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Original Article

Correlation between circulating fibrosis biomarkers with left atrial function and left atrial volume index in rheumatic mitral stenosis

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Abstract

Mitral stenosis is the most common rheumatic heart disease (RHD) disorder worldwide, including in Indonesia. This pathological condition causes left atrial pressure, leading to left atrial fibrosis that affects the structure and function of the left atrial as well as the clinical condition. The aim of this study was to assess the correlation between circulating fibrosis biomarkers with net atrioventricular compliance (Cn) as a parameter of left atrial function, and left atrial volume index (LAVI) as a parameter left atrium structure of changes. A cross-sectional study was conducted at Panti Rahayu Hospital and Permata Bunda Hospital, Purwodadi, Central Java, with a total of 40 RHD patients with severe mitral stenosis. The ELISA was used to measure the levels of carboxy-terminal propeptide of type I procollagen (PICP), matrix metalloproteinase I (MMP-1), tissue inhibitor matrix metalloproteinase 1 (TIMP-1), and transforming growth factor-β1 (TGF-β1). The left atrial function was assessed by measuring Cn, and the LAVI parameters were measured to assess left atrium structure/size. The mean levels of circulating fibrosis biomarkers were as follows: PICP 153.96±89.12 ng/mL; MMP-1 1.44±2.12 ng/mL; MMP-1/TIMP-1 ratio 0.38±0.54 and TGF-β1 2.66±1.96 pg/mL. From the echocardiographic evaluation, the mean Cn was 5.24±1.93 mL/mmHg and the mean LAVI was 152.55±79.36 mL/m^2. There were significant correlation between MMP-1 and MMP-1/TIMP-1 ratio with Cn (r=0.345 and r=0.333, respectively; both had p<0.05). PICP and TGF-β1 biomarkers did not significantly correlate with Cn (p>0.05). Meanwhile, none of the biomarkers had a significant correlation with LAVI (p>0.05). This study highlights that MMP-1 and MMP-1/TIMP-1 ratio are potentially to be used as markers to determine the Cn in RHD patients with severe mitral stenosis. However, further studies with a higher sample size are needed to confirm this finding.

Keywords: Rheumatic heart disease, mitral stenosis, fibrosis biomarkers, left atrial compliance, left atrial volume index

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Introduction

Rheumatic heart disease (RHD) is a complication of rheumatic fever after group A *Streptococcus* infection [1,2]. This condition results in valvular damage due to an abnormal immune response and causes a high health burden of mortality and morbidity [3,4]. It is estimated that there are 40.5 million cases with a mortality rate of 306,000 people globally in 2019 [5]. Indonesia is an endemic country with an estimated 1.84 million cases and ranks fourth in the prevalence of RHD worldwide [4].

Inflammation and fibrosis play an essential role in RHD pathophysiology. The molecular mimicry that occurs between the streptococcal M protein and various cardiac proteins (myosin, tropomyosin, keratin, laminin, and vimentin) will cause an adverse immune response where inflammation occurs due to the large number of mononuclear cells that secrete inflammatory cytokines in the valves and myocardial tissue. Furthermore, the healing process of rheumatic carditis will cause varying degrees of fibrosis and valve damage, including mitral stenosis (MS) [1,2]. MS is the most common RHD abnormality found worldwide, including in Indonesia [6,7]. In this disease, an interference in the opening of the mitral valve will cause left atrial stress due to increased pressure and decreased cardiac output. These hemodynamic consequences will stimulate neurohormonal activation, renin-angiotensin-aldosterone, and the sympathetic nervous system [3,4]. Increased pressure in the left atrium then plays a role in the appearance of signs and symptoms of heart failure and the clinical course of MS patients [3,4].

Inflammation due to RHD and the hemodynamic consequences of MS will cause stress on the left atrium and lead to left atrial fibrosis [8,9]. Left atrial fibrosis will affect the structure/size and function of the left atrial as well as the clinical condition of the patients [10]. Structurally, these changes can be seen from the parameters of the left atrial dimensions by measuring the left atrial volume index (LAVI) on echocardiography examination. The LAVI parameter has been studied concerning pulmonary hypertension degree, MS severity, and prognosis of the patients [11,12].

Changes in left atrial function can be evaluated with several non-invasive tests, one of which assesses left atrial compliance through echocardiography [13,14]. Net atrioventricular compliance (Cn) is a parameter that describes left atrial compliance in rheumatic MS and is associated with increased pulmonary artery pressure in patients with MS, independent of the size of the mitral valve area and the transvalvular pressure gradient (TPG) [14]. The value of Cn is known to have a relationship with the patient's prognosis after intervention as well as with pulmonary hypertension, activity intolerance, and the progression of MS in medical treatment [14].

Unfortunately, the histological examination of the atrial myocardium necessary for the correct diagnosis of atrial fibrosis is invasive, making atrial biopsy rarely performed [15]. Nevertheless, previous studies have found evidence of increased circulating cardiac fibrosis biomarkers in rheumatic MS patients, including transforming growth factor-β1 (TGF-β1), circulating carboxy-terminal propeptide of type I procollagen (PICP), matrix metalloproteinase I (MMP-1) and ratio of MMP-1 and tissue inhibitor matrix metalloproteinase 1 (TIMP-1) or MMP-1/TIMP-1 ratio [16-18].

It is unknown whether these biomarkers in the circulation are directly correlated with the changes in structure and function that occur in the left atrium due to atrial fibrosis in rheumatic MS. For this reason, this study was conducted to analyze the correlation between circulating fibrosis biomarkers and net atrioventricular compliance as a parameter of left atrial function and LAVI as a parameter of changes in left atrium structure. It is hoped that knowing the relationship between fibrosis biomarkers with the function and structure of the left atrium can add insight into rheumatic MS in the context of regulating the expression and activity of fibrosis that may become a clinically important method to prevent and even reverse atrial fibrosis.

Methods

Study design and patients

A cross-sectional study was conducted at the Panti Rahayu Hospital and Permata Bunda Hospital, Purwodadi, Central Java, Indonesia from December 2022 to February 2023. RHD patients with

severe MS were included in the study. The diagnosis used following criteria: echocardiography with morphology suggesting RHD (calcification and fusing of leaflets and commissures, as well as restricted valve movement), the planimetric mitral valve area was less than 1.5 cm^2 [19-21]; and New York Heart Association (NYHA) functional class II-III.

Patients who were hemodynamically unstable or experiencing severe acute decompensation, which was characterized by signs of congestion in the form of crackles in more than one-third of the lung fields, ascites, or signs and symptoms of cardiogenic/hypovolemic shock, were excluded. In addition, patients who were pregnant, breastfeeding, and had significant (moderate to severe) mitral and aortic valve disease other than MS were also excluded.

Measurement of biomarkers

The enzyme-linked immunosorbent assay (ELISA) method was used to measure the levels of TGF-1, PICP, MMP-1, and TIMP-1. The ELISA was carried out according to the manufacturer's instructions (ElikineTM Human TGF-1 ELISA Kit, KET6030), ABclonal Human PICP Chain ELISA Kit (RK09063), ABclonal Human Total MMP-1 ELISA Kit (RK00340), and ElikineTM Human TIMP ELISA Kit (KET6031), respectively. The fibrosis biomarkers examination was carried out in the Biomedical Laboratory of Universitas Sebelas Maret, Indonesia.

Briefly, each well was filled with 100 µl of serum sample, which was then incubated for two hours at a temperature of 37°C. Following three rounds of washing, 100 µl of the working biotin conjugate antibody was added into the well and incubated for an hour at a temperature of 37°C. Subsequently, 100 µl of the well-received working streptavidin-HRP, 90µl of the substrate solution, and 50 µl of the stop solution were used. Optical density was within a time frame of 5 to 30 minutes, utilizing a wavelength below 450 nm.

Measurement of left atrial function

Assessment of left atrial function was performed using the an echocardiography (General Electric Echocardiography Vivid T8). Evaluation of left atrial function used measurements of Cn. Cn was calculated using formula: Cn (mL/mmHg) = -1270 x mitral valve area (MVA) (cm^2)/E-wave downslope (cm/s^2). The value of the mitral valve area was obtained from an echocardiographic examination using the planimetry method on a parasternal short-axis view at the level of the mitral valve [13,22]. The E-wave downslope value was obtained from an echocardiographic examination using a pulsed wave doppler at the apical 4-chamber view. In patients with atrial fibrillation, pulsed wave Doppler examination was performed five times (five cardiac cycles), and the E-wave downslope value was the average value of the five cardiac cycles [23]. After obtaining the mitral valve area and E-wave downslope values, Cn was calculated manually.

Measurement of left atrial volume index (LAVI)

The LAVI was measured using standard apical 4-chamber views at the end of the systole immediately before the opening of the mitral valve. The boundaries of left atrium were delineated by using planimetry. The borders comprised the walls of the left atrium, except the pulmonary veins and left atrial appendage. The biplane method of disks was employed to calculate left atrial volume. Calculating the LAVI involved dividing the left atrial volume by the body surface area of the patient [24].

Statistical analysis

The normality test was carried out to determine the distribution of the data using the Shapiro-Wilk test, a value of $p>0.05$ indicates normal data distribution. The correlation between two continuous variables was measured by Pearson's correlation test. The p-value was considered significant at 0.05. Data analysis was conducted using SPSS statistics version 25 (IBM, New York, US).

Results

A total of 40 patients included in this study and their characteristics are presented in **Table 1**. The average age of the patients was 52.50±8.85 years, with the predominance of women. All patients had atrial fibrillation with an average creatinine level of 1.03±0.44 mg/dL and an estimated glomerular filtration rate (eGFR) of 65.00±25.29 mL/mL/min/1.73 m^2. N-terminal

prohormone of brain natriuretic peptide (NT-pro BNP) levels were high, averaging 6933.5±3558.41 pg/mL. The mean levels of circulating fibrosis biomarkers were as follows: PICP 153.96±89.12 ng/mL; MMP-1 1.44±2.12 ng/mL; MMP-1/TIMP-1 ratio 0.38±0.54 and TGF-β1 2.66±1.96 pg/mL. From the echocardiographic evaluation, MVA planimetry was 0.76±0.13 cm^2, LAVI values with a mean of 152.55±79.36 mL/m^2, Cn 5.24±1.93 mL/mmHg, good left ventricle function with left ventricular ejection fraction (LVEF) 55.75±9.44% and right ventricle function with tricuspid annular plane systolic excursion (TAPSE) 18.11±5.55 mm. Most patients were treated with beta-blockers, furosemide, and spironolactone—all on warfarin therapy (**Table 1**).

Table 1. Demography, comorbidities, echocardiography characteristics and treatments of rheumatic heart disease (RHD) patients with mitral stenosis (MS) included in the study (n=40)

Characteristics	Mean±SD
Demography and comorbidities	
Age, years	52.50±8.85
Female, n (%)	35 (87.5)
Body Mass Index (BMI), kg/m^2	22.01±3.01
Atrial fibrillation, n (%)	40 (100)
Hypertension, n (%)	4 (10.0)
Type 2 diabetes, n (%)	2 (5.0)
Coronary artery disease, n (%)	0 (0.0)
Smoker, n (%)	3 (7.5)
Systolic blood pressure, mmHg	115.534±22.94
Diastolic blood pressure, mmHg	76.77±12.38
Heart rate, bpm	76.22±14.72
Creatinine, mg/dL	1.03±0.44
Estimated glomerular filtration rate (eGFR), mL/ mL/min/1,73 m2	65.00±25.29
N-terminal prohormone of brain natriuretic peptide (NT-pro BNP), pg/mL	6933.5±3558.41
Carboxy-terminal propeptide of type I procollagen (PICP), ng/mL	153.96±89.12
Matrix metalloproteinase I (MMP-1), ng/mL	1.44±2.12
Ratio of MMP-1/tissue inhibitor matrix metalloproteinase 1 (TIMP-1)	0.38±0.54
Transforming growth factor-β1 (TGF-β1), pg/mL	2.66±1.96
Echocardiography parameters	
Mitral valve area (MVA) planimetry, cm^2	0.76±0.13
Left atrial diameter, mm	54.74±9.38
Right ventricular diameter, mm	34.69±5.76
Left ventricular internal end-diastolic diameter (LVIDd), mm	47.07±6.83
Left atrial volume index (LAVI), mL/m^2	152.55±79.36
Net atrioventricular compliance (Cn), mL/mmHg	5.24±1.93
Mean pressure gradient mitral, mmHg	12.81±4.52
Systolic pulmonary artery pressure, mmHg	17.30±5.93
Left ventricular ejection fraction (LVEF)	55.75±9.44
Tricuspid annular plane systolic excursion (TAPSE), mm	18.11±5.55
Pulmonary hypertension probability (intermediate to high), n (%)	33 (82.5)
Pharmacological treatment	
ACE-I/ARB, n (%)	0 (0.0)
Beta blockers, n (%)	28 (70.0)
Furosemide, n (%)	26 (65)
Spironolactone, n (%)	35 (87.5)
Antiplatelet, n (%)	0 (0.0)

There were a significant positive correlation between MMP-1 and MMP-1/TIMP-1 ratio with Cn; correlation coefficient of r=0.345 and r=0.333, respectively (**Table 2**). PICP and TGF-β1 biomarkers had no significant correlation with Cn (p=0.361 and p=0.262, respectively). None of the biomarkers had a significant correlation with LAVI (all had p>0.05) (**Table 3**).

Table 2. Correlation between circulating fibrosis biomarkers and net atrioventricular compliance (Cn) in rheumatic heart disease (RHD) patients with mitral stenosis (MS) (n=40)

Correlation	*r*	*p*-value
Propeptide of type I procollagen (PICP) with Cn	0.148	0.361
Matrix metalloproteinase I (MMP-1) with Cn	0.345	0.029
Ratio of MMP-1/tissue inhibitor matrix metalloproteinase 1 (TIMP-1) with Cn	0.333	0.036
Transforming growth factor-β1 (TGF-β1) with Cn	-0.182	0.262

Table 3. Correlation between circulating fibrosis biomarkers and left atrial volume index (LAVI) in rheumatic heart disease (RHD) patients with mitral stenosis (MS) (n=40)

Correlation	*r*	*p*-value
Propeptide of type I procollagen (PICP) with LAVI	0.019	0.910
Matrix metalloproteinase I (MMP-1) with LAVI	0.129	0.429
Ratio of MMP-1/tissue inhibitor matrix metalloproteinase 1 (TIMP-1) with LAVI	0.123	0.451
Transforming growth factor-β1 (TGF-β1) with LAVI	-0.123	0.448

Discussion

The structure of the left atrial myocardium is formed by two layers of cardiomyocytes in well-structured muscle bundles. The thin atrial interstitium is mostly made up of an extracellular matrix of type I collagen fibers that connects the muscle bundles. Adipocytes, mesenchymal cells, inflammatory cells, and fibroblasts form a significant part of the cellular structure of the interstitium [25]. In MS conditions, increased atrial pressure triggers mechanical stimuli in the atrial wall and initiates complex molecular, cellular, and neurohormonal interlinked pathways, one of which is the renin–angiotensin–aldosterone system (RAAS), which promotes fibrosis via several pathways [26,27]. These pathways include the TGF-β1/Smad pathway, mitogen-activated protein kinase (MAPK), RhoA/Rho-associated protein kinase (RhoA/ROCK) signaling pathway, protein kinase B(AKT)/S6 kinase (S6K) signaling pathway, signal transducer and activator of transcription 3 (STAT3) signaling pathway and wingless-related integration site (Wnt) signaling pathway [28,29]. A previous study found an essential role in the activation of the fibrosis pathway, one of which is via the TGF-β1 pathway in increasing collagen synthesis and extracellular matrix remodeling, where it is also known that this pathway is associated with left atrial collagen volume fraction, scar tissue formation, and tissue fibrosis in RHD patients [28]. ACEi/ARB drugs are known to have a role in cardiac remodeling and they have role in suppressing fibrosis and their effect on neurohormonal pathways involved in the heart failure [30]. However, most patients with symptomatic RHD with MS avoid this medication because of the risk of hypotension in the presence of an obstruction in MS [31]. Current guidelines for valvular heart disease also do not include ACEI/ARB as therapy in RHD patients with MS [20]. In this study, none of the patients received ACEi/ARB therapy.

MMP-1 is part of the matrix metalloproteinase enzyme group which is responsible for extracellular matrix remodeling and plays a role in tissue destruction under pathological conditions, such as causing structural and fibrillar degradation of collagen (collagen type I and III) [18,32]. A study reported that MMP-1 levels increased significantly in RHD patients [18]. Compared to the control group, MMP-1 levels in the MS patient group was higher significantly (59,610 ng/mL vs 1,361.9 ng/mL, $p<0.05$) [18].

The ratio of MMP-1 and TIMP-1 has also been extensively studied regarding RHD and myocardial remodeling in heart failure. TIMP-1 is an inhibitor of MMP-1 which is also produced by fibroblasts in relation to the regulation of fibrosis and tissue remodeling, including the myocardium [18,33]. The important role of the MMP/TIMP ratio has been found in several studies in the field of heart disease, including RHD [18,34-36]. It was found that the MMP-1/TIMP-1 ratio increased significantly in rheumatic MS patients compared to controls [18]. Even though TIMP-1 levels as an MMP-1 counter regulator were also significantly increased, the ratio between MMP-1/TIMP-1 was higher than the control [18]. The MMP/TIMP-1 ratio correlated with MVA and pulmonary artery systolic pressure in rheumatic MS patients [18].

Meanwhile, PICP is a marker of type I collagen synthesis in the extracellular matrix of the heart. Type I and type III fibrillar collagen are the main components of the cardiac extracellular matrix which are synthesized in the form of procollagen and then in the maturation process, amino and carboxy propeptides are broken down by the enzyme procollagen proteinase to form triple helical monomers [37,38]. A study found an increase of about 400% in serum PICP in RHD patients compared to normal controls [17].

However, this study only found a weak significant relationship between MMP-1 and MMP-1/TIMP-1 ratio to Cn and no significant relationship between PICP and TGF-β1 to Cn. These four biomarkers examined also did not show a significant correlation with LAVI. This result may be

due to an increase of fibrosis biomarkers in rheumatic MS and other heart structures, such as the left ventricular, left ventricle, or mitral valve.

The mitral valve of the heart is composed of 74% type I collagen, 24% type III collagen, and 2% type V collagen [39]. The process of fibrotic valves is characterized by the activation of fibroblasts and the accumulation of extracellular matrix (ECM). Valve interstitial cells (VIC) and cardiac fibroblasts are cells responsible for maintaining the cardiac ECM and are sensitive to mechanical changes in their surroundings [40,41]. Although so far it has been recognized that acute inflammation in rheumatic fever followed by sequelae of inflammatory activity in the valves is the primary pathophysiology leading to mitral valve damage and stenosis, several studies have shown that this inflammation persists even in chronic RHD [42-45].

Inflammation will initiate ECM breakdown, accumulation of inflammatory cells and fibroblast-like cells, and endothelial-to-mesenchymal-transformed cells (EndMTCs). Inflammation can lead to fibrosis, characterized by the accumulation of rigid ECM and an abundance of myofibroblasts (MyoFB) that initiate ECM remodeling and intercellular signaling pathways. The MyoFB phenotype is triggered by various mechanical and chemical factors, which are channeled through integrins and cadherins, respectively. Increased expression of α-smooth muscle actin (α-SMA) on MyoFB will further stabilize and activate integrins and cadherins. This process will increase the formation of intracellular pressure and ECM remodeling [40]. In acute RHD, mononuclear cells primarily secrete TNF-α, IFN-γ, and IL-10 in myocardial and valve tissue. Meanwhile, IL-4 in valves is only found in rare quantities. The lack of these regulatory cytokines causes permanent damage to the valves [46]. In chronic RHD, there is a shift in the role dominance of the type 1 T helper (Th1) cells to type 2 T helper (Th2) cells which in turn also encourages activation of fibroblast proliferation, myofibroblast differentiation, deposition of extracellular matrix, and production of TGF-β1 [16]. Persistent chronic inflammation will cause proinflammatory macrophages to increase IL-1β production which in turn induces MMP-1 release, TGF-β1 activation, increased PICP, and decreased MMP-1/TIMP-1 ratio towards pro-valvular fibrosis [17,18,47].

A study found the role of MMP-1 in patients with congestive heart failure due to RHD. It was found that MMP-1 expression from the papillary muscle tissue of patients with NYHA functional class III and IV was significantly higher than patients with NYHA functional class I [36]. Another study also found that in rheumatic valves, the amount of collagen was twice as large as in normal valves, and the speed of collagen biosynthesis was higher than in normal valves [48]. PICP levels also positively correlated with the degree of fibrosis of the mitral valve of RHD, which was examined histopathologically [49]. An additional study assessed the relationship between TGF-β1 and fibrosis in the valves of RHD patients and found significantly higher tissue TGF-β1 expression in the valves and higher TGF-β1 expression was correlated with myofibroblast proliferation, valvular fibrosis, inflammatory cell infiltration, neovascularization, and valve calcification mitral [42]. The ratio of proteoglycan and collagen deposition is reversed by tissue expression of TGF-β1 [42]. This chronic fibrotic process has been demonstrated in several long-term studies. When this process has begun, there will be a decrease in the mitral valve area each year by about 0.08–0.1 cm^2 [50-52].

Regarding left ventricular fibrosis, another study found that the volume of fibrotic tissue in rheumatic MS patients was 16.6% (5.5–55.8%) [53]. Fibrotic tissue volume was found to be a significant predictor of decreased LVEF, where 1% myocardial fibrotic tissue was associated with a 0.87% decrease in LVEF (95% CI 0.51%–1.24%) in RHD. Left ventricle function is determined by the degree of myocardial fibrosis in rheumatic MS [53].

Changes in fibrosis biomarkers in general can also be caused by processes in other organs besides the heart, where collagen tissue is also present in various other organs of the body [54]. Several disease conditions can affect this biochemical marker of fibrosis, including kidney disorders (especially chronic renal failure stages 4 and 5), diffuse fibrotic lung disease, bone disorders (severe osteoporosis), and cancer [32,55-57]. This study has tried to exclude several conditions such as pulmonary and chronic kidney disorders, but other factors such as osteoporosis and cancer have not been examined in detail and may affect the increase in markers of circulatory fibrosis.

Left atrial compliance reflects the change in pressure per unit change in volume in the left atrial [13,14]. Other factors besides fibrosis are known to affect this left atrial compliance score. A study found that systolic blood pressure and total cholesterol/high-density lipoprotein (HDL) affect left atrial compliance. Likewise several factors, such as left ventricle dysfunction, coronary artery disease (CAD), hypertension, obesity, and aging [58]. In this study the mean age was 52.50 years and BMI 22.01±3.01 kg/m^2, the average LVEF was within normal limits (55.75±9.44) with relatively small proportion of patients with hypertension (10%) and there were no patients with a history of CAD. Even so, no further examination has been carried out to completely rule out CAD in patients.

Left atrial enlargement with a resulting decline in left atrial function is a maladaptive structural and functional "remodeling" that encourages electrical remodeling and creates the conditions for incident atrial fibrillation. All patients in this study have been in atrial fibrillation rhythm with high LAVI value and do not show a correlation with fibrosis biomarkers. A study discovered numerous elements, primarily mechanical and electrical ones, that were linked to LAVI in progressive MS [59]. Atrial fibrillation, MVA, mean diastolic pressure gradient, and left ventricular mass index (LVMI) are contributing variables. It is not unexpected that atrial fibrillation, MVA, and mean diastolic pressure gradient arelinked to LAVI because atrial fibrillation causes the left atrial to remodel mechanically and electrically, and raising upstream pressure causes the left atrial to enlarge progressively [59].

There are some limitations in this study including a relatively small sample. This study did not directly compare fibrosis biomarkers with non-invasive measurements of fibrosis, such as magnetic resonance imaging (MRI). In addition, this study did not cover other variables that could affect circulating fibrosis biomarker levels in left atrial volume and function.

Conclusion

This study found a significant correlation between MMP-1 and the MMP-1/TIMP-1 ratio with left atrial compliance. There was no significant correlation between PICP and TGF-β1 and left atrial compliance. Likewise, in the analysis of changes in the structure of the left atrium, there was no significant correlation between PICP, MMP-1, MMP-1/TIMP-1 ratio, and TGF-β1 with LAVI.

Ethics approval

This study was approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Sebelas Maret, Indonesia (No.128/UN27.06.12/KEP/EC.2022).

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Competing interests

The authors declare no conflict of interest.

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Underlying data

All data underlying the results are available as part of the article.

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