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Factors Determining Occurrence of Arrhythmias in Patients Post-closure of Atrial Septal Defects

Nouran M. Mansour*, Raghda G. El Sheikh, Ayman M. Elsaeid, Mohammed El sayed El setiha, Seham F. Badr

Cardiovascular Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt

Abstract

Objectives: **This study aimed to determine the risk factors for the occurrence of arrhythmias after either transcatheter or surgical closure of atrial septal defect.**

Methods: **This prospective study included 150 patients admitted for transcatheter or surgical closure of atrial septal defect. Transthoracic echocardiography together with a twelve-leads ECG were done during 1 and 3 months follow up. The paired T, chi-square and Logistic regression tests were used to detect any association between any arrhythmias and factors that may affect its occurrence.**

Results: **One-hundred and twenty-three patients had percutaneous device closure while the remaining 27 patients had surgical closure. The youngest and oldest of the studied patients being 3 & 50 years old respectively with female (108) over male (42) predominance in incidence. After closure, 8 patients at one month and another 3 patients at three months follow up out of the total 150 patients had supraventricular arrhythmias in the form of frequent premature atrial contractions (6 patients), atrioventricular nodal re-entrant tachycardia (2 patients), and paroxysmal Atrial fibrillation (3 patients). No conduction abnormalities nor ventricular arrhythmias occurred. Multivariate analysis showed that age, P wave dispersion, systolic myocardial velocity of right ventricle, and systolic pulmonary artery pressure were independently associated with the occurrence of atrial arrhythmia after atrial septal defect repair.**

Conclusion: **Age, P wave dispersion, Systolic pulmonary artery pressure, and systolic myocardial velocity of the right ventricle are independent risk factors to develop arrythmias in patients after atrial septal defect closure.**

Keywords: Atrial septal defect, Atrial arrhythmias, Percutaneous closure, Surgical closure

1. Introduction

Atrial septal defects are one of the most common congenital heart defects that can be classified into ostium primum, ostium secundum, sinus venosus, and coronary sinus types. Unrepaired ASD leads to shunting of blood from the left to right side which leads to right ventricular volume overload with resultant right-sided heart failure, elevated pulmonary vascular resistance, systemic embolism, and atrial arrhythmias [1].

Percutaneous ASD closure has become the primary treatment option with advantages of satisfying efficacy, little trauma, quick recovery after surgery, as well as few complications [2]. However, primary surgical repair is still needed for large secundum defects with limited septal margins and complex ASDs, including ostium primum, sinus venosus ASDs [3].

Atrial tachyarrhythmias are a common complication associating with atrial septal defects even after closure. Atrioventricular (AV)-block is a rare but clearly recognized complication after transcatheter closure of atrial septal defects. Post interventional

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* Corresponding author.
E-mail address: Dr.nouran@hotmail.co.uk (N.M. Mansour).

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AV conductance defects can be temporarily in some patients but may progress to complete heart block (CHB) as well [4,5].

Assessment of prognosis is a standard part of a medical evaluation and it is of particular importance in patients with congenital heart disease. Based on risk stratification estimated using the different factors, it will guide decisions regarding follow-up and treatment [6].

This prospective study aimed to determine the risk factors for the development of arrhythmias 1 and 3 months after ASD closure either by transcatheter or surgical approaches.

Abbreviations

ASD	atrial septal defect
AV	atrioventricular
AEMD	atrial electromechanical delay
AVNRT	Atriventricular nodal re-entrant tachycardia
ASL	atrial septal length
ASO	atrial septal occluder
AF	atrial fibrillation
AFL	atrial flutter
A′ of LA	atrial filling velocity of the left atrium by tissue Doppler imaging
A′ of RA	atrial filling velocity of the right atrium by tissue Doppler imaging
CHB	complete heart block
ECG	electrocardiogram
HR	heart rate
LT EMD	left electromechanical dissociation
LA min	minimal left atrial volume
LA max	maximal left atrial volume
LA function	total emptying fraction of the left atrium
mPAP	mean pulmonary artery pressure
PACs	premature atrial contractions
PWD	P wave dispersion
Pmax	maximum P wave duration
Pmin	minimum P wave duration
PTFE	poly-tetra-fluoro-ethylene
PFO	patent foramen ovale
RA function	total emptying fraction of the right atrium
RT EMD	right electromechanical dissociation
RA min	minimal right atrial volume
RA max	maximal right atrial volume
SC	surgical closure
S'of RV	systolic myocardial velocity of right ventricle by tissue Doppler imaging
S′ of LV	systolic myocardial velocity of left ventricle by tissue Doppler imaging
SPAP	systolic pulmonary artery pressure
TAPSE	tricuspid annular systolic plane excursion
TTE	transthoracic echocardiography
TEE	transoesophageal echocardiography
TA TDI S′	tricuspid annular peak systolic velocity
TC	Transcatheter closure
TSL	total septal length

2. Material and methods

This prospective study included 150 patients admitted to Tanta University for closure of congenital atrial septal defect (ASD) either by transcatheter or surgical approach in the duration from February 2018 to December 2019. After approval from the institutional ethical committee (32025/12/17, The Ethical committee of Faculty of Medicine, Tanta University), an informed consent was obtained from all participants in this research by themselves or their parents. The patients' privacy was kept by making their data confidential with the use of secret codes and private files with the use of the data for the current medical research only.

Patients who had any type of ASD with left to right shunt, right ventricular volume overload and normal sinus rhythm in the ECG were included in the study. Patients who had any type of arrythmia before closure, or any other associated congenital anomalies, or any evidence of pulmonary hypertension were excluded from the study.

Before closure of ASD, all patients were subjected to detailed history taking including patient's demographic data and symptomatology, full clinical examination, twelve leads surface ECG, and Full 2D transthoracic & transesophageal echocardiography (TTE & TEE).

The twelve-lead surface ECG was performed in a supine position at a rate of 25 mm/s and a calibration of 1 mV/cm = 10 mm for all patients at baseline. All patients were in sinus rhythm during the analysis. Three consecutive beats were used for analysis and at least 10 leads were analyzable in all ECGs. The indices taken from ECG included cardiac rate, heart axis, PR interval, and P wave dispersion. Maximum & minimum P wave durations (From the onset to the offset of P wave were measured from which the P wave dispersion (PWD) was calculated). It is defined as the difference between the maximum P wave duration (P max) and the minimum P wave duration (P min).

Transthoracic echocardiographic examination (Vivid E9, General Electric Corporation, USA. With either a 3.5 or 5 Mhz phased array transducer) was performed with the patient lying either supine or in left lateral position. Electrodes were applied to the patient's shoulders and the right lower thorax so that the echocardiographic windows are freely accessible. Two-Dimensional data was done to determine the situs, AV and VA concordance, great vessel relation and abnormalities, state of cardiac valves, venous connections, and any intra-cardiac shunts, and visualizing the ASD.

Multiple Views for imaging the atrial septum after sequential analysis were essential to assess the size, shape, number, and location as well as the relation to the surrounding structure particular care to superior vena cava, inferior vena cava, the pulmonary veins, and the coronary sinus. The echocardiographic indices taken for analysis included left atrial & right atrial volumes, systolic pulmonary artery pressure, tricuspid annular systolic plane excursion (TAPSE), the systolic (S′) myocardial velocity of both the right and left ventricles, the late diastolic (A′) myocardial velocity of both the left and right atria, and atrial electromechanical delay (AEMD).

Two-dimensional Transesophageal echocardiography was performed by 2.5 MHz multi-plane probe on the same echocardiography machine. Adult patients were sedated using diazepam 0.1–0.3 mg/kg. While general anesthesia was needed in noncooperative patients and especially in young ages and the patients whom TEE was done during transcatheter closure of ASD. The distal aspect of the transesophageal probe was lubricated with a lubricant gel. With gentle pressure on the probe, the probe was advanced firmly but without force. The mid-esophageal aortic valve short-axis view, the mid-esophageal four-chamber view, the mid-esophageal bicaval view were obtained in patients with inappropriate subcostal window (especially adults) for a pre-interventional and intra-interventional proper assessment to redefine the location, size of the ASD, and size of the surrounding rims, to confirm the site of drainage of the pulmonary veins, and to assist the catheterizing physician in placing the proper atrial septal occluder (ASO).

2.1. Cardiac catheterization

Sterilization was done using povidine Iodine from the umbilicus to the knees and both groins then the patient was covered with sterile drapes. In all patients, venous access was done using the Seldinger's technique with a 6f sheath was introduced into the vein. After that 50–100 IU/Kg heparin was given to all patients. Different types of devices are available, the most widely used in our study are Figulla flex II ASD occluder (occlutech), Amplatzer septal occlude. Echocardiographic monitoring (preferably TEE) is very helpful during the procedure to guide the proper choice of size and deployment of the device.

2.2. Surgery

Closure of ASD was performed via full or partial median sternotomy using cardiopulmonary bypass at mild hypothermia. The closure was performed using a patch of poly-tetra-fluoro-ethylene (PTFE), Dacron, or autologous pericardium or by primary suture at the discretion of the surgeon.

2.3. Follow up and measurements

During follow-up, ECG together with 2D TTE follow up were done after 1 month as well as 3 months later for Re-evaluation of the same parameters taken before closure. ECG parameters included heart rate, QRS axis, P wave dispersion, and PR interval. Echocardiographic parameters included TAPSE, systolic myocardial velocity, atrial filling velocity, systolic pulmonary artery pressure, maximal & minimal left & right atrial volumes, Left & right atrial total emptying fraction, left & right intratrial EMD. Any type of arrhythmias that had been noticed either at 1 month or 3 months was recorded.

2.4. Statistical analysis

Qualitative data were analyzed by the Chi-square test and presented in the form of frequency and percentage. Quantitative data were presented in the form of mean, standard deviation, and range after it had been analyzed by Paired T-test. Logistic regression was used for multivariate risk factor analysis. Statistical significance was defined as $p < 0.05$.

3. Results

The study included 150 patients admitted for ASD closure and assessment of arrhythmia and its predictors after closure. 123 patients (82%) had transcatheter closure while 27 patients (18%) had surgical closure. The age of patients ranged from 3 to 50 years with a mean value of 11.15 ± 10.19 years. There was a significant increase in the number of females (108 patients) compared to males (42 patients) in the studied patients. The majority of those patients were asymptomatic (66 patients) and discovered accidently during regular check-up, the rest had varying symptoms between recurrent chest infection, fatiguability, dyspnea, and palpitation especially in older ages. Table 1.

Table 1. Demographic data of the studied patients.

Demographic data			
Type of intervention	Surgery	27 (18%)	
	Transcatheter closure	123 (82%)	
Age	(years)	3−50	11.150 ± 10.127
Gender	Female	108 (72%)	
	Male	42 (28%)	
Symptoms	Asymptomatic	66 (44%)	
	Chest infection	30 (20%)	
	Fatigue	24 (16%)	
	Dyspnea	15 (10%)	
	Palpitation	15 (10%)	

Data were presented as no and % or Mean ± SD.

At 1 month after closure, 8 patients had developed arrhythmias (5.33%) while after 3 months of closure 3 patients had arrhythmias (2%) while the remaining 139 patients remained arrhythmia free (92.67%). Out of the 11 patients who had supraventricular arrhythmia during follow up, 2 patients had AVNRT (18%), 3 patients had paroxysmal Atrial fibrillation (27%) while the majority 6 patients had frequent PACs (54%). No patients had any conduction abnormalities or ventricular arrhythmias at either 1 or 3 months follow up after ASD closure. Table 1.

Most of the patients with atrial fibrillation and frequent PACs were paroxysmal and resolved spontaneously without any interference. One patient only with atrial fibrillation required cardioversion by amiodarone in the CCU, while the two patients with AVNRT required termination by calcium channel blocker as they did not respond to vagal maneuvers.

The patients were divided into two groups the arrhythmia group (11 patients) and non-arrhythmia group (139 patients). Upon comparison between the two groups: There was no statistically significant difference in gender ($P = 0.226$) or type of closure (surgery or transcatheter closure) ($P = 0.116$) or QRS axis ($P = 0.123$) on the development of arrhythmia post closure. Table 2.

Table 2. Chi−Square test comparison between gender, type of closure, QRS axis between two groups.

		Arrhythmias				P- Value
		No		Yes		
		N	%	N	%	
Sex	Male	30	25.64	12	36.36	0.226
	Female	87	74.36	21	63.64	
Type of closure	Surgery	18	15.38	3	27.27	0.116
	Trans catheter	99	84.62	8	72.73	
QRS axis	0−90	106	90.6	26	78.79	0.123
	90−180	11	9.4	7	21.21	

Data were presented as no and %.

Table 3. Risk factors for atrial arrythmias after closure of ASD.

After 3 Months	Arrhythmias						P- value
	No			Yes			
Age (Years)	8.923	±	7.065	19.045	±	14.634	<0.001*
Defect size (mm)	20.667	±	6.775	19.636	±	4.827	0.416
TSL (mm)	54.333	±	12.898	53.545	±	9.210	0.744
Device size (mm)	22.513	±	6.081	21.273	±	4.785	0.282
Pw Disp (ms)	27.949	±	10.467	38.182	±	15.503	<0.001*
PR interval (ms)	168.137	±	38.805	176.364	±	44.848	0.301
LT EMD (ms)	7.128	±	1.946	7.682	±	2.011	0.154
RT EMD (ms)	13.091	±	2.578	14.846	±	2.873	0.002*
HR (bpm)	86.795	±	10.636	82.727	±	11.326	0.058
S' of RV (cm/sec)	11.410	±	2.580	9.818	±	2.833	0.003*
TAPSE (cm)	1.702	±	0.410	1.791	±	0.432	0.276
S' of LV (cm/sec)	15.564	±	2.500	15.273	±	2.295	0.548
SPAP (mmHg)	22.077	±	7.357	31.727	±	9.586	<0.001*
RA min (ml)	19.795	±	14.886	19.636	±	14.080	0.956
RA max (ml)	41.128	±	24.888	47.455	±	18.444	0.177
RA function (%)	47.564	±	21.688	58.000	±	19.170	0.013*
LA min (ml)	19.103	±	13.439	22.364	±	7.466	0.184
LA max (ml)	32.590	±	19.170	35.273	±	12.875	0.451
LA function (%)	43.974	±	13.904	32.909	±	14.161	<0.001*
A' LA (cm/sec)	7.256	±	1.108	7.727	±	1.376	0.043*
A' RA (cm/sec)	17.103	±	2.119	17.364	±	1.997	0.528

Data were presented as Mean ± SD. * denotes significant change. Abbreviation: TSL: total septal length, Pw Disp: P wave dispersion, LT EMD: left electromechanical dissociation, RT EMD: right electromechanical dissociation, HR: heart rate, S'of RV: systolic myocardial velocity of right ventricle by tissue Doppler imaging,S' of LV: systolic myocardial velocity of left ventricle by tissue Doppler imaging, TAPSE: tricuspid annular plane systolic excursion, SPAP: systolic pulmonary artery pressure, RA min: minimal right atrial volume, RA max: maximal right atrial volume, LA min: minimal left atrial volume, LA max: maximal left atrial volume, RA function: total emptying fraction of the right atrium, LA function: total emptying fraction of the left atrium, A' of LA: atrial filling velocity of the left atrium by tissue Doppler imaging, A' of RA: atrial filling velocity of the right atrium by tissue Doppler imaging.

The assessment of the risk factors for developing arrhythmias after ASDs closure revealed significant difference between arrhythmia and non-arrhythmia groups as regards age ($P < 0.001$), P-wave dispersion ($P < 0.001$), systolic myocardial velocity of RV ($P = 0.003$), right electro-mechanical delay ($P = 0.002$), systolic pulmonary artery pressure ($P < 0.001$), RA function ($P = 0.013$), LA function ($P < 0.001$), and atrial filling velocity of left atrium ($P = 0.043$). On the other hand, there was an insignificant difference between arrhythmia and non-arrhythmia groups regarding defect size, total septal length, device size, PR interval, left electromechanical delay, heart rate, TAPSE, systolic myocardial velocity of LV, minimal and maximal right and left atrial volumes, and atrial filling velocity of RA ($P > 0.05$). Table 3.

Multivariate analysis of the risk factors of arrhythmias after ASD closure showed that age (HR 1.115; 95%CI 1.036−1.199; P = 0.003), P wave dispersion (HR 1.192; 95%CI 1.098−1.294; P < 0.001),

Table 4. Multivariate analysis of the most significant factors affecting atrial arrythmia development after ASD closure.

	Odd. s ratio	95.0% C.I	P-value
Age (Years)	1.115	1.036–1.199	0.003*
Pw Disp (ms)	1.192	1.098–1.294	<0.001*
RT EMD (ms)	0.990	0.784–1.249	0.932
S' of RV (cm/sec)	0.668	0.474–0.941	0.021*
SPAP (mmHg)	1.200	1.036–1.389	0.015*
RA function (%)	1.001	0.966–1.037	0.961
LA function (%)	0.995	0.944–1.049	0.854
A' LA (cm/sec)	1.161	0.672–2.009	0.592

Data were presented as odd's ration and 95% confidence interval.
* denotes significant changes.
Abbreviations: Pw Disp: P wave dispersion, RT EMD: right electromechanical dissociation, S 'of RV: systolic myocardial velocity of right ventricle by tissue Doppler imaging, SPAP: systolic pulmonary artery pressure, RA function: total emptying fraction of the right atrium, LA function: total emptying fraction of the left atrium, A' of LA: atrial filling velocity of the left atrium by tissue Doppler imaging.

Systolic myocardial velocity of RV (HR 0.668; 95%CI 0.474–0.941; P = 0.021) and Systolic pulmonary artery pressure (HR 1.200; 95%CI 1.036–1.389; P = 0.015) were independently associated with the occurrence of atrial arrhythmia after ASD repair. Table 4.

4. Discussion

The results of this study revealed that after three months follow up of patients after transcatheter or surgical closure of ASD, 11 patients out of total 150 patients had supraventricular arrhythmias in the form of frequent PACs (6 patients), AVNRT (2 patients), and paroxysmal Atrial fibrillation (3 patients). Upon comparison between the two groups (arrhythmia & non-arrhythmia), there was a statistically significant difference in age, P-wave dispersion, systolic myocardial velocity of RV, right electromechanical delay, systolic pulmonary artery pressure, RA function, LA function, and atrial filling velocity of the left atrium. Moreover, multivariate analysis showed that age, P wave dispersion, systolic myocardial velocity of RV (S'), and systolic pulmonary artery pressure (SPAP) were independently associated with the occurrence of atrial arrhythmia after ASD repair.

Van De Bruaene et al. performed a retrospective study on 155 patients having follow up for average 40 months after ASD closure. Thirty-nine patients (25.2%) presented with late atrial arrhythmia. Multivariate analysis showed that a mPAP ≥25 mmHg, the presence of atrial arrhythmia before repair, and gender were associated with late atrial arrhythmia. They developed a risk score (0–28 points) to predict atrial arrhythmia free survival for follow-up times ranging from one to 5 years [7]. Also, Park et al., assessed risk factors for new-onset atrial tachyarrhythmia defined as a composite of atrial fibrillation or flutter (AF/AFL) after ASD closure. Nineteen patients out of the total 427 enrolled patients had documented atrial tachyarrhythmia during the follow-up period. Most new-onset atrial tachyarrhythmias were documented within 6 months of closure. In the multivariate analysis, the risk for new-onset atrial tachyarrhythmia was significant in patients with AF/AFL during the closure, deficient posteroinferior rim, and age of closure over 48 years [8].

Moreover, Lelakowska et al. analyzed the clinical history and performed 12-lead electrocardiograms, echocardiograms, and 24-h Holter electrocardiograms in129 patients with atrial septal communication (ASD & PFO), before and six months after closure. They found a reduction in P wave dispersion at 6 months after closure with a reduction in the number of supraventricular and ventricular extrasystolic beats and fewer atrial fibrillation (AF) episodes. Postprocedural AF episodes in patients with ASD were predicted by PWD of 80 ms. This emphasizes that AF/atrial flutter in heart defects (including heart defects with shunts) is caused by atrial wall remodeling, defined not only as the change in the size and the shape, but also as the changes of structure and proportions between muscular and fibrotic tissue, along with changes in metabolism and myocyte electrophysiological properties [9].

Furthermore, Foo et al. performed a retrospective analysis of echo data of 121 adult patients with ASD from 2005 to 2015 performed before surgical or transcatheter closure and within 6–8 weeks, 6 months, and 1-year post closure. The following echocardiographic parameters were selected as indicators of right heart chambers remodeling: right atrial (RA) annulus diameter, right ventricle (RV) inlet dimension, tricuspid regurgitation jet velocity, pulmonary artery systolic pressure (PASP), right ventricle inlet size, tricuspid annular plane systolic excursion (TAPSE), and tricuspid annular peak systolic velocity (TA TDI S'). When compared to baseline parameters, they found a statistically significant decrease in PASP, RV inlet size, RA annulus diameter, and TAPSE for both surgical and device closure groups starting at 6–8 weeks post-intervention and persisting up to 1-year post-intervention [10].

Of note, TA TDI S′ was significantly reduced in the surgical group on the 6–8 weeks as well as 6 months scan compared to baseline but recovered on the 1-year scan. There was no significant drop in TA

TDI S' for the device closure group post-intervention. That meant that post ASD closure patients, the RV function particularly RV long axis contraction (TAPSE) took a few months to 1 year to recover post-surgery. This could also represent the normalization of RV stroke volumes post ASD closure at a reduced functional state [10].

In order to study any effects of age on the amount of remodeling, they subsequently divided the 121 patients into two groups: younger adults with ASD intervention (age less than 40 years old when undergoing intervention) and compared it to older adults (age more than 40 years old). They found that PASP was higher in the older group. This increased pulmonary pressure is likely secondary to exposure to increased flow over longer periods. This might be suggestive of pulmonary vascular changes which persist up to 1-year post-intervention [10].

We did not notice or record any conduction abnormalities or ventricular arrhythmias on follow up at either 1 month or 3 months after ASD closure. The predisposing factors of AV block after ASD closure procedures might be associated with anatomic structures as demonstrated by Jin et al. who found that among the 651 ASD patients who underwent device closure procedures, 7 patients had different degrees of arrhythmia. Types of arrhythmia include sinus bradycardia, atrial premature beats, bundle block, and different degrees of AV block. Also, their results suggested that the ratio of ASO versus ASL showed an intermediate value in predicting arrhythmia occurrence after closure procedures with a cut-off value of 0.576 in the ratio of ASO versus ASL [11].

Furthermore, Chen et al. collected data on all patients with secundum ASD who underwent either surgical or transcatheter closure from Taiwan's National Health Insurance Research Database from 2004 to 2011. Transcatheter closure had a lower occurrence rate of AF than those undergoing surgical closure in post-operation hospitalization. However, there was no significant difference for the long-term follow up period. Moreover, there were no differences in incidence of high degree AV block between the TC and SC groups. They concluded that surgical intervention would affect the new onset of AF in the peri-operation period but not affect the long-term incidence after discharge when compared with transcatheter intervention [12].

The importance of our study is that it guides us to try to avoid certain factors that might increase the risk of post-closure arrhythmias and tailor follow up visits by focusing on these factors for better detection and early management of those arrhythmias if they develop.

The major limitation of this study was the small sample size (especially of the surgical group) which limited its power. Furthermore, the short duration of the follow up (within 3 months), which by far restricted the number of patients who developed arrhythmia after ASD closure. Asymptomatic arrhythmias are very common which could have only been detected by Holter monitoring which could have been valuable in detecting more patients with silent arrhythmic events.

5. Conclusion

Finally, we can conclude that the risk of developing arrhythmias 1 and 3 months after transcatheter or surgical closure of ASD is significantly related to age, P-wave dispersion, systolic myocardial velocity of RV, right electromechanical delay, systolic pulmonary artery pressure, RA function, LA function, and atrial filling velocity of the left atrium. Age, P wave dispersion, systolic myocardial velocity of RV (S'), and systolic pulmonary artery pressure (SPAP) are risk factors.

Author contribution

Conception and design of Study: Nouran Mostafa Mansour, Raghda Ghonimy El Sheikh, Ayman Mohamed Elsaeid. Literature review: Nouran Mostafa Mansour, Ayman Mohamed Elsaeid, Mohammed El sayed El setiha. Acquisition of data: Nouran Mostafa Mansour, Raghda Ghonimy El Sheikh, Ayman Mohamed Elsaeid. Analysis and interpretation of data: Nouran Mostafa Mansour, Raghda Ghonimy El Sheikh, Mohammed El sayed El setiha, Seham Fahmy Badr. Research investigation and analysis: Nouran Mostafa Mansour, Raghda Ghonimy El Sheikh, Mohammed El sayed El setiha. Data collection: Nouran Mostafa Mansour, Mohammed El sayed El setiha, Seham Fahmy Badr. Drafting of manuscript: Nouran Mostafa Mansour, Raghda Ghonimy El Sheikh, Ayman Mohamed Elsaeid, Mohammed El sayed El setiha. Revising and editing the manuscript critically for important intellectual contents: Nouran Mostafa Mansour, Ayman Mohamed Elsaeid, Mohammed El sayed El setiha, Seham Fahmy Badr. Data preparation and presentation: Nouran Mostafa Mansour, Mohammed El sayed El setiha, Seham Fahmy Badr. Supervision of the research: Nouran Mostafa Mansour, Raghda Ghonimy El Sheikh, Ayman Mohamed Elsaeid, Mohammed El sayed El setiha. Research coordination and management: Nouran Mostafa

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Conflict of interest

None declared.

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