International Journal of Cardiology 292 (2019) 236–240

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Circulating endothelial glycocalyx components as a predictive marker of coronary artery lesions in Kawasaki disease

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ARTICLE INFO

Article history:
Received 24 January 2019
Received in revised form 14 May 2019
Accepted 20 May 2019
Available online 22 May 2019

Keywords:
Kawasaki disease (KD)
Coronary artery lesions (CALs)
Glycocalyx
Syndecan-1
Hyaluronan

ABSTRACT

Background: Kawasaki disease (KD) is acute and self-limited vasculitis caused by unknown origin, and the critical complication in KD patients is coronary artery lesions (CALs). The endothelial glycocalyx is a network of membranes luminally covering the endothelium. This study aimed to evaluate the clinical utility of serum glycocalyx components as biomarkers of predicting the onset CALs in KD.

Methods: Seventy subjects with complete type KD, 18 subjects as febrile control (FC), and 15 subjects as afebrile controls (AC) were enrolled. Medical, demographic, echocardiography, and laboratory data from the medical records were retrospectively analyzed. Serum syndecan-1 and hyaluronan levels prior to intravenous immunoglobulin (IVIG) therapy were measured at the acute phase, immediately after IVIG, the subacute phase, and the time of discharge at the convalescent phase.

Results: Serum syndecan-1 and hyaluronan levels were higher in the KD group than in the AC and FC groups at all three phases. Further, these levels were compared between KD patients with and without the development of CALs. Serum syndecan-1 and hyaluronan levels at the acute phase were significantly elevated in KD patients with the CALs than in those without CALs. Serum hyaluronan, not syndecan-1, was determined as the most contributory parameter to predict CALs by a multiple logistic analysis.

Conclusions: Circulating syndecan-1 and hyaluronan can be useful biomarkers to predict the development of CALs in KD.

1. Introduction

Kawasaki disease (KD) is acute and febrile systemic vasculitis of unknown origin and the most common cause of acquired heart disease in children in the developed countries [1,2]. The critical complication in KD patients is coronary artery lesions (CALs), which mostly develop within the first 10 days of the illness and are associated with the late complications of myocardial infarction [3]. In a Japanese study, subsequent coronary stenosis was observed in 19% of patients with coronary aneurysms at the acute phase, resulting in myocardial infarction in 7.5% and fatality in 3% of patients [4]. Activation of macrophages and/or monocytes and elevation of serum inflammatory cytokine levels, such as tumor necrosis factor (TNF)-α, at the acute phase of KD have been reported [5,6]. A single dose of 2 g/kg intravenous immunoglobulin (IVIG) is now considered the standard therapy in several countries [5]. There is 20–25% chance of the onset of serious CALs if the treatment is not given early in the disease course [7]. Several parameters, including serum vascular endothelial growth factor, N-terminal pro-brain natriuretic peptide (NT-pro BNP), albumin, sodium, C-reactive protein (CRP), platelet-neutrophil aggregates, and inflammatory cytokine levels, are reported as biomarkers predicting CALs [8–14]. However, there is no reliable biomarker for predicting CALs in KD patients.

The endothelial glycocalyx is a network of membrane-bound proteoglycans and glycoproteins luminally covering the endothelium [15]. The glycocalyx comprises many glycoproteins and proteoglycans. Syndecan-1 is a proteoglycan, which is a core component with a firm connection to the endothelial cell membrane and soluble proteoglycans. Hyaluronan plays a crucial role in the structure and maintenance of the entangled network of the glycocalyx by providing stability due to its water-retaining properties [16]. The endothelial glycocalyx on the luminal surface functions as a barrier against the untoward effect of proteins or cytokines via direct contact to the endothelium [17]. Damage of the endothelial glycocalyx is an important factor for several illnesses, such as diabetes, ischemia/reperfusion, and atherosclerosis [15]. Several

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https://doi.org/10.1016/j.ijcard.2019.05.045
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studies have reported the relationship of serum glycocalyx component levels with the occurrence of cardiac arrest syndrome [18] or acute coronary syndrome [19]. In these studies, serum syndecan-1 and/or hyaluronan levels were measured as a biomarker for the damage of the endothelial glycocalyx. Recently, Ueno et al. [20] have reported that the disruption of endothelial cell homeostasis can be associated with the subsequent onset of coronary artery abnormalities in KD.

Therefore, in this study, it was hypothesized that damage of the endothelial glycocalyx is associated with the development of CALs in KD. The aim of this study is to evaluate the clinical utility of serum glycocalyx components, syndecan-1, and hyaluronan levels as biomarkers to predict CALs in KD.

2. Methods

2.1. Patient characteristics

This study enrolled 131 children with complete type KD diagnosed and treated at the Yamaguchi University Hospital between August 2012 and January 2018. Forty-one subjects were excluded because serum samples from 37 subjects and echocardiographic data from four subjects before initial IVIG could not be obtained (Supplementary Fig. 1). Twenty subjects were excluded because of the onset of CALs prior to initial IVIG. Eighteen subjects were recruited as febrile controls (FC) with acute febrile disease and 15 as afebrile controls (AC). FC fulfilled the criteria of systemic inflammatory response syndrome at the acute phase [21]. FC subjects included patients with urinary tract infection, human metapneumovirus bronchitis, respiratory syncytial virus bronchitis, pneumonia, lymphadenitis, cellulitis, and meningitis. AC included subjects with food allergy, atrial septal defect, ventricular septal defect, head injury, poor weight gain, or healthy subjects. Medical, demographic, and laboratory data from medical records were retrospectively analyzed. This study was approved by the Institutional Review Board of the Yamaguchi University Hospital (No. H28-047). Informed consents were obtained from parents of all patients enrolled in this study.

2.2. Blood sample collection

Blood samples in the KD and FC groups were collected at three time-points. In the KD, the first collection was performed before IVIG therapy as the acute phase, the second was immediately after IVIG therapy as the subacute phase, and the third was at the time of discharge as the convalescent phase. In the FC, the first collection was performed before antibiotics treatment, the second was immediately after antibiotics treatment, and the third was at the time of discharge. All discharges were determined because of controlled KD (diseases). Blood samples in the AC group were collected only on admission. Samples were centrifuged at 3000 $\times g$ for 5 min, and serum was collected and stored at −80 °C. We normalized NT-pro BNP values for age (Z-score) [22].

2.3. Measurement of shedding of syndecan-1 and hyaluronan

Serum syndecan-1 and hyaluronan levels were measured using an enzyme-linked immunosorbent assay kit (syndecan-1; Diaclone, Besancon, France, hyaluronan; R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. Detection limits are above 2.56 and 0.2 ng/ml, respectively.

2.4. Echocardiography measurements of coronary diameters

Two-dimensional echocardiograms were recorded at the acute, subacute, and convalescent phases in all KD subjects. Diameters of the right coronary, left main trunk, left anterior descending artery, and circumflex coronary artery were measured and normalized for body surface area (Z-scores) [23]. A Z-score of ≥2.5 at any time point was defined as the onset of CALs.

2.5. Statistical methods

Chi-square test was used to compare the ratio between male and female subjects and the existence of treatment for KD. Wilcoxon rank sum test was used to compare results of age, laboratory data, refractory score in KD, and serum syndecan-1 and hyaluronan levels between KD and control subjects or between KD subjects with and without CALs.

Possible factors associated with CALs in KD subjects before therapy were analyzed using multivariate logistic regression analysis. Explanatory variables included in the analyses were serum IgG, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, albumin, CRP, sodium, procalcitonin, ferritin, NT-pro BNP, BNP, D-dimer, syndecan-1, and hyaluronan levels, together with white blood cell (WBC), neutrophil, and platelet counts; hemoglobin levels, sex; and age (months) at the onset. Variables that showed skewed distribution (AST, ALT, total bilirubin, procalcitonin, ferritin, NT-pro BNP, BNP, D-dimer, and hyaluronan) were logarithmically transformed prior to the analyses. An optimal regression model was chosen using step-wise selection methods. The probability belonging to CAL development group was calculated from the final regression model and designated as predicted P. The efficacy of each parameter in distinguishing the absence or presence of CAL development was expressed by area under curve (AUC) using receiver operating characteristic (ROC) analysis.

These statistical analyses were conducted using JMP Pro ver. 13.0 (SAS Institute Inc., Cary, NC, USA) and StatFlex ver. 6.0 (Artech Co., Osaka Japan). Values with $p < 0.05$ were considered statistically significant.

3. Results

Laboratory data were compared to evaluate differences in the characteristics or inflammation severity among the KD, FC, and AC subjects at the acute phase (Supplementary Table 1). AST, ALT, and BNP were significantly higher in the KD group than in the FC or AC group. WBC and neutrophil counts were significantly higher in the KD group than in the AC group but lower than in the FC group. CRP, NT-pro BNP (raw date and Z-score), and D-dimer levels were higher in the KD group than in the AC group but not different between the KD and FC groups. Serum albumin levels were lower in the KD group than in the AC group. These results revealed no significant difference between the KD and FC groups before therapy.

Serum syndecan-1 and hyaluronan levels at the acute, subacute, and convalescent phases were compared to examine the dynamics of the serum glycocalyx component levels at these three phases (Fig. 1). Serum syndecan-1 and hyaluronan levels were significantly higher in the KD group than in the FC or AC groups at all phases.

The KD group was then divided into KD patients with CALs (CAL positive group, n = 18) and those without CALs (CAL negative group, n = 52), to compare clinical characteristics and required treatment between these subgroups (Table 1, Supplementary Table 2). Serum soluble interleukin-2 receptor (sIL-2R) levels were higher in the CAL positive group than in the CAL negative group, although sex, age, other laboratory data including NT-pro BNP and treatment were not significantly different. Serum syndecan-1 and hyaluronan levels were also compared between these subgroups at the three phases to examine the release of serum glycocalyx components (Fig. 2). Serum syndecan-1 levels were significantly higher in the CAL positive group than in the CAL negative group only at the acute phase, whereas serum hyaluronan levels were higher in the CAL positive group than seen in the CAL negative group at the acute and convalescent phases but not at the subacute phase. These results suggested that elevated levels of serum syndecan-1 and hyaluronan at the acute phase are related to the development of CALs, indicating the utility of syndecan-1 and hyaluronan levels as the biomarkers to predict the development of CALs.

To clarify the associated factors with the development of CALs at the acute phase, a multiple logistic analysis was conducted (Supplementary Fig. 2). Serum hyaluronan levels at the acute phase were the most useful biomarker predicting CALs (OR: 2.78; 95% CI: 1.19–6.47; $p = 0.02$), whereas serum syndecan-1 levels were not. Additionally, serum BNP, albumin, sodium, and CRP levels were not useful biomarkers. Serum NT-pro BNP levels, reported as useful biomarker, were not useful biomarker in our study (OR: 1.48; 95% CI: 0.76–2.88; $p = 0.25$). Serum IgG levels at the acute phase (OR: 1.00; 95% CI: 1.00–1.01; $p = 0.046$) was also identified as a contributory parameter. These results suggest that serum hyaluronan levels are more reliable than syndecan-1 levels as a biomarker for predicting CALs.

The clinical utility of these glycocalyx components was evaluated using AUC based on ROC analysis (Fig. 3). AUC values for predicting CALs based on measurements of serum syndecan-1 and hyaluronan levels and a combination of both these parameters were 0.707 (OR: 1.008; 95% CI: 0.99–1.02; $p = 0.26$), 0.706 (OR: 1.89; 95% CI: 1.00–3.57; $p = 0.05$), and 0.743, respectively, suggesting that the combination of syndecan-1 and hyaluronan levels is more reliable than either of these parameters alone as a biomarker predicting CALs. We show tables for predictive value when we set optimal cut off (Supplementary Table 3). We set the cutoff value to be the maximum of the product of sensitivity and specificity. The positive predictive value was 0.41, and negative predictive value was 0.85. Next, we calculated AUC based on

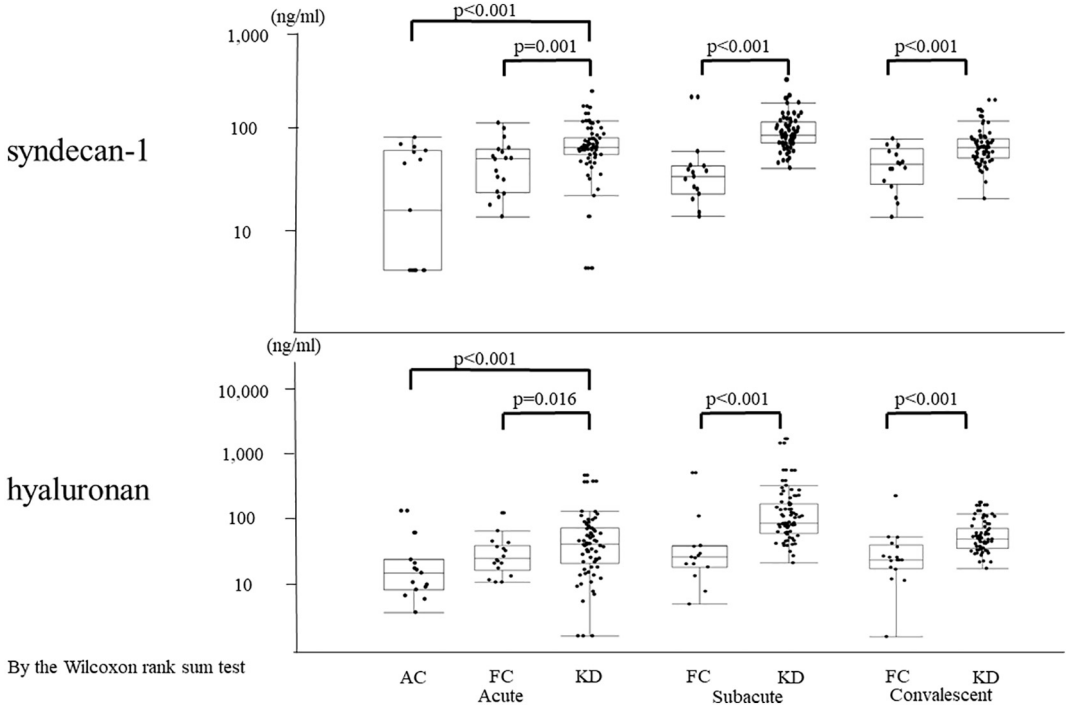

Fig. 1. Syndecan-1 and hyaluronan levels in Kawasaki disease (KD), afebrile controls (AC), and febrile control (FC). $p < 0.05$.

ROC analysis using the serum levels of NT-pro BNP or their Z-score. The AUC were 0.593 (OR: 1.40; 95% CI: 0.90–2.17; $p = 0.13$) and 0.581 (OR: 1.34; 95% CI: 0.91–1.97; $p = 0.14$), which were lower than the AUC of syndecan-1 or hyaluronan alone. AUC based on ROC analysis using the combination of the triple parameters (syndecan-1, hyaluronan, and NT-pro BNP) was 0.743, showing no significant effect in superiority by the additional combinations (Supplementary Fig. 3).

4. Discussion

Serum syndecan-1 and hyaluronan levels were peaked in KD patients at the subacute phase of disease. These levels of KD patients were higher than those of AC and FC subjects at any three phases. Furthermore, both serum syndecan-1 and hyaluronan levels were significantly higher in KD patients with the development of CALs than in those without CALs before IVIG. The AUC of the combinational calculation of measurements of serum sydecan-1 and hyaluronan levels was 0.743 by ROC analysis.

Table 1
Clinical characteristics of KD patients with and without the subsequent onset of CALs.

	CAL positive (n = 18)	CAL negative (n = 52)	*p*-Value
Sex; male:female	13:5	34:18	0.773
Age (months)	27 (3−121)	18.5 (1–88)	0.094
WBCs ($\times 10^9$/l)	13.54 (9.23–21.87)	13.10 (5.06–25.75)	0.717
Neutrophils ($\times 10^9$/l)	9.02 (5.63–18.84)	8.75 (15–18.17)	0.545
Platelets ($\times 10^9$/l)	355 (186–519)	364 (156–730)	0.870
Albumin (g/dl)	3.6 (2.6–4.2)	3.5 (2.3–4.2)	0.877
AST (IU/l)	39 (15–617)	34.5 (19–496)	0.973
ALT (IU/l)	40 (8–518)	32 (7–394)	0.536
CRP (mg/dl)	7.5 (2.1–23.0)	7.0 (0.9–17.0)	0.742
D-dimer (μg/ml)	1.7 (0.9–6.7)	1.6 (0.9–70.9)	0.910
BNP (pg/ml)	42.3 (5.5–153.4)	24.7 (4.0–1446.6)	0.501
NT-pro BNP (pg/ml)	596.5 (76.0–28,029.0)	423.5 (5.0–5718.0)	0.240
NT-pro BNP (z-score)	2.21 (−0.17–6.57)	1.86 (−3.50–4.71)	0.304
Sodium (mmol/l)	133 (127–137)	134 (127–140)	0.128
sIL-2R (IU/ml)	2610 (1327–5760)	1940 (710–5540)	0.018
IgG (mg/dl)	659 (527–1512)	733 (407–1213)	0.701

CALs: coronary arterial lesions, WBCs: white blood cells, AST: aspartate transaminase, ALT: alanine transaminase, CRP: C-reactive protein, BNP: brain natriuretic peptide, NT-pro BNP: N terminal pro brain natriuretic peptide sIL-2R: soluble interleukin-2 receptor, IgG: immunoglobulin G.

Several factors such as vascular endothelial growth factor, NT-pro BNP, albumin, sodium, CRP, platelet-neutrophil aggregates, or inflammatory cytokines were reportedly evaluated as biomarkers to predict the development of CALs in KD patients [8–14]. The AUC of NT-pro BNP in our date was lower than syndecan-1 and hyaluronan. In addition, multiple logistic analyses suggested that hyaluronan, not NT-pro BNP, albumin, sodium, and CRP, levels were the most useful biomarker predicting CALs in our study. These suggest that the combinational measurement of serum syndecan-1 and hyaluronan levels at the acute phase is a useful biomarker predicting the development of CALs in KD. Luo et al. [24] showed that serum syndecan-1 levels were increased in KD subjects and higher in KD subjects with CALs than in those without CALs, which is consistent with the results of the present study.

The endothelial glycocalyx is an important determinant of vascular permeability and modulates inflammatory responses by binding cytokines and attenuating the inflammatory functions of cytokines [15]. The disruption of endothelial cell homeostasis could be associated with the pathogenesis of coronary artery abnormalities in KD [20]. T cells, monocytes, macrophages, and neutrophils are strongly involved in the damage of the coronary artery at an early stage of KD [5,25]. These findings show that the glycocalyx contributes to endothelial homeostasis by functioning as protective elements to prevent inflammatory cells or cytokines from binding to the endothelial vessel wall that lead to coronary damages in coronary diseases, including KD. It is of great interest that serum syndecan-1and hyaluronan levels at the acute phase were higher in the CAL positive group than in the negative group, which suggests that disturbance of endothelial homeostasis at the acute phase plays an important role in the development of CALs in KD. These molecules could be candidates helps initiate therapy that may prevent the onset of CALs in KD considering that antithrombin effectively maintained microcirculation and vascular integrity by protecting the glycocalyx in a rat sepsis model [26].

Hyaluronan, not syndecan-1, was determined as the most contributory parameter for predicting CALs by multiple logistic regression analyses. Several studies [18,27] have reported measurements of serum syndecan-1 and hyaluronan levels as markers of the

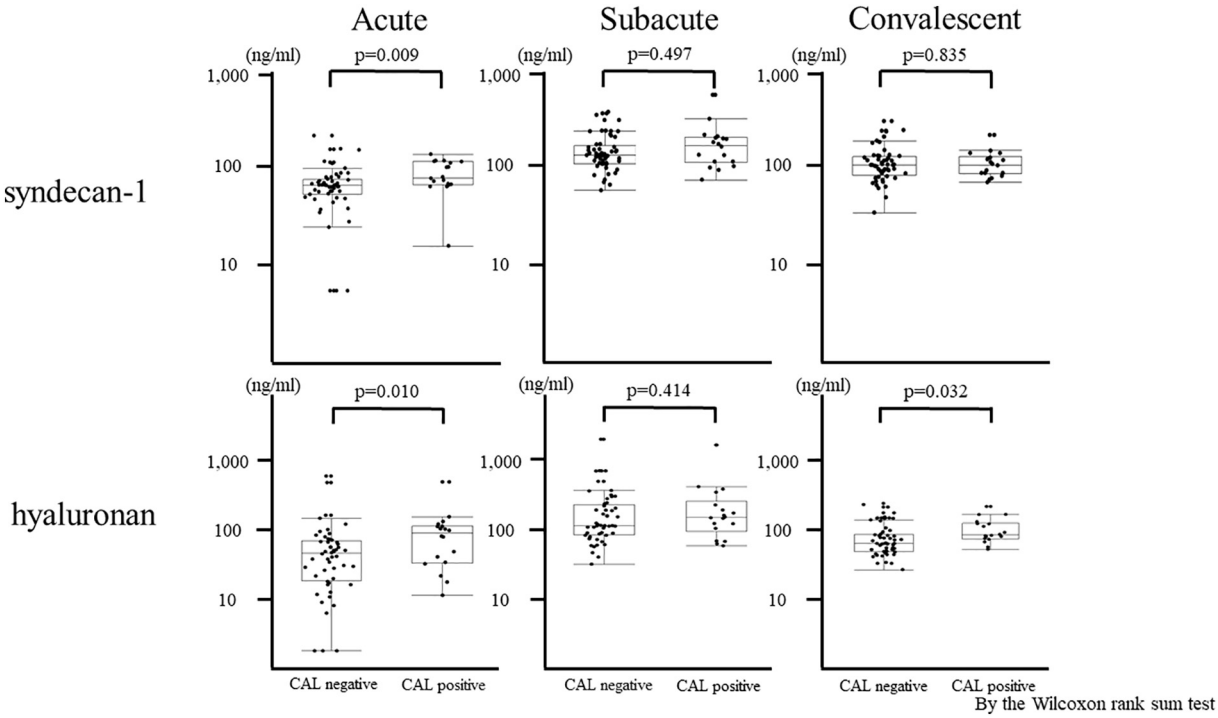

Fig. 2. Syndecan-1 and hyaluronan levels in Kawasaki disease (KD) patients with coronary artery lesions (CALs) and in those without CALs. $p < 0.05$.

glycocalyx in various diseases. However, no studies have compared the measurements of serum syndecan-1 and hyaluronan levels in terms of a better predictive biomarker. Syndecan-1 and hyaluronan have different positions and functions in the glycocalyx. Glycoproteins, including syndecan-1, form a dense inner layer of glycocalyx and act as a primary selective barrier to plasma macromolecules, and hyaluronan forms the outer less dense layer, supports the movement of red cell and other hemocytes, and restricts the access of inflammatory cells to the endothelial cell surface [26]. These suggest that hyaluronan plays a more important role in inhibiting inflammatory cell invasion into the vascular endothelium at the early phase of KD. It remains unclear why only serum hyaluronan level was higher in the CAL positive group than in the CAL negative group at the convalescent phase, but it might also be due to differences in their functions.

4.1. Study limitations

There are some limitations in this study. First, it was a pilot study in a single center, and the sample size was small. Second, all subjects were Japanese. Further studies are required, with subjects from different regions, including other races and populations, in a

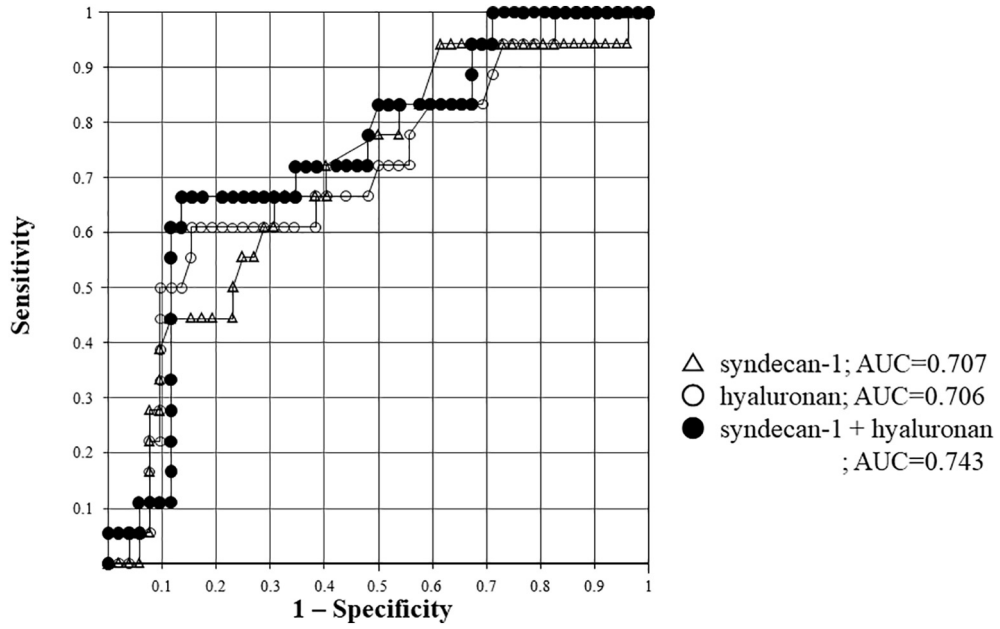

Fig. 3. ROCs of various biomarkers used to predict coronary artery lesions (CALs). Area under the curves: serum syndecan-1 (open triangles) = 0.707, serum hyaluronan (open circles) = 0.706, and combination of the two parameters (filled circles) = 0.743.

multicenter or prospective study to evaluate the diagnostic utility of serum glycocalyx component levels, such as sydecan-1 and hyaluronan levels, as a predictive biomarker of the development of CALs in KD patients.

5. Conclusions

Serum glycocalyx component (syndecan-1 and hyaluronan) levels were higher at all phases in KD patients, and both were higher at the acute phase in KD patients with development of CALs. ROC analysis showed AUC was 0.743 based on the combinational calculation of both parameters. Thus, serum syndecan-1 and hyaluronan levels may be useful biomarkers to predict the development of CALs in KD patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.05.045.

Acknowledgement

This work was supported by Japan for the Promotion of Science KAKENHI (Grant number, 16K19647) and a grant for Kawasaki Disease Research from Japan Blood Products Organization.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

References

[1] J.W. Newburger, M. Takahashi, M.A. Gerber, et al., Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association, Circulation 110 (2004) 2747–2771.
[2] J.W. Newburger, M. Takahashi, J.C. Burns, Kawasaki disease, J. Am. Coll. Cardiol. 67 (2016) 1738–1749.
[3] M.T. Lin, L.C. Sun, E.T. Wu, J.K. Wang, H.C. Lue, M.H. Wu, Acute and late coronary outcomes in 1073 patients with Kawasaki disease with and without intravenous γ-immunoglobulin therapy, Arch. Dis. Child. 100 (2015) 542–547.
[4] H. Kato, T. Sugimura, T. Akagi, et al., Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients, Circulation 94 (1996) 1379–1385.
[5] J.C. Burns, M.P. Glodé, Kawasaki syndrome, Lancet 364 (2004) 533–544.
[6] T. Matsubara, T. Ichiyama, S. Furukawa, Immunological profile of peripheral blood lymphocytes and monocytes/macrophages in Kawasaki disease, Clin. Exp. Immunol. 141 (2005) 381–387.
[7] J.C. Burns, H.I. Kushner, Bastian, et al., Kawasaki disease: a brief history, Pediatrics 106 (2000), E27.
[8] T. Ohno, T. Yuge, H. Kariyazono, et al., Serum hepatocyte growth factor combined with vascular endothelial growth factor as a predictive indicator for the occurrence of coronary artery lesions in Kawasaki disease, Eur. J. Pediatr. 161 (2002) 105–111.
[9] K. Kaneko, K. Yoshimura, A. Ohashi, T. Kimata, T. Shimo, S. Tsuji, Prediction of the risk of coronary arterial lesions in Kawasaki disease by brain natriuretic peptide, Pediatr. Cardiol. 32 (2011) 1106–1109.
[10] M. Kuwabara, M. Yashiro, K. Kotani, et al., Cardiac lesions and initial laboratory data in Kawasaki disease: a nationwide survey in Japan, J. Epidemiol. 25 (2015) 189–193.
[11] Y. Nakamura, M. Yashiro, R. Uehara, et al., Use of laboratory data to identify risk factors of giant coronary aneurysms due to Kawasaki disease, Pediatr. Int. 46 (2004) 33–38.
[12] H. Koyanagi, H. Yanagawa, Y. Nakamura, M. Yashiro, Serum C-reactive protein levels in patients with Kawasaki disease: from the results of nation-wide surveys of Kawasaki disease in Japan, Acta Paediatr. 86 (1997) 613–619.
[13] K. Ueno, Y. Nomura, Y. Morita, T. Eguchi, K. Masuda, Y. Kawano, Circulating platelet-neutrophil aggregates play a significant role in Kawasaki disease, Circ. J. 79 (2015) 1349–1356.
[14] C.Y. Lin, C.C. Lin, B. Hwang, B.N. Chiang, Cytokines predict coronary aneurysm formation in Kawasaki disease patients, Eur. J. Pediatr. 152 (1993) 309–312.
[15] Reitsma S. Slaaf, Vink H. DW, M.A.M.J. van Zandvoort, M.G.A. oude Egbrink, The endothelial glycocalyx: composition, functions, and visualization, Pflugers Arch. 454 (2007) 345–359.
[16] L.N. Broekhuizen, H.L. Mooij, J.J. Kastelein, E.S. Stroes, H. Vink, M. Nieuwdorp, Endothelial glycocalyx as potential diagnostic and therapeutic target in cardiovascular disease, Curr. Opin. Lipidol. 20 (2009) 57–62.
[17] Y.H. Kim, P. Nijst, K. Kiefer, W.H. Tang, Endothelial glycocalyx as biomarker for cardiovascular diseases: mechanistic and clinical implications, Curr. Heart Fail. Rep. 14 (2017) 117–126.
[18] S. Grundmann, K. Fink, L. Rabadzhieva, et al., Perturbation of the endothelial glycocalyx in post cardiac arrest syndrome, Resuscitation 83 (2012) 715–720.
[19] C.H. Miranda, M. de Carvalho Borges, A. Schmidt, J.A. Marin-Neto, A. Pazin-Filho, Evaluation of the endothelial glycocalyx damage in patients with acute coronary syndrome, Atherosclerosis 247 (2016) 184–188.
[20] K. Ueno, Y. Ninomiya, D. Hazeki, K. Masuda, Y. Nomura, Y. Kawano, Disruption of endothelial cell homeostasis plays a key role in the early pathogenesis of coronary artery abnormalities in Kawasaki disease, Sci. Rep. 7 (2017), 43719.
[21] B. Goldstein, B. Giroir, A. Randolph, International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics, Pediatr. Crit. Care Med. 6 (2005) 2–8.
[22] A. McNeal-Davidson, A. Fournier, L. Spigelblatt, et al., Value of amino-terminal pro B-natriuretic peptide in diagnosing Kawasaki disease, Pediatr. Int. 54 (5) (2012 Oct) 627–633.
[23] M. Miura, T. Kobayashi, T. Kaneko, et al., Association of severity of coronary artery aneurysms in patients with Kawasaki disease and risk of later coronary events, JAMA Pediatr. 172 (5) (2018 May 7), e180030.
[24] L. Luo, S. Feng, Y. Wu, Y. Su, F. Jing, Q. Yi, Serum levels of syndecan-1 in patients with Kawasaki disease, Pediatr. Infect. Dis. 38 (1) (2019 Jan) 89–94.
[25] K. Takahashi, T. Oharaseki, S. Naoe, M. Wakayama, Y. Yokouchi, Neutrophilic involvement in the damage to coronary arteries in acute stage of Kawasaki disease, Pediatr. Int. 47 (2005) 305–310.
[26] T. Iba, J.H. Levy, T. Hirota, M. Hiki, K. Sato, T. Murakami, I. Nagaoka, Protection of the endothelial glycocalyx by antithrombin in an endotoxin-induced rat model of sepsis, Throm. Res. 171 (2018) 1–6.
[27] D. Bruegger, F. Brettner, I. Rossberg, et al., Acute degradation of the endothelial glycocalyx in infants undergoing cardiac surgical procedures, Ann. Thorac. Surg. 99 (2015) 926–931.