Original Article

Hepatic steatosis index at diagnosis has the potential for forecasting end-stage kidney disease in patients with antineutrophil cytoplasmic antibody-associated vasculitis

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Objective: This study evaluated whether the hepatic steatosis index (HSI) at antineutrophil cytoplasmic antibody-associated vasculitis (AAV) diagnosis could forecast poor outcomes during the disease course in AAV patients.
Methods: This study included 260 AAV patients. The equation for HSI is as follows: HSI=8×(alanine aminotransferase/aspartate aminotransferase)+body mass index+(2, diabetes mellitus)+(2, female). The cut-off of HSI was obtained using the receiver operating characteristic curve.
Results: The median age of the 260 patients was 59.5 years, and 65.0% were female. Among the continuous variables excluding the parameters composing the equation for HSI, HSI was significantly correlated with Birmingham vasculitis activity score, five-factor score, haemoglobin, blood urea nitrogen, serum creatinine, and total cholesterol. Among poor outcomes, the area under the curve of HSI for end-stage renal disease (ESRD) was significant, and the cut-off of HSI for ESRD was set at ≤30.82. AAV patients with HSI ≤30.82 exhibited a significantly higher risk of ESRD (relative risk 3.489) and a significantly lower cumulative ESRD-free survival rate than those with HSI >30.82.
Conclusion: This study is the first to demonstrate that HSI at AAV diagnosis could forecast ESRD during the disease course in AAV patients.

Keywords: Hepatic steatosis index, End-stage renal disease, Antineutrophil cytoplasmic antibody, Vasculitis, Forecasting

INTRODUCTION

Small vessel vasculitis is divided into two categories, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and immune complex vasculitis, in accordance with the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides and the 2007 European Medicine Agency algorithm for the classification of AAV and polyarteritis nodosa [1,2]. The Birmingham vasculitis activity score (BVAS) has nine systemic and major organ-based items; however, an

item of liver manifestation is not included in BVAS [3]. The five-factor score (FFS) and the vasculitis damage index are used for forecasting poor outcomes of AAV and evaluating major-organ damage owing to AAV, respectively. These two indices also do not include items related to liver manifestation [4,5]. In fact, serious and advanced liver damage in AAV patients, in particular, at the time of AAV diagnosis or in the early phase of AAV, has rarely been reported to date [6,7].

Meanwhile, apart from the liver involvement of AAV, several studies on the link between liver fibrosis-related indices and poor outcomes of AAV have been conducted [8-12]. These studies found that although AAV did not directly cause serious liver fibrosis, liver fibrosis-related indices at AAV diagnosis could forecast poor outcomes of AAV during the disease course. Recently, the hepatic steatosis index (HSI), an additional non-invasive index, was developed to evaluate the extent of liver fibrosis [13]. Furthermore, in addition to liver fibrosis, non-alcoholic fatty liver disease (NAFLD) can also be estimated by the range of HSI values [14,15]. Therefore, as in previous studies [12-15], it could be reasonably assumed that HSI at AAV diagnosis may forecast poor outcomes of AAV during the disease course; however, to date, there has been no study regarding the potential of HSI for forecasting poor outcomes of AAV. Hence, this study evaluated whether HSI at AAV diagnosis could forecast poor outcomes of AAV during the disease course in AAV patients.

MATERIALS AND METHODS

Patients

This study retrospectively screened 287 AAV patients by reviewing their medical records and included 260 patients in this study based on the inclusion criteria as follows: i) all patients met both the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides and the 2007 European Medicine Agency algorithm for the classification of AAV [1,2]; ii) the first classification of AAV was made at this hospital from October 2000 to December 2021; iii) the electronic medical records were well-written sufficiently for collecting clinical, laboratory, radiological, and histological data [3,4]; iv) the parameters composing the equation for HSI were particularly included in clinical and laboratory data [13,14]; v) patients with the concurrent serious medical conditions mimicking AAV, such as malignancies and infectious diseases at AAV diagnosis,

were excluded [9-12]; vi) the follow-up duration was more than three months after the AAV diagnosis; vii) AAV patients who have been exposed to glucocorticoids >20 mg (equivalent to prednisolone) or immunosuppressive drugs before the AAV diagnosis were excluded [9-12]; and viii) patients who took drugs that could provoke false positivity of ANCA, such as propylthiouracil and hydralazine, were also excluded [16].

Ethical disclosure

This study was approved by the Institutional Review Board (IRB) of Severance Hospital (Seoul, Korea, IRB No. 4-2020-1071) and was conducted in accordance with the Declaration of Helsinki. Given the retrospective design of the study and the use of anonymized patient data, the requirement for written informed consent was waived by the IRB.

Clinical data at the time of AAV diagnosis

The clinical and laboratory variables are described in Table 1. Demographic data included age, sex, and body mass index (BMI). AAV-related variables were presented as AAV subtype, ANCA type, and positivity and AAV-specific indices (BVAS and FFS). Diabetes mellitus (DM), hypertension, and dyslipidaemia were considered comorbidities. Data on acute-phase reactants, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were also collected. Myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA were measured using an immunoassay, whereas, perinuclear (P)-ANCA and cytoplasmic (C)-ANCA were assessed using an indirect immunofluorescence assay [17].

Equation for HSI

The equation for HSI is as follows: $HSI=8\times$(alanine aminotransferase [ALT]/aspartate aminotransferase [AST])+BMI+(2, DM)+(2, female) [13-15]. When HSI is less than 30, NAFLD can be ruled out [18].

Poor outcomes of AAV and Medications administered during the disease course

Five poor outcomes of AAV were assessed in this study including all-cause mortality, relapse, end-stage renal disease (ESRD), cerebrovascular accident (CVA), and acute coronary syndrome (ACS). For patients with each poor outcome, the follow-up duration based on each poor outcome was defined as the period between AAV diagnosis and each poor outcome

Table 1. Characteristics of AAV patients at diagnosis and during follow-up (n=260)

Variable	Value
At the time of diagnosis	
Demographic data	
Age (yr)	59.5 (20.0)
Female sex (%)	169 (65.0)
BMI (kg/m^2)	22.5 (4.2)
AAV subtype (%)	
MPA	139 (53.5)
GPA	69 (26.5)
EGPA	52 (20.0)
ANCA type and positivity (%)	
MPO-ANCA (or P-ANCA) positivity	174 (66.9)
PR3-ANCA (or C-ANCA) positivity	46 (17.7)
Both ANCA positivity	10 (3.8)
ANCA negativity	50 (19.2)
AAV-specific indices	
BVAS	12.0 (11.0)
FFS	1.0 (1.5)
Comorbidities (%)	
DM	66 (25.4)
Hypertension	103 (39.6)
Dyslipidaemia	50 (19.2)
Laboratory result	
White blood cell count (/mm^3)	9,110.0 (6,485.0)
Haemoglobin (g/dL)	11.4 (3.7)
Platelet count (×1000/mm^3)	295.0 (164.0)
Fasting glucose (mg/dL)	101.0 (33.8)
Blood urea nitrogen (mg/dL)	17.7 (18.5)
Serum creatinine (mg/dL)	0.9 (1.1)
Protein (g/dL)	6.7 (1.1)
Serum albumin (g/dL)	3.7 (1.1)
Acute phase reactant	
ESR (mm/hr)	59.0 (74.0)
CRP (mg/L)	13.8 (65.4)
Liver-related variable	
ALP (IU/L)	73.0 (36.3)
AST (IU/L)	18.0 (9.0)
ALT (IU/L)	16.0 (14.0)
Total bilirubin (mg/dL)	0.5 (0.3)
Cholesterol profile	
Total cholesterol (mg/dL)	168.0 (65.0)
HSI-related variable	
ALT (IU/L)	18.0 (9.0)
AST (IU/L)	16.0 (14.0)
BMI (kg/m^2)	22.5 (4.2)
Female gender (%)	169 (65.0)
DM (%)	66 (25.4)
HSI	31.4 (6.8)

Table 1. Continued

Variable	Value
During the follow-up duration	
Poor outcome (%)	
All-cause mortality	33 (12.7)
Relapse	82 (31.5)
CVA	19 (7.3)
ACS	11 (4.2)
ESRD	42 (16.2)
Follow-up duration based on each poor outcomes (mon)	
All-cause mortality	37.2 (65.4)
Relapse	22.3 (44.2)
CVA	33.7 (65.5)
ACS	36.9 (65.6)
ESRD	28.7 (60.9)
Medication (%)	
Glucocorticoids	244 (93.8)
Cyclophosphamide	145 (55.8)
Mycophenolate mofetil	37 (14.2)
Azathioprine	139 (53.5)
Tacrolimus	22 (8.5)
Rituximab	44 (16.9)
Methotrexate	25 (9.6)

Values are presented as a median (interquartile range) or number (%). AAV: ANCA-associated vasculitis, ANCA: antineutrophil cytoplasmic antibody, BMI: body mass index, MPA: microscopic polyangiitis, GPA: granulomatosis with polyangiitis, EGPA: eosinophilic granulomatosis with polyangiitis, MPO: myeloperoxidase, P: perinuclear, PR3: proteinase 3, C: cytoplasmic, BVAS: Birmingham vasculitis activity score, FFS: five-factor score, DM: diabetes mellitus, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ALP: alkaline phosphatase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, HSI: hepatic steatosis index, CVA: cerebrovascular accident, ACS: acute coronary syndrome, ESRD: end-stage renal disease.

occurrence. Conversely, for patients who did not have a poor outcome, it was defined as the period between AAV diagnosis and the last visit [9,10]. The number of patients who had taken glucocorticoids and immunosuppressive drugs during the disease course was counted.

Statistical analyses

All statistical analyses were performed using the SPSS Statistics for Windows version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as medians with interquartile ranges, whereas categorical variables were expressed as numbers (percentages). The correlation coefficient (r) between

the two variables was obtained using Pearson correlation analysis. The optimal cut-off was extrapolated using the receiver operating characteristic (ROC) curve analysis, and one value with the maximum sum of sensitivity and specificity was selected. The odds ratio (OR) of the cut-off for each poor outcome of AAV was analyzed using contingency tables and the chi-square test. A comparison of the cumulative survival rates between the two groups was performed using Kaplan-Meier survival analysis with the log-rank test. $p < 0.05$ was considered statistically significant.

RESULTS

Characteristics of AAV patients at AAV diagnosis and during the disease course

In terms of the variables at AAV diagnosis, the median age of the patients was 59.5 years, and 65.0% were female. Among them, 139, 69, and 52 had microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic GPA (EGPA), respectively, and 103, 66, and 50 patients were diagnosed with concurrent hypertension, DM, and dyslipidaemia, respectively. The median BVAS, FFS, ESR, and CRP levels were 12.0, 1.0, 59.0 mm/h, and 13.8 mg/L, respectively. Regarding the parameters composing the equation for HSI, the median ALT, AST, and BMI were 18.0 IU/L, 16.0 IL/L, and 22.5 kg/m^2, respectively, and finally, the median HSI was 31.4. The remaining clinical and laboratory data are presented in Table 1. Regarding the variables during the disease course, 33 of the 260 AAV patients died, and 82 patients experienced a relapse. Forty-two, 19, and 11 patients had ESRD, CVA, and ACS, respectively. Glucocorticoids were administered to 244 patients (93.8%); the most commonly administered immunosuppressive drug was cyclophosphamide (55.8%), followed by azathioprine (53.5%) (Table 1).

Correlation analysis of HSI with continuous variables

Among the continuous variables excluding the parameters composing the equation for HSI, HSI was significantly correlated with BVAS (r=−0.159), FFS (r=−0.168), haemoglobin (r=0.212), blood urea nitrogen (r=−0.141), serum creatinine (r=−0.174), and total cholesterol (r=0.141). Among the parameters comprising the equation for HSI, HSI was significantly correlated with BMI and ALT but not with AST (Table 2).

ROC curve analysis of HSI for each poor outcome

Among five poor outcomes of AAV, the area under the curve (AUC) of HSI for ESRD was statistically significant. According to the presence or absence of ESRD, the AUCs of the HSI were 0.330 (95% confidence interval [CI] 0.248, 0.413; p<0.001) and 0.670 (95% CI 0.587, 0.752; p<0.001), respectively. Since there was a tendency toward an inverse association between HSI at AAV diagnosis and progression to ESRD during the disease course, the latter of the two AUCs was selected and used to obtain the cut-off for forecasting progression to ESRD (Figure 1).

The relative risk of the cut-off of HSI for ESRD

When the optimal cut-off of HSI for progression to ESRD was set at ≤30.82, the sensitivity and specificity were 58.3% and 71.4%, respectively. When AAV patients were divided into two groups based on HSI ≤30.82, 121 and 139 patients belonged to

Table 2. Correlation of HSI with continuous variables at diagnosis in AAV patients (n=260)

	Correlation coefficient (r)	p-value
Age (yr)	−0.077	0.214
BMI (kg/m^2)*	0.668	<0.001
BVAS	−0.159	0.010
FFS	−0.168	0.007
White blood cell count (/mm^3)	−0.047	0.453
Haemoglobin (g/dL)	0.212	0.001
Platelet count (×1,000/mm^3)	−0.008	0.892
Fasting glucose (mg/dL)	0.103	0.097
Blood urea nitrogen (mg/dL)	−0.141	0.023
Serum creatinine (mg/dL)	−0.174	0.005
Protein (g/dL)	−0.068	0.277
Serum albumin (g/dL)	0.085	0.172
ESR (mm/h)	−0.080	0.198
CRP (mg/L)	−0.001	0.987
ALP (IU/L)	0.118	0.057
AST (IU/L)*	0.076	0.223
ALT (IU/L)*	0.417	<0.001
Total bilirubin (mg/dL)	0.064	0.303
Total cholesterol (mg/dL)	0.141	0.023

HSI: hepatic steatosis index, AAV: ANCA-associated vasculitis, BMI: body mass index, BVAS: Birmingham vasculitis activity score, FFS: five-factor score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ALP: alkaline phosphatase, AST: aspartate aminotransferase, ALT: alanine aminotransferase. *The parameters composing the equation for HSI=8×(ALT/AST)+BMI+2×(if female=1)+2×(if diabetes=1).
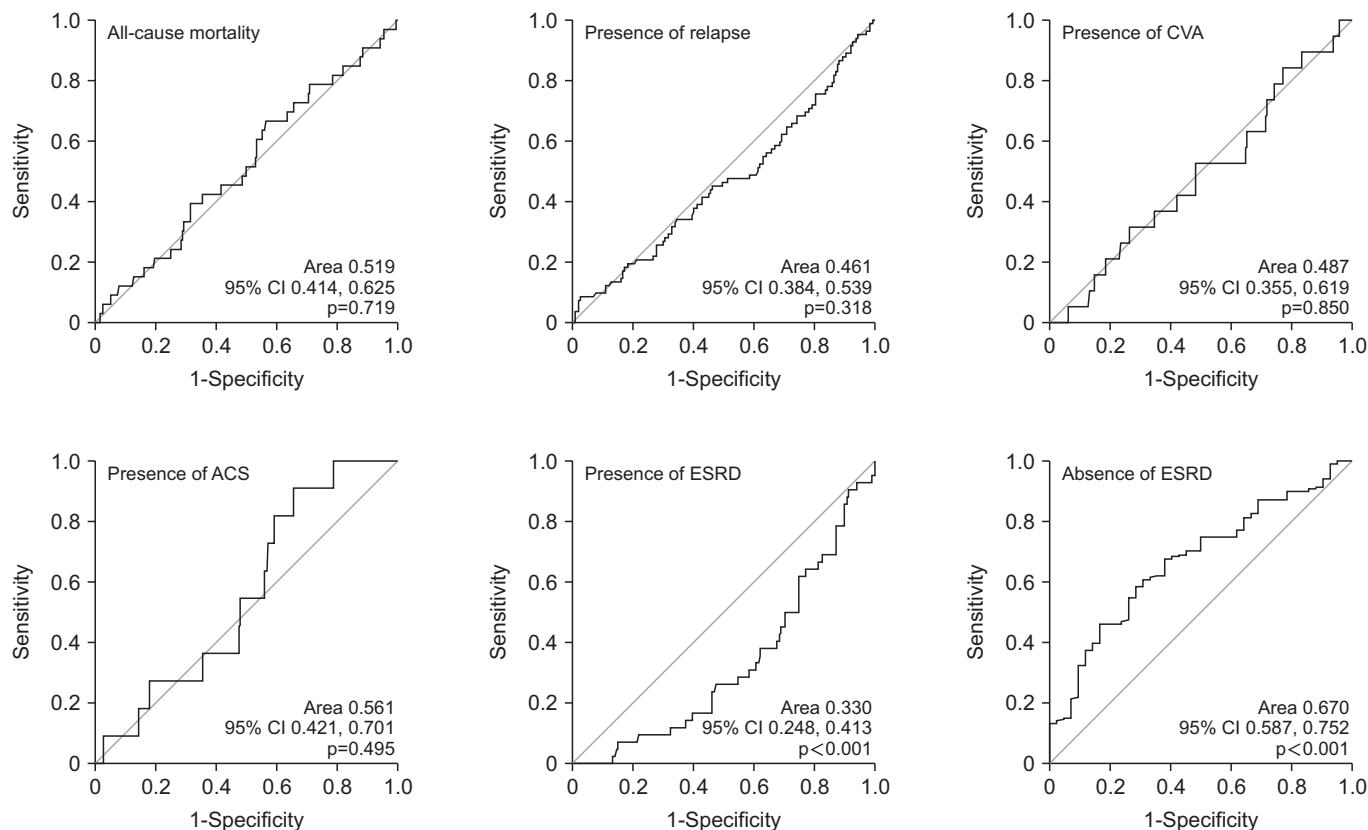
Figure 1. Receiver operator characteristic curve analysis. Among five poor outcomes of antineutrophil cytoplasmic antibody-associated vasculitis, only hepatic steatosis index (HIS) for ESRD showed statistical significance (area under the curve 0.333 for the presence of ESRD, p<0.001 and 0.670 for the absence of ESRD, p<0.001). The optimal cut-off of HSI for ESRD was set at ≤30.82. CI: confidence interval, CVA: cerebrovascular accident, ACS: acute coronary syndrome, ESRD: end-stage renal disease.
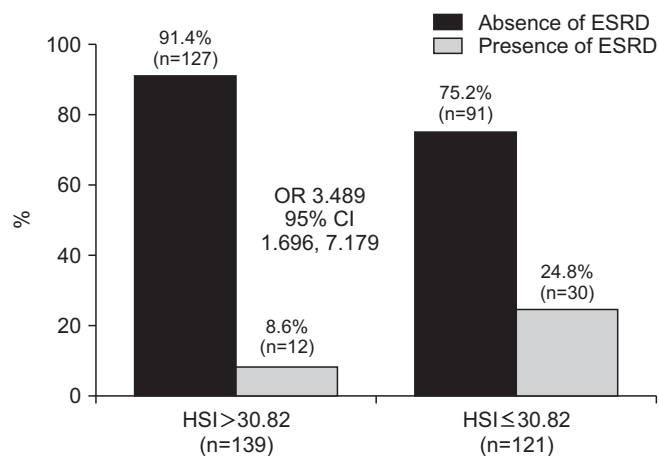

Figure 2. Relative risk for ESRD. Antineutrophil cytoplasmic antibody-associated vasculitis patients with HSI ≤30.82 exhibited a significantly higher risk of progression to ESRD than those with HSI >30.82. ESRD: end-stage renal disease, HSI: hepatic steatosis index.

a group of HSI ≤30.82 and a group of HSI >30.82, respectively. ESRD was identified more frequently in AAV patients with

HSI ≤30.82 (30 of 121 patients [24.8%]) than in those with HSI >30.82 (12 of 139 patients [8.6%]) (p<0.001). Furthermore, AAV patients with HSI ≤30.82 exhibited a significantly higher risk of progression to ESRD than those with HSI >30.82 (OR 3.489, 95% CI 1.696, 7.179) (Figure 2).

Comparison of cumulative ESRD-free survival rates

AAV patients with HSI ≤30.82 exhibited a significantly lower cumulative ESRD-free survival rate than those with HSI >30.82 (p=0.001) (Figure 3).

DISCUSSION

In this study, we investigated whether HSI, an index for estimating the extent of hepatic steatosis and the presence of NAFLD, could forecast poor outcomes of AAV in AAV patients, and obtained several new findings [18]. First, HSI was inversely correlated with BVAS, FFS, and serum creatinine levels. Second,
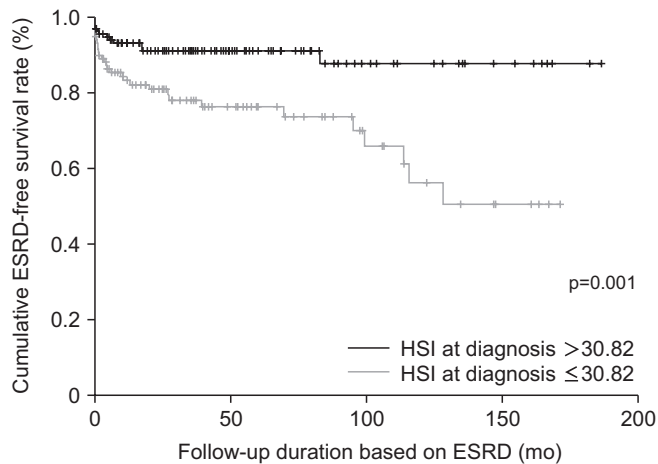
Figure 3. Cumulative ESRD-free survival rates. Antineutrophil cytoplasmic antibody-associated vasculitis patients with HSI ≤30.82 exhibited a significantly lower cumulative ESRD-free survival rate than those with HSI >30.82 (p=0.001). ESRD: end-stage renal disease, HSI: hepatic steatosis index.

HSI exhibited the potential for forecasting ESRD in AAV patients. Third, when the cut-off of HSI for ESRD was set at 30.82, AAV patients with HSI ≤30.82 exhibited a significantly higher risk for ESRD than those with HSI >30.82, and AAV patients with HSI ≤30.82 showed a significantly lower cumulative ESRD-free survival rate than those with HSI >30.82.

To date, it has been reported that liver and kidney fibrosis could share several pathogenic mechanisms, such as nuclear transcription factors, cellular sensors, and effectors of redox regulation, which may increase insulin resistance, cholesterol accumulation, oxidative stress, proinflammatory cytokine/chemokine production and fibrogenesis [19]. In addition, focusing on the relationship between HSI and chronic kidney disease (CKD) occurrence, a previous study reported that, compared to individuals with HSI <30, both individuals with 30≤HSI≤36 and those with HSI >36 exhibited significantly higher risks for CKD among middle-aged individuals in Japan [20]. Therefore, given that CKD is a strong risk factor for ESRD progression, it could be theoretically assumed that ESRD during the disease course may be identified more often in AAV patients having higher HSI at diagnosis. However, the present study showed an inverse association between HSI at diagnosis and ESRD during the disease course in AAV patients. On the other hand, in the correlation analysis, HSI was significantly correlated with BVAS, FFS, and serum creatinine levels, which have been known as important risk factors for poor renal prognosis in AAV patients [21,22]. Therefore, we conclude that HSI at diagnosis could

forecast ESRD during the disease course by an indirect correlation of HSI with the initial risk factors for ESRD rather than a direct relation with substantial liver fibrosis in AAV patients.

In terms of the clinical implication of HSI for forecasting ESRD based on the AAV subtype, we divided the study population into two groups according to the subtype of AAV such as MPA/GPA and EGPA and reanalyzed the ability of HSI at diagnosis for forecasting ESRD during the disease course. First, we included 208 MPA/GPA patients and performed the ROC curve of HSI for ESRD. The AUC of HSI for ESRD was statistically significant (AUC 0.333, 95% CI 0.247, 0.419; p=0.001). When the optimal cut-off of HSI for ESRD was set at ≤30.82, the sensitivity and specificity were 60.1% and 70.0%, respectively. Coincidently, the cut-off obtained in MPA/GPA patients was the same as that obtained among all AAV patients. When MPA/GPA patients were divided into two groups according to HSI of 30.82, ESRD was identified more often in patients with HSI ≤30.82 than in those without (29.5% vs. 10.6%, p=0.001). OR was as high as 3.517 (95% CI 1.672, 7.398) (Supplementary Figure 1A).

Additionally, MPA/GPA patients with HSI ≤30.82 exhibited a significantly lower cumulative ESRD-free survival rate than those without (Supplementary Figure 1B). Second, we included only 52 EGPA patients and performed the ROC curve of HSI for ESRD, which showed no significant AUC of HSI for ESRD. We concluded that the ability of HSI for forecasting ESRD was valid in MPA/GPA patients but not EGPA patients. Nevertheless, we suggest applying the results of the present study to all patients with AAV for the following reasons: first, there may be discordance in the diagnosis of the subtypes of AAV among several classification criteria and definitions; second, there may be cases which could fulfil the classification criteria for the two subtypes of AAV; and third, there may be cases which could change from one subtype to another during the disease course [23-25].

In addition, in terms of the clinical usefulness of HSI in forecasting ESRD based on ANCA type, we included 174 AAV patients having MPO-ANCA (P-ANCA) at diagnosis and performed the ROC curve, which showed a significant AUC of HSI for ESRD (AUC 0.346, 95% CI 0.249, 0.442, p=0.005). When the optimal cut-off of HSI for ESRD was set at ≤30.82, the sensitivity and specificity were 55.0% and 73.5%, respectively. AAV patients with MPO-ANCA (or P-ANCA) and HSI ≤30.82 exhibited a significantly higher risk of ESRD than those without (OR 3.395, 95% CI 1.478, 7.797, p=0.003). Furthermore, AAV

patients with MPO-ANCA (or P-ANCA) and HSI ≤30.82 exhibited a significantly lower cumulative ESRD-free survival rate than those without (p=0.005) (Supplementary Figure 2). However, the clinical usefulness of HSI for forecasting ESRD disappeared among AAV patients with PR3-ANCA (or C-ANCA). Nevertheless, suggest applying the results of the present study to all patients with AAV regardless of the ANCA type. This is because the detection methods for ANCA include both an immunoassay and an indirect immunofluorescence assay in the new classification criteria for AAV proposed in 2022, which made the clinical meaning of the ANCA type less clinically significant.

This study has several limitations. First of all, the small number of AAV patients and the retrospective study design were primary limitations. Another critical limitation of this study was that liver ultrasonography and transient elastography were not performed to confirm the extent of liver fibrosis or the presence of NAFLD. Additionally, given that the frequency of DM was relatively high and kidney biopsy was not performed in all patients with ESRD, we could not totally exclude the contribution of DM nephropathy to ESRD occurrence in AAV patients in the present study. Nevertheless, the advantage of this study is that it is the first to demonstrate the potential of HSI for forecasting ESRD in AAV patients as a pilot study. We believe that a multicentre and prospective future study with more patients will overcome these limitations and validate the results of this study.

CONCLUSION

This study is the first to demonstrate that HSI at AAV diagnosis could forecast ESRD during the disease course in AAV patients. Therefore, as a complementary index, it is expected that assessing HSI at diagnosis in patients newly diagnosed with AAV will help to cope with the development of ESRD in AAV patients.

SUPPLEMENTARY DATA

Supplementary data can be found with this article online at https://doi.org/10.4078/jrd.2023.0032.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

H.J.C., P.G.P., J.H.H., and S.W.L. conceived the work. H.J.C. and P.G.P. performed data curation. All authors performed formal analysis. Y.B.P. and S.W.L. performed funding acquisitions. H.J.C. and P.G.P. wrote the original draft. J.H.H. and S.W.L. reviewed and edited the manuscript. All authors approved the final version of manuscript.

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