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Impact of Cardiac Computed Tomographic Angiography on Diagnostic and Therapeutic Decisions in Patients with Suspected Prosthetic Heart Valve Dysfunction

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Abstract

Introduction: Computed Tomography (CT) scan is a helpful tool to assess the coronary arteries and the great vessels. However, its routine use in the assessment of patients with suspected prosthetic valve dysfunction (PVD) has not been studied thoroughly.

Objective: To determine the impact of routine cardiac computed tomography angiography (CCTA) on diagnostic and therapeutic decisions in patients with suspected PVD.

Methods and results: This was a prospective cohort study that was conducted on 50 consecutive patients with suspected PVD who underwent both 64-slice ECG-gated CT and transesophageal echocardiography (TEE). The gold standard was the intraoperative findings. Surgery was performed in forty-six patients. ECG-gated CT showed findings that were not detected by TEE in sixteen patients (32%) namely aortic root abscess, aortic pseudoaneurysm, paravalvular leakage (PVL), sclero-calcific disruption of sutures as cause of PVL, mechanical prosthesis occluder malfunction, an underlying thrombus as cause of malfunction and finally presence of aortic dissection. Furthermore, CTA findings dictated treatment changes in fourteen patients (28%).

Conclusion: This study demonstrates that ECG-gated CTA has a complementary role to TEE in patients with suspected PVD. CCTA is more accurate in diagnosis of periannular complications (Aortic root abscess and Pseudo-aneurysm) and in delineating their anatomical relation to surrounding cardiac structures. Therefore CCTA can have important role in deciding and planning the method of correction whether surgical or percutaneous and has to be considered after TEE in patients with a high suspicion on PVD.

Keywords: Prosthetic valves, Cardiac CT, Transoesophageal echocardiography

1. Introduction

Heart valve replacement is the second most common cardiac surgical procedure after coronary artery bypass graft surgery [1]. Complications related to prosthetic heart valves (PHV) are not uncommon and are estimated to occur at a rate of 2–3% per patient-year. These complications include thromboembolism, endocarditis, prosthesis-patient mismatch, structural valve dysfunction, and hemolysis [2].

Transthoracic echocardiography (TTE) is the initial assessment of suspected PHV-related complications. However, TTE is limited by image resolution and reverberation artifacts that can lead to missing of periannular complications, vegetations, and paravalvular regurgitation [3–5].
Although Transesophageal Echocardiography (TEE) has a good sensitivity and specificity as compared to TTE, many complications can still be missed especially periannular complications that can elude detection in 30% of patients [3,4].

The main causes behind echocardiographic limitations of TEE are again acoustic shadowing of the PHV which masks adjacent anatomical structures. These missed findings as periannular complications are common (53–55%) and are associated with a mortality of 30–54% [4,6].

The main advantage of Multislice computed tomography (MSCT) scanners is the advanced spatial resolution that promotes high resolution imaging. Computed Tomography (CT) provide morphologic information and functional 4-dimensional (4D) cine-imaging which results in better valvular imaging [7–10].

However, there is a paucity of data on the additional value of cardiac computed tomographic angiography over TEE in the assessment patients with prosthetic cardiac valves, so the aim of this study was to determine the impact of cardiac computed tomography angiography (CTA) on diagnostic and therapeutic decisions in patients with suspected PHV dysfunction.

2. Methods

2.1. Inclusion criteria

All patients with clinically suspected prosthetic valve malfunction (e.g., suspected prosthetic heart valve obstruction, endocarditis or paravalvular leak). Eighty eight patients were recruited. Fifty patients were included in the study, whereas 33 patients were excluded as mentioned in Fig. (1).

2.2. Exclusion criteria

1. The usual contraindications to multislice Computed Tomographic angiography (MSCTA) (i.e., contrast material allergy and pregnancy).
2. Patient whom labs revealed renal impairment. (Renal impairment defined as serum creatinine > 1.3 mg/dl or Estimated GFR < 45 ml/min/m$^2$)
3. Patients with prosthetic heart valves (PHVs) containing cobalt-chrome alloy rings (Björk-Shiley and pyrolytic carbon tilting-disk PHVs) cause severe PHV-related artifacts that prevent diagnostic assessment.
4. Patients presented with prosthetic valve disorders (e.g., PHV obstruction) and hemodynamic instability as congestive heart failure class IV and necessitating emergency surgery.
5. Patients who refused to participate in the study and refused to sign consent.

![Fig. 1. Diagram for enrolled patients.](image-url)
2.3. Study design and population

From March 2016 to March 2018, we prospectively enrolled all patients who presented with suspected prosthetic valve dysfunction (as indicated by symptoms or signs suggestive of prosthetic valve endocarditis or symptoms of congestive heart failure and/or significant hemolysis suggestive of prosthetic valve obstruction or PVL). Patients were referred to the echocardiography laboratory in Cairo University hospital.

All patients were subjected to the following workup on initial presentation:

- Full clinical history with emphasis on age, gender, comorbidities, number of previous heart valve surgeries, duration since last valve surgery was performed (in months), congestive heart failure, fever, sepsis, antibiotic treatment before clinical presentation, and previous valve surgeries.
- Physical examination including heart rate, blood pressure, auscultations for clicks of prosthetic valves (mitral, aortic or both), murmurs of stenotic or regurgitant lesions across prosthetic or native valves.

Laboratory work included complete blood count, Erythrocyte sedimentation rate (ESR), C reactive protein (CRP), Blood culture, Serology for Brucella, Bartonella, Coxiella, Aspergillus, kidney function tests including blood urea nitrogen and serum creatinine.

2.4. Complete transthoracic and transesophageal echocardiography

All echocardiographic studies were conducted and analyzed by certified non-invasive cardiologists with a Philips iE33 ultrasound system and X7-2t transesophageal transducer (Philips Medical Systems, Andover, MA, USA). Standard views for TTE were (parasternal long- and short-axis views, apical 2-, 3-, 4-, and 5-chamber views. Quantification of the cardiac chambers was done according to the American Society of Echocardiography for assessment of cardiac chambers including calculation of aortic and left atrium diameter, left ventricle end diastolic and end systolic volume and diameter, septal and posterior wall thickness, Right sided chamber volume and dimensions [11]. Assessment of prosthetic cardiac valves was done according to the American Society of Echocardiography for transesophageal echocardiography [12].

Assessment of prosthetic cardiac valves was done specifically for better assessment of prosthetic cardiac valves. Transesophageal echocardiography was done for better assessment of prosthetic cardiac valves specifically looking for variables listed in Table (1) [13].

From March 2016 to March 2018, we prospectively enrolled all patients who presented with suspected prosthetic valve dysfunction (as indicated by symptoms or signs suggestive of prosthetic valve endocarditis or PVL). Patients were referred to the echocardiography laboratory in Cairo University hospital.

Table 1. Definitions of infective endocarditis-related findings on TEE and cardiac CT.

| variable | TEE | CT |
|----------|-----|----|
| Vegetation | Intracardiac mass (Oscillating or nonoscillating) on a valve or other endocardial structure or on implanted intracardiac material | Irregular mass (Hypodense, homogeneous) on a valve or endocardial structure or on implanted intracardiac material |
| Perivalvular abscess | Irregularly shaped (inhomogeneous, Thickened) perivalvular area or (echodense or echolucent) mass | Perivalvular collection of liquid density. Thick layer of inflammatory tissue enhanced by contrast media |
| Pseudoaneurysm | Perivalvular echo-free space (Pulsatile) detected with color Doppler | Abnormal cavity close to a valve enhancing concomitantly with cardiac or aortic lumen |
| Prosthetic valve dehiscence | Perivalvular regurgitation (with or without) rocking motion of the prosthesis | Gap between the annulus and the opposing margin of the artificial valve allows visualization of a continuous column of contrast material |

* Surgery was considered the reference standard for both comparing the results of both modalities.
2.5. CT acquisition and image reconstruction

All the cardiac computed tomographic angiography studies were done with a 64-MDCT Toshiba Aquilion scanner (Toshiba Medical Systems Europe B.V. Zoetermeer, The Netherlands) using the protocol: collimation, 0.75 mm; rotation time, 0.5 s; table feed per rotation, 15 mm (pitch, 1.25); and reconstruction parameters 0.75 mm with an interval of 0.4 mm.

For contrast material—enhanced imaging, we planned the acquisition from 2 cm above the carina (including the ascending aorta) to the bottom of the heart to achieve complete imaging of the heart. If desired, the scanning range can be reduced in the craniocaudal direction to reduce radiation exposure.

Injection of 90 mL of non-ionic contrast material was started before scanning at a flow rate of 3.5 mL/s. Other parameters were 120 kV, 100 mAs, 512×512 pixels, and a field of view of 200 mm. Our 64-section multidetector CT protocol was based on retrospectively ECG gated CT aortography protocols.

Raw data were reconstructed into 10 equally spaced datasets within the R-R interval of the cardiac cycle and were sent to dedicated workstations. All reconstructed datasets were loaded simultaneously into the dedicated cardiac analysis software (Vitrea vital image). The imaging planes were aligned parallel with and perpendicular to the valve leaflets as well as in plane with the valve in three perpendicular imaging planes.

For dynamic evaluation, cine images in the plane perpendicular to the valve leaflets were recorded after appropriate alignment and windowing. For anatomic assessment, the best systolic and diastolic reconstruction phases are selected. All examinations were reviewed and discussed by two experienced Cardiologists.

CT study was done on the same day of TEE study and CT Interpreter was blinded to findings of TEE. The proposed report included several items:

- **PHV:**
  - Type: Mechanical, bioprosthesis
  - Position: Mitral or aortic and/or both.
- **Dynamic PHV assessment.**
  - Normal opening and closing angle/presence of rocking motion: CT, opening and closing valve angles were defined by frame-by-frame analysis of a single cardiac cycle. For bileaflet valves, opening and closing angles were measured between the two leaflets in the fully open and closed positions. For single-leaflet valves, measurements of the lesser angle between the disk and the valve strut at full opening and full closure were recorded.
  - A valve was defined as stuck when motion of one valve leaflet was absent. Prosthetic valve obstruction was diagnosed when motion of a leaflet or leaflets was persistently restricted, with a calculated opening angle of more (for bileaflet valve) or less (for disk valves) than the values for a normal valve, as specified by the manufacturer [14].

- **Anatomical PHV assessment.**
  - Presence of thrombus, size and its location.
  - Paravalvular regurgitation: presence, location. We also measured the para-prosthetic anatomical regurgitant orifice area to determine the accuracy and reproducibility of Cardiac CT in assessment of prosthetic paravalvular regurgitation.

The size of the mitral PVL was assessed by measuring the area on the short-axis view. When CT image quality was bad and not assessable for PVL evaluation, PVL was considered to be absent for the purpose of data analysis [15,16].

- Signs of PHV endocarditis listed in Table (1) [17].

2.6. Surgical data

Forty-six of fifty patients underwent cardiac surgery. The indications for surgery were based on the American Heart Association guidelines for the management of patients with valvular heart disease [18]. The surgeons evaluated valve abnormalities by direct visualization, digital inspection, and intraoperative TEE. Surgery consisted of valve replacement or repair in patients with infection limited to the valvular leaflets or of resection of abscess or pseudoaneurysm and reconstruction with patches and valve replacement in patients with abscesses.

The surgical data that were reported by the surgeon during the open heart surgery were considered the gold standard for comparing the diagnostic accuracy of transesophageal echocardiography and cardiac computed tomographic angiography.

2.7. Statistical analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Science; SPSS Inc, Chicago, IL, USA) version 22. Data were described using the mean, standard deviation, in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Categorical variables are presented in numbers (percentages).

Diagnostic and therapeutic changes are expressed in numbers and percentages. Diagnostic accuracy
measures (sensitivity, specificity, positive and negative predictive values).

Diagnostic change has been defined as a major diagnostic change as the novel detection of a Pathology (thrombus, vegetation or abscess/aortic pseudoaneurysm) by CTA not detected by TEE.

Minor diagnostic change was defined as detection of an increased number and/or size of peri-anular extensions (aneurysms/abscesses) or better depiction of the relationship of the perianular extension with relevant cardiac structures such as coronary arteries. Change in the treatment strategy was defined as conversion from conservative to surgical treatment or change of surgical strategy.

2.8. Consent and ethical committee approval

Patient’s written consent was obtained. The design of the work has been approved by Kasr al Ainy Teaching Hospital ethical committees and it conforms to standards currently applied in Egypt.

3. Results

3.1. Patient population

Eighty eight patients with a suspected PHV dysfunction were enrolled. Fifty patients were eventually included in the study as shown in Fig. (1).

Table 2. Population characteristics.

| variable                      | No. (%)                  |
|-------------------------------|--------------------------|
| Mean Age (years)              | 37 ± 12.0                |
| Gender                        |                          |
| Male                          | 32 (64%)                 |
| Female                        | 18 (36%)                 |
| Prosthetic site               |                          |
| Mitral                        | 19 (38%)                 |
| Aortic                        | 18 (36%)                 |
| Both                          | 13 (26%)                 |
| Prosthetic Type               |                          |
| Mechanical                    | 46 (92%)                 |
| Bioprosthesis                 | 3 (6%)                   |
| Both                          | 1 (2%)                   |
| Duration from last surgery    |                          |
| Less than one year            | 32 (64%)                 |
| More than one year            | 18 (36%)                 |
| Blood culture:                |                          |
| Positive                      | 10 (20%)                 |
| Negative                      | 21 (42%)                 |
| Not done                      | 19 (38%)                 |
| Serology:                     |                          |
| Positive                      | 6 (12%)                  |
| Negative                      | 25 (50%)                 |
| Not done                      | 19 (38%)                 |
| Mean Hemoglobin level (g/dl)  | 10.54 ± 2.09             |
| Mean Total leucocytic count (10^3)/cmm | 9.67 ± 5.17         |
| Mean creatinine (mg/dl)       | 0.83 ± 0.25              |
| Mean CRP level (mg/L)         | 59.16 ± 6.89             |
| Mean ESR level (mm/hr)        | 60.93 ± 36.2             |

3.2. Population characteristics

The mean age of the patients included was 37.5 ± 12 years. 64% of our study population were males. Thirty-two (64%) had symptoms within one year from surgery.

Almost all patients included in the study had symptoms suggestive of heart failure, on the other side, more than half of the study population had symptoms suggestive of endocarditis.

Blood culture and serology were done for patients with suspected prosthetic valve endocarditis and were positive in ten (20%) and six (12%) patients respectively. The mean ESR and CRP were elevated in patients with suspected prosthetic IE as shown in Table (2).

3.3. Occluder motion of prosthetic cardiac valves

Occluder motion of prosthetic valves was evaluated by both echocardiography (TTE and TEE) and cardiac computed tomographic angiography as shown in Fig. (2). The intraoperative assessment of occluder motion was considered the gold standard. Sensitivity and specificity of the TEE for occluder motion was 88.8% and 97% respectively, on the other hand, sensitivity and specificity of CT for diagnosing occluder motion were both 100%.

3.4. Vegetation on prosthetic cardiac valves

CT identified vegetation correctly in twelve patients (75%) compared with intraoperative findings, on the other hand TEE identified vegetation correctly in fourteen patients (88%) compared with intraoperative findings as summarized in Table (3).

Sensitivity and specificity of TEE for diagnosis of presence of vegetation was 94% and 100% respectively while the sensitivity and specificity of CT was 75% and 100% respectively.

3.5. Periannular complications

CT diagnosed aortic root abscess in fifteen patients with both sensitivity and specificity of 100%, on the other hand TEE diagnosed aortic root abscess in thirteen patients and missed the diagnosis in two patients with both sensitivity and specificity were 87% and 97% respectively as summarized in Table (3).

CT diagnosed aortic root pseudoaneurysms in five patients with sensitivity and specificity was 100%, on the other hand TEE diagnosed pseudoaneurysm in three patients and missed the diagnosis in two patients with sensitivity and specificity 60% and 100%
respectively (Fig. 3). The aortic root pseudoaneurysm missed by the TEE were anteriorly located along the ascending aorta and were often small in size.

3.6. Prosthetic paravalvular leakage

CT correctly diagnosed 26 patients with paravalvular leakage as summarized in Table (3) and negated the presence of aortic prosthetic paravalvular leakage in one patient that was diagnosed with TEE Fig. (4). In this patient, TEE study was done while the patient was tachycardic and acoustic showing of mechanical aortic prosthesis hindered proper assessment of aortic prosthesis. Sensitivity and specificity of CT for diagnosing PVL is 100%, while the sensitivity and specificity of TEE was 95 and 100%.

3.7. Diagnostic and treatment changes implicated by CT findings

In our study, ECG-gated CT detected findings that were missed by TEE in sixteen patients (32%). This included additional aortic root abscess in four patients (8%), additional aortic root pseudoaneurysm in four patients (8%), vegetation in one patient (2%), and sclero-degenerative change across one occluder of the aortic prosthesis as cause of PVL in another patient (2%) missed by TEE. CT negated the presence of aortic root abscess in one patient (2%). and negated the presence of PVL in another patient (2%) both were detected by TEE.

CT diagnosed occluder malfunction in one patient and underlying cause in another patient both were not detected by TEE. CT diagnosed presence of

| Variables               | Echocardiography | CT     | Accuracy of Echo | Accuracy of CT |
|-------------------------|------------------|--------|------------------|----------------|
| Vegetation              | 14 (TP) 0 (FP)   | 12 (TP) 0 (FP) | 92%             | 91%            |
| Abscess                 | 13 0 2 (FN) 30 (TN) | 15 0 4 (FN) 30 (TN) | 96%             | 100%           |
| Pseudoaneurysm          | 3 0 2 41       | 5 0 41     | 96%             | 100%           |
| Paravalvular leakage    | 26 1 0 19   | 20 0 20   | 98%             | 100%           |

TP: True positive, FN: False negative, FP: False positive, TN: True negative.
aortic arch dissection in one patient (2%) with large aortic root pseudoaneurysm which was not detected by TEE.

ECG-gated CT showed minor diagnostic change in six patients (12%). CT showed better delineation of site and periannular extension of aortic root abscess diagnosed by TEE in four patients (8%).

CT showed better assessment of severity of paravalvular leakage in one patient (2%) and cause of PVL across mechanical aortic prosthesis in another patient (2%).

In this study, ECG-gated CT resulted in change of treatment strategy in 14 patients (28%). The change of treatment strategy included surgical excision of additional aortic root abscess or aortic root pseudoaneurysm in five patients (10%), surgical removal of prosthesis for underlying pathology (vegetation, malfunction due to underlying thrombus or PVL) in four patients (8%), aortic arch replacement with tubular graft and reimplantation of coronaries in one patient (2%) and conservative treatment with antibiotic therapy for small aortic root abscess not detected by TEE in two patients (4%), proper anticoagulation therapy and close monitoring of INR in one patient (2%).

4. Discussion

Our study is the first to evaluate agreement between TEE and ECG-gated CT in determining prosthesis function (Occluder motion) against surgical finding (Reference standard).

Superiority of CT was not only in evaluation of prosthesis occluder malfunction, but also in identifying causes of prosthetic valve malfunction that constitute indications for surgery but were missed at echocardiography or fluoroscopy and this included the presence of thrombus on mechanical mitral
prosthesis which was not detected by TEE in one patient and that was confirmed intraoperatively. The reason for this was due to the small size of the thrombus (7.5 mm) and acoustic shadowing of the mechanical prosthesis which hindered visualization of the thrombus by TEE.

CT diagnosed aortic tissue prosthesis structural valve degeneration and severe calcification (not detected by TEE) in another patient with heart failure symptoms and unexplained elevated gradient across the aortic prosthesis and this patient was referred for aortic bio-prosthesis replacement.

Other studies, Konen et al reported that MDCT is a reliable technique for functional evaluation of bileaflet mechanical valves [19]. LaBounty et al. reported that the opening angle with CT strongly correlates with cinefluoroscopy [20]. In line with our findings, Feuchtner, et al reported high accuracy of CTA for identification of thrombi/pannus using surgery as the reference standard [21].

4.1. Prosthetic valve endocarditis

TEE diagnosed vegetations in fifteen patients and CT diagnosed vegetation in eleven patients. TEE missed diagnosis of vegetation in one patient with mechanical mitral prosthesis as the vegetation was small and located on the ventricular aspect of the prosthesis with acoustic showing hampered its visualization. Most of the vegetation missed by CT were small in size (<3 mm) and mobile and this may be due to the limited temporal resolution of the CT.

CT diagnosed presence of aortic root abscess in fifteen patients, on the other hand TEE diagnosed aortic root abscess in thirteen patients and missed the diagnosis in two patients. The patient (in whom TEE missed diagnosis) had small para-aortic root abscesses that were located along anterior aspect of the ascending aorta and couldn’t be visualized with TEE. In another patient, CT negated the presence of aortic root abscess that was suspected and appeared as a filling defect along the anterior aspect of aortic prosthesis by TEE.

CT diagnosed presence of aortic root pseudoaneurysms in five patients, on the other hand TEE diagnosed pseudo-aneurysm in three patients and missed the diagnosis in two patients. The aortic root pseudo-aneurysm missed by the TEE were anteriorly located along the ascending aorta and were often small in size. In consistent with our findings, Fagman et al concluded that electrocardiogram-gated CT detected vegetations in 7 patients and TEE in 13 patients [17] Habets et al concluded that the addition of complementary CT to TEE increased the sensitivity and specificity for diagnosis of vegetation to 100% [22]. Feuchtner et al. results (close to our results) revealed that the diagnostic performance of CT for the detection of abscesses/pseudoaneurysms...
combined was: sensitivity 100%, specificity 100%. Whereas, the diagnostic accuracy of TEE for the detection of paravalvular abscesses and pseudoaneurysms was: sensitivity 89%, specificity 100%, PPV 100%, and NPV 98% [13]. Gahide et al. reported that CT had a sensitivity of 100% and a specificity of 87.5% for depicting aortic perivalvular pseudoaneurysms [23].

4.2. Paravalvular leakage

CT correctly diagnosed twenty-six patients with paravalvular leakage and negated the presence of aortic prosthetic paravalvular leakage in one patient that was diagnosed with TEE.

In this patient, TEE study was done while the patient was tachycardic and acoustic showing of mechanical aortic prosthesis hindered proper assessment of aortic prosthesis. Sensitivity and specificity of CT for diagnosing PVL is 100%, while the sensitivity and specificity of TEE is 95 and 100%.

In line with our study, Hara et al. reported that there were perfect agreements between MDCT and 2D-TTE, 2D-TEE, or intra-operative findings in aortic prosthetic regurgitation (APR) [15]. Suh et al. reported that diagnostic performance for the detection of PVL for CT, TTE, and TEE were compared with surgical findings as the standard reference with sensitivity and specificity to diagnose mitral PVL 96.9% and 97.8% respectively for CT, 96.2% and 95.8% respectively for TEE [16].

4.3. Diagnostic and therapeutic changes

ECG gated CT revealed diagnostic and therapeutic changes in sixteen (32%) and fourteen (28%) patients respectively. In line with our findings, Habet et al. (included twenty-eight patients) demonstrated that in six out of the 28 (21%) patients [22]. These major diagnostic changes included detection of four additional mycotic aneurysms and two vegetations. MDCT imaging also provided information that resulted in minor additional diagnostic changes in thirteen (46%) patients. Close to our results, Habets et al. demonstrated that treatment strategy changed after CTA compared to clinical routine workup in seven out of twenty eight (25%) patients [22].

Our study didn’t include 3 D echo, however there are specific 3D-based artifacts such as stitching artifacts, dropout, “blurring” or thickening, blooming, and railroad artifacts. Additionally dropout artifacts can mimic valvular perforations and periprosthetic leaks in 3 D echo [24–27].

5. Limitations of the study

The study had a relatively small sample size and some patients didn’t go for surgery. In the non-operated patients, we relied on clinical follow up. Our cohort had a predominance of mechanical valves because of economic reasons as biological valves weren’t readily available for all patients. We realized that the CT scan has limitations of radiation exposure and liability to artifacts in the older generations ball and cage valve, so this study was limited to include mechanical valves with minimal or low artifact on MSCT.

6. Conclusion

ECG-gated CT and TEE are complementary in patients with prosthetic valve dysfunction. CTA is more accurate in diagnosis of perianullar complications (Aortic root abscess and Pseudo-aneurysm) and in delineating their anatomical relation to surrounding cardiac structures. Therefore CTA can have important role in deciding and planning the method of correction whether surgical or percutaneous and has to be considered after clinical routine workup and TEE in patients with a high suspicion on PVD.

Author contribution

Conception and design of Study: Amr Youssef Hassan, Hussien Heshmat Kassem, Hossam Ibrahim Kandil. Literature review: Amr Youssef Hassan. Acquisition of data: Amr Youssef Hassan, Mohamed Ali Salem. Analysis and interpretation of data: Amr Youssef Hassan, Hussien Heshmat Kassem, Marwa Sayed Meshaal, Mohamed Ali Salem. Data collection: Amr Youssef Hassan, Mohamed Ali Salem, Ahmed Shehata Mohamed. Drafting of manuscript: Amr Youssef Hassan. Revising and editing the manuscript critically for important intellectual contents: Hussien Heshmat Kassem. Research investigation and analysis: Amr Youssef Hassan, Hussien Heshmat Kassem, Marwa Sayed Meshaal, Mohamed Ali Salem. Data collection: Amr Youssef Hassan, Mohamed Ali Salem, Ahmed Shehata Mohamed. Drafting of manuscript: Amr Youssef Hassan. Revising and editing the manuscript critically for important intellectual contents: Hussien Heshmat Kassem. Data preparation and presentation: Amr Youssef Hassan, Hussien Heshmat Kassem, Hossam Ibrahim Kandil. Supervision of the research: Hussien Heshmat Kassem, Hossam Ibrahim Kandil. Research coordination and management: Hussien Heshmat Kassem. Funding for the research: Hossam Ibrahim Kandil.

Conflict of interest

No conflict of interest to declare.
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