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Original Article

Clinical characteristics and prognostic value of autoantibody profile in children with monogenic lupus

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Objective: To report the frequency of selected autoantibodies and their associations with clinical features in Arab children with monogenic lupus.

Methods: This study was retrospective single-center study of genetically confirmed monogenic lupus cases at childhood lupus clinic at King Faisal Specialist Hospital and Research Center, from June 1997 to July 2022. We excluded familial lupus without genetic testing and patients with insufficient data. Collected data comprised clinical and laboratory findings, including the autoantibody profile, which included the anti-double-stranded DNA (anti-dsDNA), anti-Smith, anti–Sjögren's-syndrome-related antigen A (anti-SSA), anti–Sjögren's-syndrome-related antigen B (anti-SSB), and antiphospholipid (APL) antibodies. Also, disease activity and accrual disease damage were collected at the last follow-up visit.

Results: This study enrolled 27 Arab patients (14 males) with a median age of 11 years (interquartile range 8.0~16 years), with 63% having early-onset disease. The consanguinity rate and family history of lupus were high (74.1% and 55.6%, respectively). The most frequent clinical features were hematological (96.3%), fever (81.5%), mucocutaneous lesions (85.2%), and renal (66.7%). The frequency of the APL antibodies was 59.3%, anti-dsDNA was 55.6%, and anti-Smith and anti-SSA were 48.2% and 44.4%, respectively. Moreover, dsDNA antibodies were significantly associated with musculoskeletal complaints ($p<0.05$). Likewise, both anti-Smith and anti-SSA antibodies were linked to failure to thrive and recurrent infections in the univariate analysis ($p<0.05$).

Conclusion: Our study reveals autoantibody frequencies and their association with clinical and prognostic in a substantial monogenic lupus cohort. Distinct clinical manifestations and prognosis association with certain autoantibodies support the idea that monogenic lupus is a distinctive form of lupus. Larger studies needed to validate these findings.

Keywords: Autoantibodies, Monogenic lupus, Systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a classic systemic autoimmune disease characterized by the immune system's production of antibodies against self-antigens. This process leads to the formation of immune complexes that are widely distributed and deposited in affected tissues, causing a diverse range of clinical and laboratory features [1,2]. Autoantibodies against several nuclear and cytoplasmic antigens, including antinuclear antibodies (ANA), anti-Smith antibodies, anti-double-stranded DNA (anti-dsDNA), anti–Sjögren's-syndrome-related antigen A (anti-SSA), and anti-Sjögren's-syndrome-related antigen B (anti-SSB) antibodies, are the serological hallmarks of SLE [3]. Interestingly, autoantibodies have been found as clusters related

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with particular clinical manifestations of lupus [4-10]. SLE is often regarded as a polygenic, complex disease characterized by the interaction of numerous genes and epigenetic alterations, as well as environmental and hormonal factors. Interestingly, autoantibodies have been found as clusters related with particular clinical manifestations of lupus [4-10]. SLE is often regarded as a polygenic, complex disease characterized by the interaction of numerous genes and epigenetic alterations, as well as environmental and hormonal factors [11,12]. It is worth noting that there is a distinctive subset of patients who exhibit distinct lupus features that can be attributed to a single genetic variant, either through association or as a cause [13-15]. Accordingly, they are labeled as patients with monogenic lupus. Typically, individuals with monogenic lupus exhibit parental consanguinity and an early onset of devastatingly severe disease manifestations [13].

To the best of our knowledge, to date, there have been no reports thus far that identify an association between autoantibody clusters with clinical manifestations in monogenic lupus.

Our study aimed to report the frequency of selected autoantibodies and explore the associations of the identified autoantibody profile with clinical features, including the occurrence of major organ manifestations and prognosis, in a cohort of Arab children with monogenic lupus.

MATERIALS AND METHODS

This is an observational retrospective cohort study that comprised all patients with monogenic lupus who were followed at childhood lupus clinic at King Faisal Specialist Hospital and Research Center (KFSHRC), Riyadh, from June 1997 to July 2022. To ensure that all children with monogenic lupus were included, we retrieved our pediatric rheumatology database, and coordinated with the medical records department. The included patients were younger than 14 years of age at diagnosis and fulfilled the EULAR/ACR 2019 classification criteria for SLE [16,17]. It is worth mentioning that our standard practice is to perform genetic testing on individuals who have high-risk criteria such as early onset of specific lupus features, a lupus family history, and paternal consanguinity. All enrolled patients were required to have a confirmed pathogenic gene variant and a complete autoantibody profile, which included anti-dsDNA, anti-Smith, anti-SSA, anti-SSB, and anti-phospholipid (APL) antibodies, including anticardiolipin and β2-glycoprotien. Furthermore, the disease activity and damage were calculated using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and the pediatric adaptation of the Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage Index (pSDI) respectively [18,19].

For a patient to be considered positive in the autoantibody test, the test had to yield positive results on more than two separate occasions. All the tests were conducted following the standard protocol in the pathology and laboratory department at KFSHRC, Riyadh, Suadi Arabia.

All enrolled patients' medical records were reviewed for demographic, clinical manifestations.

Of note, patients with familial SLE without proven genetic testing and patients with insufficient data were excluded from the analysis. Calculating the sample size was impossible due to the rarity of monogenic lupus.

This study was approved by the Ethics Committee of the Research Affairs Council at KFSHRC, Riyadh, under RAC# 2221105. All clinical and laboratory assessments were done as part of standard clinical practice. In addition, written consent was obtained from patients' parents for genetic testing. All collected data analyzed under confidentiality practice and no personal identity was required. Thus, the Declaration of Helsinki (2013) principles were followed during the preparation of this study.

Statistical considerations

Data were analyzed using STATA software version 17 for Windows (Stata Co., College Station, TX, USA). Continued data were reported as medians, interquartile range (IQR), means and standard deviations as appropriate. Categorical data were reported as frequencies and percentages. Furthermore, the chi-square

Table 1. Demographic characteristics of 27 patients with monogenic lupus

Characteristic	Value
Sex	
Female	13 (48.1)
Male	14 (51.9)
Current age (yr)	11 (8~16)
Early disease onset (<5 yr)	17 (63.0)
Consanguinity	20 (74.1)
Family history of lupus	15 (55.6)

Values are presented as number (%) or median (interquartile range).

test was used to report the relationship between autoantibodies and clinical variables such as organ involvement, then adjusted using multivariable logistic regression. In addition, to determine the correlation between severity scores (pSDI and SLEDAI) and clinical features, univariate and multivariable linear regression were performed due to the normality assumption by Shapiro–Wilk test. A p-value <0.05 was considered significant.

RESULTS

Demographic characteristics and gene mutations

The study cohort comprised 27 patients with monogenic lupus, proved by genetic testing, with no gender preponderance, as indicated by a male: female ratio of 1.1:1. Demographic characteristics are detailed in Table 1. The cohort exhibited a spectrum a diverse range of underlying genetic variants, with complement deficiency being the most common. Eight patients had the *C1q* variant, two patients having the *C3* variant, and one patient each having the *C4* a and *C8b* variants. Additionally, there were four patients with the *DNase1L3* variant, two patients with the *DNase II* variant, and nine patients with various other genetic variants, including variants associated with interferonopathies. Our cohort consisted exclusively of Arab patients, among whom there were high rates of consanguinity (74.1%) and a significant family history of lupus (55.6%). The median current age of the included patients was 11 years (IQR 8.0~16 years). Moreover, a high proportion (63.0%) had early-onset disease, with a median age at disease onset of 3.5 years (IQR 1.0~6.0 years).

The clinical manifestations and laboratory findings

Table 2 summarizes the frequency of clinical and laboratory features. Most of the patients (85.2%) experienced mucocutaneous lesions, including maculopapular rash, facial photosensitivity and rash, oral ulcerations, and alopecia. Twenty-two patients had constitutional manifestations, particularly fever (81.5%); additionally, 48.1% and 66.7% of the patients presented with lymphadenopathy and failure to thrive (FTT) respectively. Renal involvement among our patients was 66.7%. Of those patients, ten had biopsy-proven nephritis; five had class V (membranous glomerulonephritis); four had class III and IV (proliferative glomerulonephritis); and one had class II nephritis as per the ISN/RPS classification [20]. Furthermore, hypertension was noticed in eleven patients (40.7%), and seven patients suffered renal impairment. Sixteen patients (59.3%) suffered musculoskeletal complaints ranging from persistent arthralgia and non-erosive polyarthritis.

Other organ involvement was variable and less prevalent; for instance, the gastrointestinal tract (44.4%), cardiovascular (22.2%), neurological (37.1%), and pulmonary system (29.6%). Thirteen patients (48.2%) experienced recurrent bacterial infections; however, six patients had viral infections, and two patients proved to have fungal infections. Five patients died because of severe infections.

Laboratory results showed that a large proportion (96.3%) had hematological abnormalities, including anemia, leucopenia, and thrombocytopenia. Fourteen patients with anemia showed positive Coombs tests. Only sixteen patients had low complement (C3/C4) levels; and ten patients had low CH50 levels. Of

Table 2. The clinical manifestations and laboratory findings

Characteristic	Value
Fever	22 (81.5)
Failure to thrive	18 (66.7)
Hypertension	11 (40.7)
Lymphadenopathy	13 (48.1)
Hematological involvement	26 (96.3)
Mucocutaneous involvement	23 (85.2)
Renal involvement	18 (66.7)
Renal impairment	7 (25.9)
Musculoskeletal involvement	16 (59.3)
Gastrointestinal involvement	12 (44.4)
Neurological involvement	10 (37.1)
Ocular involvement	8 (29.6)
Pulmonary involvement	8 (29.6)
Cardiovascular involvement	6 (22.2)
Recurrent infections	13 (48.2)
Low C3/C4	16 (59.3)
APL	16 (59.3)
Anti-dsDNA	15 (55.6)
Anti-Smith	13 (48.2)
Anti-SSA	12 (44.4)
Anti-SSB	7 (25.9)
SLEDAI	19 (12~23)
pSDI	2.0 (1.0~4.0)

Values are presented as number (%) or median (interquartile range). APL: anti-phospholipid, Anti-dsDNA: anti-double-stranded DNA, anti-SSA: anti–Sjögren's-syndrome-related antigen A, anti-SSB: anti–Sjögren's-syndrome-related antigen B, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index, pSDI: pediatric adaptation of the Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage Index.

note, eleven patients had low C1q levels; most of them were C1q deficient. The frequency of selected autoantibodies in our cohort were as follows: sixteen patients (59.3%) positive for APL, fifteen patients (55.6%) anti-dsDNA positive, thirteen (48.2%) anti-Smith positive, twelve patients (44.4%) anti-SSA positive, and seven patients (25.9%) anti-SSB positive.

The association between clinical features and autoantibodies

Tables 3 and 4 outline the association between clinical features and autoantibodies. The presence of anti-ds DNA antibodies exhibited a robust association with musculoskeletal involvement, both in univariate and multivariable analysis ($p<0.05$). On the contrary, mucocutaneous manifestations were significantly associated with the cluster of anti-Smith, anti-SSA, and APL antibodies in the univariate analysis, but this significance association did not hold in the multivariable analysis. Moreover, both anti-Smith and anti-SSA antibodies were linked to FTT and recurrent infections in the univariate analysis ($p<0.05$). Furthermore, FTT and proteinuria were associated with anti-Smith, although only the FTT remained significant in the multivariable analysis ($p<0.05$). Both autoantibodies were associated with FTT and recurrent infections. Additionally, anti-Smith showed a significant association with proteinuria.

Disease activity and damage in monogenic lupus

At the last follow-up visit, the median SLEDAI score was 19 (IQR 12~23), while the median accrual damage index (pSDI) was 2.0 (IQR 1.0~4.0) (Table 2).

The association between autoantibodies, disease severity, and organ involvement is detailed in Table 5. Both univariate and multivariable analyses demonstrated a noteworthy increase in SLEDAI scores for patients with fever and musculoskeletal involvement ($p<0.05$). In contrast, patients with neuropsychiatric involvement, FTT, and positive anti-SSB autoantibodies displayed significantly elevated pSDI scores ($p<0.05$) as revealed by both univariate and multivariable analyses.

DISCUSSION

Lupus has a complex relationship between autoantibodies and clinical manifestations that can provide diagnostic and prognostic value. The presence of specific autoantibodies in patients, including children with lupus, has been associated with distinct

Table 3. The association between autoantibodies and clinical features using the chi-square test

Clinical features	No. of cases	Positive Anti-dsDNA (n=15)		Positive Anti-Smith (n=13)		Positive Anti-SSA (n=12)		Positive Anti-SSB (n=7)		Positive APL (n=16)	
		No. (%)	p	No. (%)	p	No. (%)	p	No. (%)	p	No. (%)	p
Musculoskeletal	16	12 (75.0)	0.019*	7 (43.8)	0.582	7 (43.8)	0.930	4 (25.0)	0.895	10 (62.5)	0.680
Ocular	8	6 (75.0)	0.199	4 (50.0)	0.901	2 (25.0)	0.199	1 (12.5)	0.319	4 (50.0)	0.527
Neurological	10	7 (70.0)	0.253	6 (60.0)	0.348	5 (50.0)	0.656	3 (30.0)	0.712	5 (50.0)	0.455
Renal	18	11 (61.1)	0.414	11 (61.1)	0.069	10 (55.6)	0.113	6 (33.3)	0.237	12 (66.7)	0.273
Gastrointestinal	12	5 (41.7)	0.199	6 (50.0)	0.863	5 (41.67)	0.795	4 (33.3)	0.436	8 (66.7)	0.485
Pulmonary	8	6 (75.0)	0.199	5 (62.5)	0.338	4 (50.0)	0.707	3 (37.5)	0.379	6 (75.0)	0.289
Cardiovascular	6	2 (33.3)	0.227	3 (50.0)	0.918	3 (50.0)	0.757	3 (50.0)	0.143	4 (66.7)	0.677
Hematological	26	15 (57.7)	0.255	13 (50.0)	0.326	12 (46.2)	0.362	7 (26.9)	0.547	16 (61.5)	0.219
Skin rash	19	10 (52.6)	0.638	9 (47.4)	0.901	9 (47.4)	0.638	5 (26.3)	0.943	14 (73.7)	0.028*
Facial rash (discoid)	13	8 (61.5)	0.548	9 (69.2)	0.041*	9 (69.2)	0.017*	5 (38.5)	0.165	9 (69.2)	0.145
Photosensitivity	13	7 (53.9)	0.863	8 (61.5)	0.185	8 (61.5)	0.092	5 (38.5)	0.165	11 (84.6)	0.016*
Proteinuria	19	12 (63.2)	0.228	12 (63.2)	0.034*	11 (57.9)	0.052	6 (31.6)	0.319	13 (68.4)	0.145
Failure to thrive	18	11 (61.1)	0.414	12 (66.7)	0.018*	11 (61.1)	0.030*	6 (33.3)	0.237	13 (72.2)	0.061
Recurrent infections	13	8 (61.5)	0.548	9 (69.2)	0.041*	9 (69.2)	0.017*	5 (38.5)	0.165	11 (84.6)	0.016*
Mortality	5	3 (60.0)	0.074	4 (33.3)	0.106	3 (60.0)	0.560	3 (60.0)	0.825	5 (100.0)	0.970

Values are presented as frequency (row %). Anti-dsDNA: anti-double-stranded DNA, anti-SSA: anti–Sjögren's-syndrome-related antigen A, anti-SSB: anti–Sjögren's-syndrome-related antigen B, APL: anti-phospholipid. *$p<0.05$.

Table 4. The association between autoantibodies and clinical features using multivariable logistic regression

Variable	Multivariable analysis	
	95% CI	p-value
Anti-Smith		
Facial rash	(0.32, 28.51)	0.332
Proteinuria	(0.51, 122.37)	0.136
Failure to thrive	(1.21, 210.53)	0.035*
Recurrent infections	(0.24, 22.60)	0.461
Anti-SSA		
Recurrent infections	(0.59, 43.26)	0.136
Facial rash	(0.59, 43.26)	0.136
Failure to thrive	(0.01, 1.10)	0.060
APL		
Skin rash	(0.65, 49.94)	0.114
Photosensitivity	(0.48, 39.78)	0.190
Recurrent infections	(0.48, 39.78)	0.190
Anti-dsDNA		
Musculoskeletal	(1.44, 64.96)	0.019*
Facial rash	(0.28, 16.94)	0.456
Recurrent infections	(0.15, 7.63)	0.937
Failure to thrive	(0.25, 12.31)	0.566

CI: confidence interval, anti-SSA: anti–Sjögren's-syndrome-related antigen A, APL: anti-phospholipid, anti-SSB: anti–Sjögren's-syndrome-related antigen B, Anti-dsDNA: anti-double-stranded DNA. *p<0.05.

clinical manifestations and disease outcomes; certain autoantibodies can also indicate an increased risk of specific complications [21-23]. Monogenic lupus is a distinctive subset of lupus; patients, typically exhibit features such as parental consanguinity and an early onset of distinct lupus features [15]. This study aimed to report the frequency of selected autoantibodies and explore the associations of the identified autoantibody profile with clinical features, major organ involvement, and prognosis in a large cohort of Arab children with monogenic lupus. Our patients had a high prevalence of consanguinity and a family history of lupus, as well as early onset of disease with a multisystem disease, which may be related to the underlying genetic variants. Our cohort exhibited a diverse range of underlying genetic variants, with complement deficiency being the most common, followed by *DNase1L3* variant. Our findings revealed differences in the frequency of clinical manifestations compared to previous studies [24]. In comparison to pre-pubertal patients (those under the age of seven years at the onset of the disease) with sporadic lupus, our patients exhibited a higher prevalence of various clinical manifestations, including hematological, musculoskeletal, mucocutaneous, and gastrointestinal manifestations. However, the occurrence of renal involvement was comparable between the two groups. However, they showed comparable findings to those with early disease onset, particularly in the presence of genetic variants [25]. This observation might support the idea that monogenic lupus is a unique form of lupus. Furthermore, the frequency of the selected autoantibodies was similar to reported previously in patients with early disease onset [25]. In general, anti-dsDNA antibodies are the most studied and considered a diagnostic marker for sporadic lupus and have a pivotal role in lupus nephritis. The current study revealed an unexpected finding: anti-dsDNA showed a significant association with a higher prevalence of musculoskeletal involvement, while there was no significant association with nephritis [26]. The exact reason behind this observation remains uncertain, but one possibility that might be considered is the genetic factors contributing to the etiopathogenesis of monogenic lupus. The cluster of anti-Smith, anti-SSA, and APL antibodies was found to be more frequent in patients with facial rashes, particularly discoid lesions as noted by the univariate analysis; this result was like previous reports [22,25]. But this significance did not hold in the multivariable analysis. On the contrary, these autoantibodies did not show a significant association with neuropsychiatric manifestations, vasculopathy, or thrombosis. Anti-Smith autoantibodies might contribute to lupus nephritis and renal failure [27,28]. However, in this study, anti-Smith autoantibodies were associated with heavy proteinuria; but the multivariable analysis did not show significant association. Interestingly, there was an association with recurrent infections. It is difficult to draw a conclusion from the current study. However, it might be considered a paradoxical phenomenon, which means these autoantibodies can be detected in recurrent infections. Although the SLEDAI score was high in our patients, there was no significant association with any of the selected autoantibodies. Nevertheless, the cluster of anti-Smith and anti-SSB autoantibodies was associated with accrued disease damage.

The current study confirms previously reported associations between certain autoantibodies and clinical manifestations. However, it also shows unique and unexpected clinical and prognostic associations with certain autoantibodies. It is important to highlight that the prevalence and sensitivity of autoantibodies can vary among lupus patients of different ethnicities, specifically Caucasian, African American, and Asian individuals [26]. This aspect should be considered when dealing with lupus

Table 5. The association between severity scores (SLEDAI, pSDI), autoantibodies and organ involvement

Variable	Univariate analysis		Multivariable analysis	
	95% CI	p-value	95% CI	p-value
SLEDAI				
Anti-dsDNA	(−12.26, 2.86)	0.213		
Anti-Smith	(−9.26, 6.22)	0.690		
Anti-SSA	(−9.81, 5.71)	0.592		
Anti-SSB	(−14.12, 2.98)	0.192		
APL	(−7.11, 8.67)	0.840		
Skin rash	(−12.18, 4.52)	0.354		
Facial rash	(−12.69, 2.24)	0.162		
Renal	(−14.14, 1.47)	0.107		
Gastrointestinal	(−4.66, 10.76)	0.423		
Pulmonary	(−14.08, 2.20)	0.145		
Cardiovascular	(−9.19, 9.48)	0.975		
Hematology	(−22.04, 19.04)	0.882		
Musculoskeletal	(−14.64, −0.04)	0.049*	(−13.20, −1.45)	0.017*
Neurological	(−16.24, −2.03)	0.014*	(−12.66, 0.17)	0.056
Failure to thrive	(−6.71, 9.71)	0.710		
Recurrent infections	(−12.56, 2.40)	0.175		
Fever	(−20.93, −3.71)	0.007*	(−17.53, −1.57)	0.021*
Hypertension	(−13.63, 1.33)	0.103		
pSDI				
Anti-dsDNA	(−2.52, 0.78)	0.291		
Anti-Smith	(−3.26, −0.21)	0.027*	(−0.77, 0.50)	0.674
Anti-SSA	(−3.10, 0.03)	0.055		
Anti-SSB	(−3.77, −0.32)	0.022*	(−1.33, −0.07)	0.031*
APL	(−2.35, 1.03)	0.430		
Skin rash	(−2.50, 1.13)	0.446		
Facial rash	(−3.38, −0.39)	0.015*	(−2.48, 0.43)	0.160
Renal	(−3.22, 0.11)	0.066		
Gastrointestinal	(−2.02, 1.35)	0.688		
Pulmonary	(−3.34, 0.09)	0.063		
Cardiovascular	(−2.46, 1.56)	0.648		
Hematology	(−6.90, 1.75)	0.232		
Musculoskeletal	(−2.49, 0.86)	0.329		
Neurological	(−3.95, −1.18)	0.001*	(−3.46, −1.23)	0.000*
Failure to thrive	(−3.62, −0.48)	0.012*	(0.13, 2.79)	0.032*
Recurrent infections	(−2.89, 0.30)	0.107		
Fever	(−4.05, −0.07)	0.043*	(−2.73, 1.03)	0.361
Psychosis personality cognitive	(−4.93, 0.02)	0.052		
Spasticity rigidity	(−5.53, −0.87)	0.009*	(−4.00, 0.86)	0.194
Hypertension	(−3.69, −0.81)	0.003*	(−2.88, 0.29)	0.106

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index, Anti-dsDNA: anti-double-stranded DNA, anti-SSA: anti–Sjögren's-syndrome-related antigen A, anti-SSB: anti–Sjögren's-syndrome-related antigen B, APL: anti-phospholipid, pSDI: pediatric adaptation of the Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage Index, CI: confidence interval. *p<0.05.

patients who have underlying genetic variants.

Our study's main strength, to the best of our knowledge, is the first report of autoantibodies associations in a large cohort of patients with monogenic lupus from a high rate of consanguinity in the Arab population. Nevertheless, this study has several limitations that warrant cautious interpretation. It relied on the analysis of retrospectively collected data spanning a lengthy time frame. Moreover, the data originated from a solitary childhood lupus clinic, and all patients were of Arab descent from a community with a notable consanguinity rate. These factors may have introduced bias in patient selection, and the potential influence of ethnicity cannot be disregarded.

CONCLUSION

This study presents the first and largest data highlighting the clinical and prognostic associations with the selected autoantibodies in monogenic lupus. Distinct clinical manifestations and prognosis association with certain autoantibodies support the idea that monogenic lupus is a distinctive form of lupus; however, due to the rarity of monogenic lupus, thus, international collaboration is warranted in the future to shed light on a better understanding of the associations between a wide set of autoantibodies and clinical manifestations.

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CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

S.M.A.: conception and design of study, analysis and/or interpretation of data, drafting the manuscript, revising the manuscript critically for important intellectual content. A.H.: acquisition of data. W.K.: acquisition of data. RA: analysis and/or interpretation of data, revising the manuscript critically for intellectual content. A.A.: analysis and/or interpretation of data, revising the manuscript critically for important intellectual content.

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