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Serological Biomarkers and Indices for the Current Activity and Prognosis of ANCA-Associated Vasculitis: Experience in a Single Centre in Korea

Sung-Soo Ahn[1], Yong-Beom Park[1,2], and Sang-Won Lee[1,2]

[1]Division of Rheumatology, Department of Internal Medicine, and [2]Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, Seoul, Korea.

Small vessel vasculitis is composed of two types of vasculitis based on immune-complex deposits, immune-complex vasculitis and antineutrophil cytoplasmic antibody-associated vasculitis (AAV) according to the 2012 Chapel Hill Consensus Conferences Nomenclature of Vasculitis. In general, the current disease-states are assessed in three ways in real clinical practice such as activity, damage and functional status. Birmingham vasculitis activity score (BVAS, version 3) and five-factor score were calculated for assessing the cross-sectional activity and for predicting the prognosis of AAV, respectively. Since BVAS includes a wide spectrum of nine systemic items with differently weighted scores based on new-onset/worsening or persistent each symptom, it has been considered as the most reliable tool to assess AAV activity to date. However, since BVAS represents both cross-sectional and chronic clinical features, it has a limitation in flexibly reflecting the cross-sectional activity or severity of AAV. In addition, the heterogeneous items of BVAS are difficult to reflect the close correlation between BVAS and AAV pathogenesis. It is practically difficult to discover new biomarkers or indices that exceed the reliability of AAV-specific indices or acute-phase reactants established by long clinical experience. However, efforts to discover and develop new biomarkers or indices are expected to complement the clinical unmet need of existing AAV-specific indices and acute-phase reactants. In this review, we reviewed the serological biomarkers and indices that have been reported to date and introduced studies that investigated serological biomarkers and indices in Korean patients with AAV.

Key Words: Antineutrophil cytoplasmic antibody, vasculitis, serological, biomarkers, indices, activity, prognosis

INTRODUCTION

Small vessel vasculitis is composed of two types of vasculitis based on immune-complex deposits, immune-complex vasculitis and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) according to the 2012 Chapel Hill Consensus Conferences Nomenclature of Vasculitis.[1] Moreover, AAV is divided into three subtypes including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA).[1,2]

Three subtypes of AAV share the same histological feature of small-vessel necrotising vasculitis. MPA has a predilection to cause necrotising glomerulonephritis and pulmonary capillaritis, whereas GPA often induces the formation of granuloma at the upper and lower respiratory tracts and occasionally causes necrotising glomerulonephritis. On the other hand, EGPA is characterised by eosinophilic infiltration. EGPA has both allergic and vasculitic components and its clinical mani-

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Corresponding author: Sang-Won Lee, MD, PhD, Division of Rheumatology, Department of Internal Medicine and Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Tel: 82-2-2228-1987, Fax: 82-2-393-6884, E-mail: sangwonlee@yuhs.ac

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festation may differ according to the presence of ANCA.[2]

In general, the current disease-states are assessed in three ways, such as activity, damage, and functional status, in real clinical practise. Birmingham vasculitis activity score (BVAS, version 3) and five-factor score (FFS) were calculated to assess the cross-sectional activity and to predict the prognosis of AAV, respectively;[3,4] vasculitis damage index (VDI) was evaluated for estimating the current extent of organ damage;[5] and the Korean version of the Short-Form 36-Item Health Survey Physical and Mental Component Summaries (SF-36 PCS and SF-36 MCS) was collected to evaluate the current functional status.[6] Since BVAS includes a wide spectrum of nine systemic items with differently weighted scores based on new-onset/worsening or persistent each symptom, it has been considered as the most reliable tool to assess AAV activity to date. However, since BVAS represents both cross-sectional and chronic clinical features, thus it has a limitation in flexibly reflecting the cross-sectional activity or severity of AAV.[3] Also, although the frequency of clinical expression of AAV and the degree of its effect on the prognosis may vary depending on the ethnicity or regions, the scores assigned for each organ-involvement may also be biased to specific organs, which could be another limitation of BVAS. In addition, the heterogeneous items of BVAS are difficult to reflect the close correlation between BVAS and AAV pathogenesis. Acute-phase reactants such as erythrocyte sedimentation (ESR) and C-reactive protein (CRP), are also widely used in assessing the inflammatory burden and reflecting the current activity in AAV patients. Nevertheless, ESR and CRP cannot show absolute confidence in the assessment of AAV activity in actual clinical practice, due to their nonspecific changes that can also be elevated by infection, tumour, and other inflammation.

It is practically difficult to discover new biomarkers or indices that exceed the reliability of AAV-specific indices or acute-phase reactants established by long clinical experience. However, efforts to discover and develop new biomarkers or indices are expected to complement the clinical unmet need of existing AAV-specific indices and acute-phase reactants. In this review, we reviewed the serological biomarkers and indices, which have been discovered and validated to date, in estimating the current activity and predicting the prognosis. Furthermore, we introduced serological biomarkers in Korean AAV patients in the Severance Hospital ANCA associated VasculitidEs (SHAVE) cohort and serological indices of those in both the SHAVE and retrospective cohorts that have been studied.

BRIEF OVERVIEW OF AAV PATHOGENESIS

In the pathogenesis of AAV, endogenous and exogenous triggering factors prime neutrophils by inflammatory cytokines or chemokines. Once neutrophils are primed, the expression and production of neutrophil adhesion molecules (CD11b) and Fc receptors are upregulated and ANCA antigens are translocated to the surfaces and released. In inflammatory conditions, endothelial adhesion molecules are also overexpressed.[7] Circulating ANCA binds to not only ANCA antigens bound to neutrophil-surface but also secretory ANCA antigens, leading to ANCA mediated activation of neutrophils. In particular, dimers of neutrophils through ANCA bridge are highly pathogenic. Activated neutrophils transmigrate into the adjacent tissues through an interaction between adhesion molecules of both neutrophils and endothelial cells. They also trigger the production of reactive oxygen radicals and provoke degranulation of neutrophils, resulting in inflammation on and beyond vessel-walls.[8]

In addition, activated neutrophils secrete complement activating factors, which switch on the alternative complement pathway. Subsequently, the elevated serum level of C5a augments neutrophil priming and activation, leading to accelerating AAV.[9] Eventually, various immune cells in addition to neutrophils, such as T_H and T_{EM} cells, B cells and macrophages, participate in AAV pathogenesis and granuloma formation in GPA and EGPA.[8] Therefore, serological substances related to immune cells, complement, cytokines, chemokines, and other types of antibodies involved in AAV pathogenesis can be candidates for new serological biomarkers and indices for estimating the current activity and predicting the prognosis in AAV patients.

SEROLOGICAL BIOMARKERS INVESTIGATED IN AAV

Biomarkers are defined as substances that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[10] Similarly, they are also defined as a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.[11] On the other hand, biomarkers are also defined as any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease.[10] Biomarkers can be identified and developed from various human-derived materials, including blood, cell lines, tissues, and fluids. Also, more information may be obtained from the same human-derived materials by advanced detection methods, such as next generation sequencing, gene fusion, multispectral tissue immunohistochemical staining, multiple secreted protein analysis, and functional signalling pathway analysis.[12]

From the clinical point of view, biomarkers can be useful in classifying or diagnosing diseases, estimating the current disease activity, and predicting the prognosis, in particular, poor

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outcomes of diseases. In general, biomarker development goes through four steps, including discovery, quantification, verification, and qualification. Verification and validation are important processes for the practical use of new biomarkers, while discovery and qualification of biomarker candidates related to pathogenesis are important processes in the stage of discovering new biomarkers.[13] As for ANCA, both myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA play a critical role in AAV diagnosis in patients without histological confirmation.[2] ANCA positivity may be related to the prognosis and serial changes may be correlated to disease activity, despite some controversy.[14] In terms of acute-phase reactants are well-known indicators for higher inflammation; however, they have low sensitivity and lack of specificity for the current activity of AAV.[15] In terms of circulating antibodies, anti-human lysosome-associated membrane protein-2, anti-plasminogen, anti-moesin, and anti-pentraxin-3 may contribute to AAV diagnosis, specific organ-involvement, and the current activity.[16-19] In terms of B-cell related biomarkers, B-cell activating factor is suggested as a therapeutic target, but its serological level may not reflect the current activity in AAV patients.[20] In terms of T-cell related biomarkers, T cell population was reported to be polarisation toward T_H2 and T_H17 cells.[21] In terms of complement related biomarkers, complement (C)3a, C5a, soluble C5b-9 and the alternative pathway components factor B may be associated with active AAV.[22] In terms of neutrophil related biomarkers, neutrophil extracellular traps are correlated with the current activity and may be suggested as a therapeutic target.[23,24] In terms of tissue injury markers, tissue inhibitor of MMP-1 and metalloproteinase may reflect the current activity of AAV.[25] Serological levels of cytokines and chemokines involved in the pathogenesis have been widely used serologic markers for estimating the current activity of rheumatic diseases.[26,27] Similarly, since various cytokines and chemokines are involved in AAV pathogenesis, they can be useful serological biomarkers in AAV patients. Interleukin (IL)-6 is a pro-inflammatory cytokine, and its serum level may reflect the current activity of AAV, and also predict severe relapse during follow-up.[28] Serum level of IL-17A and the ratio of T_H17 and Treg cells may serve as indicators to identify renal involvement and disease remission in AAV patients.[29] On the other hand, a previous study evaluated circulating cytokine profiles in AAV patients, and demonstrated that distinctly different cytokine profiles depend on MPO-ANCA and PR3-ANCA rather than clinical diagnosis.[30]

APPLYING SEROLOGIC INDICES TO CLINICAL USE IN RHEUMATIC DISEASES

In this review, "indices" referred to a newly established formula that can estimate the current activity and predict poor outcomes. In this review, there were several conditions for selecting indices with predictive potential. For instance, they should consist of only variables included in routine laboratory tests, and it should be a formula using two to four variables. Moreover, it might be better if the selected variables have theoretical backgrounds that can represent the nutritional status or inflammatory burden.[31] Most of these indices were first applied for predicting the prognosis in tumour patients. First, in terms of neutrophil-to-lymphocyte ratio (NLR), it was initially introduced as an inflammation-based prognostic indicator, and high ratio was significantly associated with the poor prognosis in patients with unresectable pancreatic cancer.[32] Furthermore, both pre- and postoperative NLR can predict the rate of all-cause mortality in patients with hepatocellular carcinoma after partial hepatectomy.[33] On the other hand, they may be also applied for estimating the current activity and predicting the prognosis of chronic inflammatory diseases. NLR above the optimal cut-off value was proposed as a determining factor for the current active systemic lupus erythematosus.[34] In addition, baseline NLR below the cut-off value predicted sustained remission in rheumatoid arthritis.[35] Next, in terms of albumin-to-globulin ratio (AGR), it may be related to either the current nutritional status or the current inflammatory burdens, as albumin is an indicator of both conditions.[36] Preoperative AGR was inversely associated with the poor prognosis in patients with hepatocellular carcinoma after curative hepatectomy.[37] Also, its preoperative value was found to be an independent prognostic factor for predicting the overall survival and recurrence-free survival rates in patients with non-metastatic renal cell carcinoma after partial or radical nephrectomy.[38] Meanwhile, AGR was also reported to be correlated with inflammatory markers in various systemic rheumatic diseases.[39] Compared to serological biomarkers, an advantage of indices is that they do not need to newly measure the substances in human-derived materials, since they use the results of tests that are routinely performed in real clinical practice. As this can be applied to almost all patients, it can be said to be highly convenient and universal in clinical perspective. However, it has a disadvantage of being an index with low specificity because it has a low association with pathogenesis.

THE SHAVE COHORT AND RETROSPECTIVE COHORT OF AAV

The SHAVE cohort is a prospective and observational cohort of patients with MPA, GPA, and EGPA, which was established in November 2016. In the SHAVE cohort, AAV-specific indices with clinical and laboratory data are generally obtained for an interval of 3 to 6 months. On the same day of visitation when AAV-specific indices were collected, whole blood sample was obtained from each AAV patient with the patient's consent. Serum was immediately isolated from the whole blood sample and stored at -80°C. Based on AAV-specific indices and clinical data, we investigated whether new serological substances

could be useful biomarkers for estimating the current activity. Here, we introduced several serological biomarkers of which clinical implications have been demonstrated in the SHAVE cohort. On the other hand, the retrospective cohort included AAV patients who were diagnosed with AAV from 2000 until the present. All patients in the SHAVE cohort were included in the retrospective cohort. Unlike the SHAVE cohort, only clinical and laboratory data, as well as BVAS, FFS, and VDI at diagnosis were collected from medical records. Instead, data collected during follow-up, such as the medications administered, systemic complications, and poor outcomes (all-cause mortality, relapse, end-stage renal disease, cerebrovascular accident and cardiovascular) have been reviewed and obtained every 3 months from 2000 until the present. For convenience and better understanding, the retrospective cohort is referred to as both "SHAVE" and "retrospective cohorts" in this review.

SEROLOGICAL BIOMARKERS IN KOREAN PATIENTS WITH AAV

Serological biomarkers in Korean patients with AAV are summarised in Table 1. First of all, the mean platelet volume (MPV) is known to be associated with inflammation in rheumatic diseases. Also, MPV shows a biphasic pattern according to the grade of inflammation and decreased MPV is associated with high-grade inflammatory diseases. MPV was inversely correlated with BVAS; and furthermore, it increased as the activity of AAV improved in MPA patients.[40] Aminoacyl-tRNA synthetase-interacting multifunctional protein-1 (AIMP1) is one of the non-enzymatic factors used in assembling the enzyme complex. In addition, AIMP1 is secreted by pro-inflammatory cytokines and may modulate immune reactions.[41] Serum AIMP1 level was measured in 61 Korean AAV patients in the SHAVE cohort. Serum AIMP1 level could estimate the cross-sectional activity, and patients with AIMP1 level over the cut-off value for high activity of AAV showed a relative risk (RR) of 8.615 compared to those without.[42] IL-21 is primarily produced and secreted by T_H17 cells and T follicular helper (T_{FH}) cells. IL-21 stabilises and expands T_H17 cells and enhances IL-23 receptor expression. It also inhibits Treg cell survival and induces plasma cell differentiation.[43] Serum IL-21 level was measured in 60 Korean AAV patients in the SHAVE cohort. Patients with serum IL-21 positivity showed a higher risk of generalised AAV compared to those without (RR 5.250). We suggested the clinical significance of serum IL-21 positivity as a biomarker to indicate the current activity of AAV.[44] Programmed cell death protein 1 (PD-1) is one of the immune checkpoint proteins that may modulate immune responses of stimulated and activated T cells by biding to PD ligand 1 (PD-L1) and PD-L2.[45] Soluble PD-1 (sPD-1) gene is located in the down-stream of PD-1 gene and sPD-1 is produced along with PD-1 as negative feedback after T cell receptor activation.[46] Serum sPD-1 level was measured in 59 Korean AAV patients in the SHAVE cohort. Serum sPD-1 level was significantly correlated with the current activity and high activity was more frequently observed in patients with sPD-1 over the cut-off than in those without. Consequently, serum sPD-1 level could estimate the current activity and severity of AAV.[47] IL-16 is the first reported T cell chemoattractant produced by peripheral mononuclear cells. IL-16 enhances T cell proliferation and stimulates B cell development,[48] leading to the assumption that serum level of IL-16 might be correlated with the current activity of AAV. Serum IL-16 level was measured in 78 Korean AAV patients in the SHAVE cohort. Interestingly, serum IL-16 level was correlated with only the current VDI but not with BVAS, FFS, or SF-36. The correlation between serum IL-16 level and the current VDI might be derived from the following two hypotheses. The first hypothesis was that it might reflect the extent of end-organ damage related to fibrosis, and the other was that serum IL-16 might be associated with the secondary necrosis of neutrophils.[49] Soluble lectin-like oxidized low-density lipoprotein (LDL) receptor 1 (LOX1) is a receptor recognising oxidised LDL (oxLDL) which is mainly expressed in various cells such as endothelial cells and macrophages. Binding of oxLDL to LOX1 may induce endothelial cell dysfunction and monocyte infiltration via inflammatory substances and intracellular signalling.[50] Moreover, pro-inflammatory cytokines may augment the cleavage of extracellular domain of LOX1, leading to an increase in serum soluble LOX1 (sLOX1) level.[51] Therefore, sLOX1 has been suggested as serological biomarkers in inflammatory diseases but not in AAV.[52] Serum sLOX-1 level was measured in 78 Korean AAV patients in the SHAVE cohort. Serum sLOX-1 was negatively correlated with the current activity; however, it was not affected by gender, hypertension, diabetes mellitus or clinical manifestations.[53] Mannose-binding lectin (MBL) is involved in the activation of the lectin complement pathway and its multimers interact with MBL-associated serine proteases, resulting in cleaving C5 into C5a and C5b.[54] C5b participates in the formation of membrane attack complex, whereas C5a accelerates the alternative complement pathway, leading to aggravating AAV.[7] Based on this theoretical background, serum MBL level was measured in 80 Korean AAV patients in the SHAVE cohort. Serum MBL level was significantly correlated with the current activity and associated with pulmonary manifestation score based on BVAS.[55] In addition, various serological substances are being investigated to predict the current activity of AAV.

SEROLOGICAL INDICES IN KOREAN PATIENTS WITH AAV

Serological indices in Korean patients with AAV are summarised in Table 1. In this section, we briefly introduce indices, including several variables of the initial routine laboratory

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Table 1. Serological Biomarkers and Indices for Activity and Prognosis in Korean Patients with AAV

Indicator	Description	Clinical relevance	Reference number
Serological biomarkers for the current AAV-specific indexes			
MPV	MPV increases in a condition of increased platelet production	Reflects current activity	40
AIMP-1	AIMP-1 increases according to the production of proinflammatory cytokines such as tumour necrosis factors-α, IL-6, IL-8, and IL-12 by activated immune cells	Reflects current activity	42
IL-21	IL-21 stabilises and expands T_H17 cells and enhances IL-23 receptor expression	Reflects current activity	44
Soluble PD-1	Negative feedback: T cell receptor activation augments PD-1 transcription, resulting in an increase of soluble PD-1 section	Reflects current activity and severity	47
IL-16	IL-16 enhances cell proliferation and B cell development as a T cell chemoattractant produced by peripheral mononuclear cells	Reflects current activity	49
Soluble LOX1	LOX1 is associated with inflammation in various vascular disorders	Inversely reflects current activity (different pattern from other vascular diseases)	53
MBL	MBL plays a crucial role in the innate immune system and the activity of lectin complement pathway	Reflects current activity and pulmonary manifestations	55
Serological indices at diagnosis for prognosis during follow-up			
DNI	DNI at diagnosis associated with neutrophil consumption	Reflects current activity and predicts relapse of MPA and GPA	57
RDW	RDW is associated with AAV activity and poor prognosis	Predicts refractory disease of GPA	60
CAR	CAR consists of two acute-phase reactants	Predicts all-cause mortality	61
NLR	Neutrophil count increases whereas lymphocyte count decreases along with current activity	Reflects current activity and predicts relapse	63
PLR	Platelet count increases whereas lymphocyte count decreases along with current activity	Reflects current activity and predicts no poor prognosis	65
AGR	Globulin level increases whereas serum albumin level decreases along with current activity	Inversely predicts all-cause mortality	68
CONUT score	CONUT score consists of albumin level, lymphocyte count and serum total cholesterol level	Predicts all-cause mortality	70
SII	SII=platelet count×neutrophil count/lymphocyte count	Reflects current activity and predicts relapse and ESRD	72
HALP score	HALP=haemoglobin level×serum albumin level×lymphocyte count/platelet count	Reflects current activity and predicts no poor prognosis	74
AIP	AIP=Log (triglyceride/high-density lipoprotein cholesterol)	Predicts cerebrovascular accidents	76

AAV, antineutrophil cytoplasmic antibody-associated vasculitis; MPV, mean platelet volume; AIMP-1, aminoacyl-tRNA synthetase-interacting multifunctional protein-1; IL, interleukin; PD-1, programmed cell death protein 1; LOX1, lectin-like oxidized low-density lipoprotein receptor 1; MBL, mannose-binding lectin; DNI, delta neutrophil index; RDW, red blood cell distribution width; CAR, C-reactive protein/serum albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; AGR, albumin-to-globulin ratio; CONUT, controlling nutritional status; SII, systemic immune-inflammation index; HALP, haemoglobin, albumin, lymphocyte and platelet; AIP, atherogenic index of plasma; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis.

tests, that are also useful in estimating the current activity at diagnosis and prognosis during follow-up in Korean AAV patients in both SHAVE and retrospective cohorts. First, as for a single variable included in the complete blood cell test, delta neutrophil index (DNI) is leukocyte sub-fraction automatically measured by subtracting the fraction of mature polymorphonuclear leukocytes from the sum of MPO-reactive cells. DNI was reported to be associated with neutrophil-consumption.[56] In AAV pathogenesis, both neutrophils and ANCA are crucial factors, and they may be reduced as a part of neutrophil-consumption via transmigration and degranulation.[8] Therefore, the immature granulocytes count can be theoretically elevated as with the progression of AAV. DNI at diagnosis was collected from 97 Korean AAV patients in both SHAVE and retrospective cohorts. DNI at diagnosis could reflect the current activity of AAV and also, predict relapse during follow-up in patients with MPA and GPA.[57] Red blood cell (RBC) distribution width (RDW) is calculated from the coefficient of variation of RBC volume distribution. RDW has been known to be associated with the current disease activity or the prognosis of inflammatory diseases.[58,59] RDW at diagnosis was obtained from 150 Korean AAV patients in both SHAVE and retrospective cohorts. Among three subtypes of AAV, RDW at diagnosis could estimate the current activity of GPA and also, predict refractory dis-

ease of GPA during follow-up.[60] Next, as for indices containing two to four variables of the initial routine laboratory tests, CRP/serum albumin ratio (CAR) is a formula using two acute-phase reactants that are in the reciprocal direction. CAR at diagnosis was calculated in 170 Korean AAV patients in both SHAVE and retrospective cohorts. CAR at diagnosis could independently predict all-cause mortality compared to conventional risk factors of mortality in AAV patients.[61] NLR is a formula using two blood cell lineages where neutrophil count may increase and lymphocyte count may decrease in autoimmune inflammatory diseases.[62] NLR at diagnosis was calculated in 160 Korean AAV patients in both SHAVE and retrospective cohorts. NLR at diagnosis could estimate the current activity and also, predict relapse during follow-up in AAV patients.[63] Platelet-to-lymphocyte ratio (PLR) is another formula consisting of two blood cell lineages that have reciprocal patterns in response to the inflammatory burden of AAV.[64] PLR at diagnosis was calculated in 163 Korean AAV patients in both SHAVE and retrospective cohorts. PLR at diagnosis was associated with the current activity of AAV.[65] AGR is a formula where albumin is often reduced and globulin fraction is mainly increased in cases of infection, chronic inflammation and autoimmune diseases.[66,67] Therefore, AGR was considered to decrease as the inflammatory burden increased in AAV patients. AGR at diagnosis was calculated in 88 Korean MPA patients in both SHAVE and retrospective cohorts. AGR at diagnosis could not estimate the current activity, but the inverse value of AGR at diagnosis could predict all-cause mortality in MPA patients.[68] The controlling nutritional status (CONUT) score was initially developed for detecting undernutrition in patients. The CONUT score is calculated based on serum albumin, lymphocyte count, and total cholesterol levels as stratified scores.[69] CONUT score at diagnosis was calculated in 196 Korean AAV patients in both SHAVE and retrospective cohorts. CONUT score at diagnosis was found to be associated with all-cause mortality during follow-up in AAV patients.[70] Systemic immune-inflammation index (SII) is a formula using three blood lineages as follows: SII=platelet count×neutrophil count/lymphocyte count.[71] In theory, the inflammatory burden of AAV may have the capability to increase the number of neutrophils and platelets, and decrease that of lymphocytes. Therefore, SII could be assumed to be correlated with the current activity of AAV. SII at diagnosis was calculated in 163 Korean AAV patients in both SHAVE and retrospective cohorts. Consequently, SII at diagnosis was proved to be a good indicator to not only estimate the cross-section severe AAV but also predict the poor outcomes in AAV patients.[72] Haemoglobin, albumin, lymphocyte and platelet (HALP) score was recently introduced and it is derived from the following formula: HALP score=haemoglobin×serum albumin×lymphocyte count/platelet count. Similar to other nutritional indices, HALP score was demonstrated to presuppose the prognosis in several types of cancer.[73] HALP score was calculated in 212 Korean AAV patients in both SHAVE and retrospective cohorts. Unlike SII, HALP score at diagnosis could estimate the current activity but not predict the prognosis during follow-up in AAV patients.[74] Chronic inflammations are generally associated with deregulated lipid metabolism skewed towards an atherogenic profile. Atherogenic index of plasma (AIP), which is calculated based on serum triglyceride and high-density lipoprotein cholesterol, has been used to predict the potential of developing systemic thrombotic events in various medical conditions.[75] With this concept, AIP at diagnosis was measured in 167 Korean AAV patients in both SHAVE and retrospective cohorts, and the clinical significance of AIP was investigated. AIP was a significant predictor of CVA during follow-up in AAV patients.[76]

CONCLUSION

In this review, we introduced several serological biomarkers and indices for estimating the current activity and predicting the prognosis in Korean AAV patients in a single centric cohort. The development of absolute and standardized serological biomarkers or indices may be practically difficult and not clinically useful, due to the ethnic and environmental differences. Therefore, given the ethnic and geographical differences, the currently recommended serological biomarkers and indices should be validated. In contrast, the serological biomarkers and indices with no clinical significance should be re-evaluated. The methods for estimating the current activity will help in the selection of therapeutic agents that target substances in the pathogenesis mechanisms related to biomarkers and indices. In addition, biomarkers and indices that predict the prognosis are expected to help determine the frequency of monitors, treatment dose, and maintenance period. We expect that more serological biomarkers and indices specific to AAV will be developed and validated so that they can be used as commercial kits in real clinical practice in the near future.

AUTHOR CONTRIBUTIONS

Conceptualization: Sang-Won Lee. Data curation: Sung-Soo Ahn and Sang-Won Lee. Formal analysis: Sang-Won Lee. Investigation: Sung-Soo Ahn and Sang-Won Lee. Methodology: Sang-Won Lee. Project administration: Sang-Won Lee. Resources: Sung-Soo Ahn and Sang-Won Lee. Software: Sung-Soo Ahn and Sang-Won Lee. Supervision: Sang-Won Lee. Validation: Sung-Soo Ahn and Yong-Beom Park. Visualization: Sung-Soo Ahn and Sang-Won Lee. Writing—original draft: Sung-Soo Ahn and Sang-Won Lee. Writing—review & editing: Yong-Beom Park and Sang-Won Lee. Approval of final manuscript: all authors.

ORCID iDs

Sung Soo Ahn https://orcid.org/0000-0002-9002-9880
Yong-Beom Park https://orcid.org/0000-0003-4695-8620
Sang-Won Lee https://orcid.org/0000-0002-8038-3341

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