 137(20.4) | 152(19.9) | 0.327 |
| S1 | 1447(80.7) | 720(80.5) | 727(81.0) | | 625(79.6) | 610(80.1) | |
| Tubular atrophy/interstitial fibrosis, n (%) | | | | | | | |
| T0-1 | 1669(93.1) | 854(95.5) | 815(90.8) | **<0.001** | 724(95.0) | 712(93.2) | 0.188 |
| T2 | 123(6.9) | 44(4.5) | 83(9.2) | | 38(5.0) | 50(6.8) | |
| Crescents, n (%) | | | | | | | |
| C0-1 | 1647(91.9) | 837(93.6) | 810(90.2) | **0.008** | 709(93.0) | 700(91.9) | 0.383 |
| C2 | 145(8.1) | 57(6.4) | 88(9.8) | | 53(7.0) | 62(8.1) | |
| Steroid with/without immunosuppressants treatment, n(%) | 513(28.6) | 228(25.5) | 285(31.7) | **0.004** | 200(26.2) | 228(29.9) | 0.110 |
| Composite event, n(%) | 130(7.3) | 39(4.4) | 91(10.1) | **<0.001** | 36(4.7) | 60(7.9) | **0.011** |

**Notes**: Continuous variables are expressed as mean±standard deviation or as median (interquartile range); Categorical variables are expressed as frequency (%); Bold values was that the differences were significant. Bold values was that the differences were significant (P<0.05).

**Abbreviations**: Hb, hemoglobin; ALB, albumin; TCH, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; UA, uric acid; Scr, serum creatinine; 24h Upro, 24-hour urine protein; eGFR, estimated glomerular filtration rate.




| | Mean follow-up time (months) | 95%CI |
|---|---|---|
| Low AISI Group | 104.00 | 101.88-106.13 |
| High AISI Group | 96.59 | 94.25-98.94 |
| Total | 100.47 | 98.81-102.14 |

| | Mean follow-up time (months) | 95%CI |
|---|---|---|
| Low AISI Group | 103.41 | 101.02-105.80 |
| High AISI Group | 99.18 | 96.85-101.51 |
| Total | 101.59 | 99.85-103.32 |

**Figure 6** Relationship between AISI and renal outcomes in the full cohort and the propensity score-matched cohort (Kaplan–Meier curves).

and uric acid levels above 420μmol/L. However, in contrast to the more severe tubulointerstitial lesion (T2), AISI exhibits greater predictive value in T0-T1. The reduced relevance of AISI in T2 lesions, which are predominantly

**Table 5** Multivariate Cox Regression Analysis AISI According to Cut-off Value and Renal Outcomes in the Full Cohort and the Propensity Score Matched Cohort

| | Before matching | | | After Matching | | |
|---|---|---|---|---|---|---|
| | **Low AISI Group (≤198.78)** | **High AISI Group (>198.78)** | **P value** | **Low AISI Group (≤198.78)** | **High AISI Group (>198.78)** | **P value** |
| Number of participants with events/n | 39/894 | 91/898 | | 36/762 | 60/762 | |
| Crude Model | 1.00(reference) | 2.279(1.565–3.317) | **<0.001** | 1.00(reference) | 1.570(1.038–2.376) | **0.033** |
| Model 1 | 1.00(reference) | 1.769 (1.185–2.643) | **0.005** | 1.00(reference) | 1.685(1.082–2.626) | **0.021** |
| Model 2 | 1.00(reference) | 1.638(1.094–2.454) | **0.017** | 1.00(reference) | 1.603(1.031–2.493) | **0.036** |
| Model 3 | 1.00(reference) | 1.620(1.079–2.432) | **0.020** | 1.00(reference) | 1.568(1.007–2.442) | **0.046** |

**Notes**: Model 1: was adjusted for age, gender+ clinic factors (hemoglobin, albumin, triglyceride, low-density lipoprotein, uric acid, 24h Upro and eGFR). Model 2: was adjusted for Model 1+Oxford (MEST-C). Model 3: was adjusted for Model 2+treatment. eGFR was transformed into a binary variable with a cutoff of 30. Tubulointerstitial atrophy/interstitial fibrosis (T)was transformed into a binary variable of T0+T1 and T2. Crescent(C) was transformed into a binary variable of C0+C1 and C2. Bold values was that the differences were significant (P<0.05).

**Abbreviations**: 24h Upro, 24h urine protein; eGFR, estimated glomerular filtration rate; CI, confidence intervals; HR, hazard ratios.

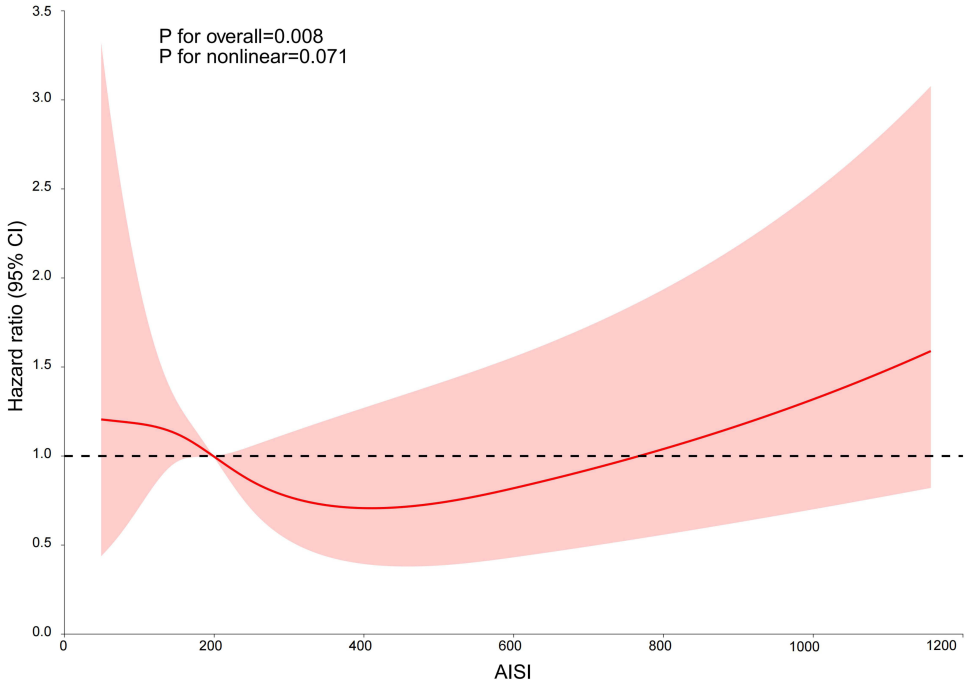



**Figure 7** Restricted cubic splines curve of AISI and renal outcomes in the propensity score matched cohort.
**Abbreviation**: AISI, aggregate index of systemic inflammation.

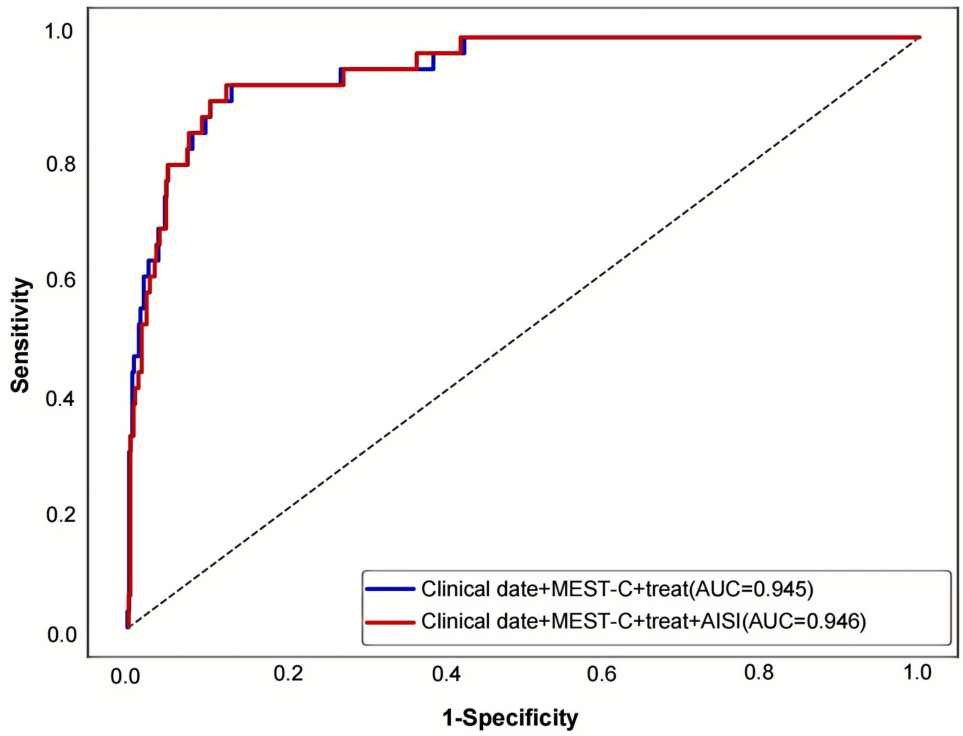



**Figure 8** The ROC of Multivariate models with and without AISI.
**Abbreviations**: ROC, the receiver operating characteristic; AUC, the area under the receiver operating characteristic curve; MEST-C, the Oxford classification of renal pathology; AISI, aggregate index of systemic inflammation.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characterized by chronic pathological changes, could be due to the clinical indices included in AISI primarily indicating acute inflammatory states.

Previous studies have already verified the prognostic value of PLR and PAR in renal prognosis of IgAN.[13] In this study, we observed that AISI has the best predictive efficiency, with an AUC of 0.626 Compared with PLR and PAR. According to the AISI cut-off of 198.78, all patients were then divided into two groups, and to minimize the influence of other parameters, we conducted propensity score matching among all participants. The results indicated that high AISI was associated with an escalating risk of poor renal outcome in IgAN both in the full cohort and the matched cohort. And as the AISI level increases, the risk of IgAN patients progressing into ESRD also increases significantly. Consequently, for patients with IgAN, an AISI value above 198.78 could act as an indicator of enhanced proteinuria, worsened renal function, and more serious pathological grading, potentially indicating a poorer prognosis. Previous investigations have revealed that proteinuria,[23] decline of kidney function,[24] and hyperuricaemia[25] are the risk factors for the progression of IgAN, in our study, after eliminating the influence of confounding factors such as proteinuria, renal function and uric acid through propensity score matching and multivariable Cox regression analysis, AISI still remains an independent and significant prognostic factor for prognosis of IgAN. Furthermore, we conducted a comparative analysis of the AUC values of the IIgAN-PRT model both with and without AISI, the results demonstrated that the inclusion of AISI enhanced the performance evaluation of the multi-index model. Hence, in comparison with diverse clinicopathological factors, we believed that AISI mainly reflects the inflammatory status of the patients to indicate the prognosis value of IgAN.

Overall, our research disclosed the combined role of neutrophils, monocytes, lymphocytes, and platelets in the advancement of IgAN patients. AISI can be readily obtained through routine clinical blood tests and is significantly cheaper than other inflammatory indicators and pathology examinations, as it demands no complex procedures or special reagents. Although AISI exhibited a statistically significant independent yet modest predictive accuracy for IgAN progression (AUC=0.626), compared to the established biomarkers such as Egfr (AUC=0.912) and 24h proteinuria (AUC=0.810) in our cohort, however its integration into multi-parameter prognostic models enhanced overall predictive performance (ΔAUC=0.001). These findings position AISI as a novel yet modest independent predictor of IgAN outcomes, with clinical utility likely optimized through its incorporation into multi-parameter risk models.

Nevertheless, this study possesses certain limitations, firstly, as a single-centre retrospective study, there may have been selection bias and the generalizability of our results is limited. Secondly, the duration of follow-up was relatively brief. As a chronic disease, the short follow-up period in IgAN might lead to some endpoint events remaining undetected, thereby influencing the predictive efficacy of AISI. Hence, our discoveries need to be verified in other populations, preferably in the setting of prospective and multicentric studies and in evaluating long-term prognosis.

## Conclusion

In conclusion, AISI, a highly accessible laboratory indicator, is a novel yet modest independent predictor for the progression to ESRD in IgAN patients, particularly when patients are male, have more heavy proteinuria, or hyperuricaemia and early stage of renal tubulointerstitial disorder. Patients whose AISI level exceeds 198.78 at renal biopsy require greater attention and more active intervention.

## Data Sharing Statement

The data sets used or analysed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Hangzhou Hospital of Traditional Chinese Medicine.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflicts of interest.

## References

1. Stamellou E, Seikrit C, Tang SCW, et al. IgA nephropathy. *Nat Rev Dis Primers*. 2023;9(1):67. doi:10.1038/s41572-023-00476-9
2. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(4S):S1–S276. doi:10.1016/j.kint.2021.05.021
3. Filippone EJ, Gulati R, Farber JL. Contemporary review of IgA nephropathy. *Front Immunol*. 2024;12(15):1436923. doi:10.3389/fimmu.2024.1436923
4. Paliogiannis P, Ginesu GC, Tanda C, et al. Inflammatory cell indexes as preoperative predictors of hospital stay in open elective thoracic surgery. *ANZ J Surg*. 2018;88(6):616–620. doi:10.1111/ans.14557
5. Hosseninia S, Ghobadi H, Garjani K, et al. Aggregate index of systemic inflammation (AISI) in admission as a reliable predictor of mortality in COPD patients with COVID-19. *BMC Pulm Med*. 2023;23(1):107. doi:10.1186/s12890-023-02397-5
6. Göçmen A, Gesoglu Demir T. The aggregate index of systemic inflammation as a predictor of mortality in stroke patients. *Cureus*. 2024;16(7):e64007. doi:10.7759/cureus.64007
7. Akdogan M, Ustundag Y, Cevik SG, et al. Correlation between systemic immune-inflammation index and routine hemogram-related inflammatory markers in the prognosis of retinopathy of prematurity. *Indian J Ophthalmol*. 2021;69(8):2182–2187. doi:10.4103/ijo.IJO_2745_20
8. Tang R, Deng JP, Zhang L, et al. Prognostic significance of the skeletal muscle index and systemic inflammatory index in patients with lymph node-positive breast cancer after radical mastectomy. *BMC Cancer*. 2022;22(1):234. doi:10.1186/s12885-022-09312-x
9. Zinellu A, Collu C, Nasser M, et al. The Aggregate Index of Systemic Inflammation (AISI): a novel prognostic biomarker in idiopathic pulmonary fibrosis. *J Clin Med*. 2021;10(18):4134. doi:10.3390/jcm10184134
10. Xiu J, Lin X, Chen Q, et al. The aggregate index of systemic inflammation (AISI): a novel predictor for hypertension. *Front Cardiovasc Med*. 2023;17(10):1163900. doi:10.3389/fcvm.2023.1163900
11. Yang Y, Xu Y, Liu S, et al. The systemic inflammation indexes predict all-cause mortality in peritoneal dialysis patients. *Ren Fail*. 2023;45(1):2160348. doi:10.1080/0886022X.2022.2160348
12. Medjeral-Thomas NR, Cook HT, Pickering MC. Complement activation in IgA nephropathy. *Semin Immunopathol*. 2021;43(5):679–690. doi:10.1007/s00281-021-00882-9
13. Tan J, Song G, Wang S, et al. Platelet-to-albumin ratio: a novel IgA nephropathy prognosis predictor. *Front Immunol*. 2022;13:842362. doi:10.3389/fimmu.2022.842362
14. Wang HK, Wei Q, Yang YL, et al. Clinical usefulness of the lymphocyte-to-monocyte ratio and aggregate index of systemic inflammation in patients with esophageal cancer: a retrospective cohort study. *Cancer Cell Int*. 2023;23(1):13. doi:10.1186/s12935-023-02856-3
15. Yan Q, Liu G, Wang R, et al. The association between the aggregate index of systemic inflammation and cardiovascular risk in peritoneal dialysis patients. *Nutr Metab Cardiovasc Dis*. 2024;20:103774. doi:10.1016/j.numecd.2024.10.012
16. Rungelrath V, Kobayashi SD, DeLeo FR. Neutrophils in innate immunity and systems biology-level approaches. *Wiley Interdiscip Rev Syst Biol Med*. 2020;12(1):e1458. doi:10.1002/wsbm.1458
17. Guilliams M, Mildner A, Yona S. Developmental and functional heterogeneity of monocytes. *Immunity*. 2018;49(4):595–613. doi:10.1016/j.immuni.2018.10.005
18. Zheng Y, Lu P, Deng Y, et al. Single-cell transcriptomics reveal immune mechanisms of the onset and progression of IgA nephropathy. *Cell Rep*. 2020;33(12):108525. doi:10.1016/j.celrep.2020.108525
19. Suzuki Y. B cell targeting in IgA nephropathy. *Nephrology*. 2024;29(Suppl 2):39–43. doi:10.1111/nep.14367
20. Wang S, Dong L, Pei G, et al. High neutrophil-to-lymphocyte ratio is an independent risk factor for end stage renal diseases in IgA nephropathy. *Front Immunol*. 2021;12:700224. doi:10.3389/fimmu.2021.700224
21. Kömürcü HF, Erkalaycı C, Gozke E. Hemogram and inflammatory indices in pain-free periods in migraine patients without aura. *Neurol Res*. 2024;6:1–7. doi:10.1080/01616412.2024.2438616
22. Sági B, Vas T, Csiky B, et al. Are platelet-related parameters prognostic predictors of renal and cardiovascular outcomes in IgA nephropathy? *J Clin Med*. 2024;13(4):991. doi:10.3390/jcm13040991
23. Shen X, Chen P, Liu M, et al. Long-term outcomes of IgA nephropathy in China. *Nephrol Dial Transplant*. 2024;19:gfae252. doi:10.1093/ndt/gfae252
24. Bharati J, Jhaveri KD. Prognosis of IgA nephropathy: a lifetime story. *Clin J Am Soc Nephrol*. 2023;18(6):699–701. doi:10.2215/CJN.0000000000000171
25. Russo E, Drovandi S, Salvidio G, et al. Increased serum uric acid levels are associated to renal arteriolopathy and predict poor outcome in IgA nephropathy. *Nutr Metab Cardiovasc Dis*. 2020;30(12):2343–2350. doi:10.1016/j.numecd.2020.07.038