

# A review of aortic disease research in Malaysia

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## ABSTRACT

**Introduction:** Aortic disease includes conditions such as chronic aortic aneurysms, acute aortic syndromes and congenital aortic abnormalities, amongst others. This paper reviews all research on aortic disease performed in Malaysia and published between 2000-2016.

**Methods:** A literature search was conducted in PubMed, Scopus, MyJurnal and the UKM Journal Repository. The search process was based on a previously published methodology. The medical subject headings (MeSH) search terms used were “aortic”, “aorta” and “Malaysia”.

**Results:** Two-hundred-thirteen papers were identified, of which 60 papers were selected and reviewed on the basis of their relevance. The epidemiology, pathophysiology, clinical presentations, case reports, investigations, treatment and outcomes of aortic disease in Malaysia were reviewed and summarised. The clinical relevance of the studies performed are discussed.

**Conclusion:** The review provided an insight into the pathophysiology, prevalence and epidemiology of aortic diseases in Malaysia, how the condition is managed, and the outcomes of treatment. Limitations of the research performed in Malaysia to date were identified and recommendations for further research and improvement in clinical practice were recommended.

## KEY WORDS:

*Aorta, aortic disease, Malaysia*

## INTRODUCTION

Aortic diseases can be defined as a cluster of a wide range of arterial diseases, which mainly include aortic aneurysms, pseudoaneurysms, atherosclerotic and inflammatory

conditions. Acute aortic syndromes such as aortic dissection (AD), intramural hematoma (IMH), penetrating atherosclerotic ulcer (PAU) and traumatic aortic injury (TAI) also form part of the aortic disease spectrum as do some genetic and congenital abnormalities like Marfan’s syndrome and coarctation of the aorta. Aortic diseases may be diagnosed after a long period of asymptomatic development or having an acute presentation. Acute aortic syndrome is often the first indication of the disease manifestation, which requires swift diagnosis and management to decrease the poor rates of prognosis. Recently, it has been published that the overall global death rate from aortic aneurysms and aortic dissection has increased from 2.49 per 100 000 to 2.78 per 100 000 people between the years 1990 and 2010, with higher rates for men.<sup>1,2</sup>

Conversely, the prevalence and incidence of abdominal aortic aneurysms have declined over the last two decades. However, the burden was found to increase with age, and men are more often affected than women.<sup>2</sup>

## METHODS

This review covers all research studies on aortic disease performed in Malaysia. A review of research carried out in the country on aortic disease is important as the condition may not necessarily be the same as in developed Western countries. The PICO (patients, interventions, comparisons, outcomes) framework for this review is outlined according to respective inclusion and exclusion criteria in Table I as below:

### Literature Search

A literature search was conducted in PubMed, Scopus and a few Malaysian journals such as MyJurnal and UKM Journal Repository. The authors used the medical subject headings (MeSH) search terms, “aortic”, “aorta” and “Malaysia” to

Table I: Patients, interventions, comparisons and outcomes (PICO) framework with inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Patients	Studies on patients in Malaysia with aortic disease.	Studies on patients outside Malaysia with aortic & non-aortic disease.
Interventions	Any medical or surgical intervention specifically treating aortic disease.	Any adjunct treatment methods targeting non-aortic disease.
Comparisons	Treatment interventions performed within Malaysia.	Treatment interventions performed outside of Malaysia.
Outcomes	Not applicable	Not applicable

This article was accepted: 3 September 2018  
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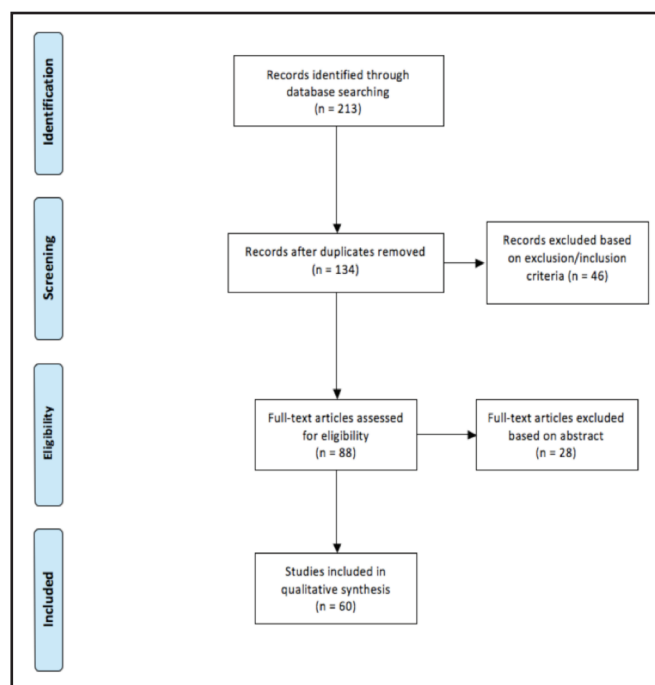


Fig. 1: Preferred reporting Items for systematic reviews flow diagram of study selection.

identify primary articles reporting on patients of aortic disease in Malaysia. The search process for this review was based on the methodology described in the paper “Bibliography of clinical research in Malaysia: methods and brief results” covering the years 1990-2016.<sup>3</sup>

*Eligibility Criteria*

We included all primary articles that reported on one or more multivariable prediction models, tools, or scores used in the studies. Included articles had to report original research involving humans and be written in the English language whereas reviews and letters were excluded. Articles were excluded if the studies were performed outside of Malaysia and not exclusively on aortic diseases. There are no restrictions or limits on age, ethnicity, gender or social background on the patients included in this review. Furthermore, we excluded methodological articles and articles for which no full text was available through a license at our institutes. External validation articles were excluded if the corresponding development article was not available.

*Screening Process*

Initially, a pair of two reviewers (GTJS & PKLZ) independently screened retrieved articles for eligibility on title and subsequently on abstract in order to reduce any form of bias. Any forms of disagreement were resolved by iterative screening rounds. After consensus, full text articles were retrieved and one reviewer (SMK) screened the full text articles and extracted data. In case of doubt, a second (GTJS or PKLZ) or third (JCKM) reviewer was involved.

After screening, 88 papers were identified, of which 60 were selected in agreement with all authors, to be reviewed based on their relevance. A PRISMA flow diagram showing the selection process of articles is presented in Figure 1.

*Descriptive Analysis*

Results were summarised using descriptive statistics. There was insufficient data from the studies available to perform formal quantitative meta-analysis.

**SECTION 1: REVIEW OF THE LITERATURE AORTIC ANEURYSMS**

*Incidence & Prevalence*

It is estimated that aortic aneurysms have a prevalence of 15,299 cases among the total population in Malaysia of approximately 23 million.<sup>6</sup> Following that, Malaysia was found to be one of the three countries within Asia with the highest mortality rates and disability-adjusted life years (DALYs) from aortic aneurysms together with Brunei and Oman respectively. The annual mortality rate in Malaysia was 5.2 per 100,000 while the Annual Years of Healthy Life Lost was 73.4 per 100,000 in the year 2013.<sup>7-9</sup>

A study was performed in the University Malaya Medical Centre to determine the number of fatalities due to rupture of aortic and intracranial aneurysms in autopsies, thus to determine the pattern of deaths relating to ethnicity, age group, sex and correlation with its known risk factors and medical history. A total of 29 deaths were found due to rupture of aneurysms in autopsies from 1996 to 2005. Aneurysms were found to contribute to 0.005% of deaths during that period.<sup>11</sup>

*Ethnicity*

All races and ethnicity in Malaysia are generally affected by aortic aneurysms.<sup>10</sup> However, there may be differences in terms of susceptibility among the 4 main races in the nation. In a study by Murty et al. done in the state of Sarawak, aortic aneurysms were more common in the Chinese, contributing 69% of cases, followed by Malay (17%), Indian (7%) and others (7%).<sup>11</sup>

*Age & Gender*

The incidence rate for the at-risk male population older than 50 years was 25.6/100,000. The incidence rate reached 78.3/100,000 for males older than 70 years. The incidence rate for females older than 50 years was 7.6/100,000 and for those older than 70 years it was 18.7/100,000.<sup>10</sup> It generally affects the middle age groups (60%) with sex ratio of M:F = 3:1.<sup>11</sup>

*Risk Factors/Correlation*

Abdominal aortic aneurysm (AAA) is an important under-diagnosed vascular pathology. As it shares common risk factors with coronary arterial disease (CAD), Leong et al. attempted to establish a link by screening 102 patients with CAD at Queen Elizabeth Hospital, Sabah for the prevalence of AAA among them. However, a significant association between AAA and CAD could not be identified in the study, which suggests that CAD may not be a strong risk factor for AAA. Risk factors profile is as follows: hypertension-68.6%, smoking-56.9%, hypercholesterolemia-52.9%, diabetes mellitus-35.3% and history of stroke-5.9%. Atherosclerosis was noted in 57% and obesity in 59% of cases, thus depicting a satisfactory correlation. 47% of the total cases had possessed one or more risk factors such as hypertension, obesity, alcohol consumption and smoking.<sup>12</sup> In another

study in Sarawak, smoking, hypertension or respiratory disorders were present in more than 40% of the patients.<sup>10</sup>

#### *Pathophysiology*

Aortic aneurysms typically form due to abnormal weakening of the aortic wall and failure of the major structural proteins of the aorta, namely elastin and collagen. They are known to comprise of dilatation in all layers of the vessel wall but tend to develop after degeneration of the media. This may eventually lead to widening of the vessel lumen and loss of structural cohesion. The failure of the aortic wall and expanding growth in aorta diameter may lead to rupture of the inner layer due to excessive blood pressure and consequently, the blood flows into the space between the lumen and epithelial layers, forming a thrombus.<sup>13</sup> According to the US National Heart, Lung, and Blood Institute, the mechanisms that are vital in the development of aortic aneurysms include proteolytic degradation of aortic wall connective tissue, inflammation and immune responses, biomechanical wall stress and molecular genetics.<sup>14</sup>

#### *Biomechanical Wall Stress*

In this review, the majority of Malaysian studies have explored particularly towards the aspect of biomechanical wall stress in the pathophysiology of aortic aneurysms. One method to stratify this is with the use of fully coupling fluid structure interaction analysis of aortic aneurysms. In a study done in Universiti Teknologi Malaysia, Giurma et al., investigated the effects of three geometry parameters using fully coupling fluid structure interaction analysis, which namely are the maximum aneurysm diameter, aneurysm length and length of the distal neck on the flow pattern and stress distribution.<sup>15</sup> The study demonstrated that those parameters affected the size and location of vortices and the flow direction, thus denoting its potential contribution towards the prediction of maximum stress in aortic aneurysms.

Biomechanical wall stress further instigates the consideration of the risk of rupture in those with advanced levels of aneurysms. This component of its pathophysiology is highly investigated by researchers and numerical modellers who have been contributing to the prediction of this rupture. A recent study also done in Universiti Teknologi Malaysia had explored the effect of different physiological conditions on the risk of rupture using a model to simulate the shape of an advanced level of aneurysm.<sup>16</sup> Patients with advanced level aneurysms were observed to have vortex formation as the flow reaches late systole, in the distal region. This process increases the risk of rupture due to the high fluctuation of wall shear stress in this area. For instance, high blood pressure under exercise conditions approximately doubles the risk for rupture as compared to normal blood pressure at rest.

#### *Flow Dynamics & Computational Modelling*

Clinical applications of computational modelling are a fundamentally new approach in medical treatment planning and the development of predictive methods. In the case of cardiovascular disease, these methods enable the risk prediction of rupture and to determine the optimal hemodynamic conditions in patients. In a study done in

Universiti Teknologi Malaysia, Paramasivam et al., presented a computational simulation to be used in predictive medicine, especially in the diagnosis and treatment of AAAs.<sup>17</sup> The computational application was based on the three-dimensional finite element method. A typical fusiform AAA model was utilised to study the flow effects, flow-induced wall shear stresses and pressure, all of which play an important role in assessing the hemodynamic in AAAs. A similar study on computational modelling also investigated a mixed velocity-pressure (v-p) finite element method that solves the pulsatile blood flow in arteries.<sup>18</sup> This process and method is applied to model biological flows that are important in predicting growth and rupture risks in abdominal aortic aneurysms (AAA).

The numerical results were used to quantify clinically relevant flow dynamics that play a significant role via computational modelling for assessing AAAs.

Flow dynamics have been investigated in model aneurysms under physiologically realistic pulsatile flow condition via computational modelling techniques.<sup>19</sup> The presence of flow recirculation at the area of abdominal aortic aneurysm (AAA) yields unpredictable failure of the aneurysmal wall. It is closely linked to hemodynamic factors such as pressure and velocity distribution, which have significant roles in aneurysm growth and rupture. Researchers at Universiti Tun Hussein Onn and Universiti Teknologi Malaysia investigated the influence of hemodynamic factors using a computational fluid dynamic (CFD) method on a virtual AAA model.<sup>20</sup> The results demonstrated the formation of vortices to be observed at the aneurysm bulge. These vortices are formed at the aneurysmal region, which are consequently destroyed rapidly by flow recirculation. This phenomenon will lead to an increase in the likelihood of aneurysm growth and rupture. In addition, another study identified that flow in larger models become increasingly unstable compared to smaller models.<sup>19</sup> It was also noted that these unstable flow fields were more significant towards the distal half of the bulge models. This increases the intensity of turbulent flow fields in larger models, which may contribute significantly to wall shear stress magnitude and subsequently contributing to higher rupture risks.

## **CASE REPORTS**

### *Abdominal Aortic Aneurysms*

The diagnosis of ruptured abdominal aortic aneurysms (AAA) is quite commonly delayed or initially missed. Patients tend to present with atypical manifestations in the absence of the classical diagnostic triad of abdominal and back pain, hypotension, and a pulsatile abdominal mass. A local case report had described an elderly patient who underwent an urgent inguinal exploration of a possibly strangulated left inguinal scrotal hernia.<sup>21</sup> He was found to have inguinal extension of a retroperitoneal hematoma secondary to abdominal aortic aneurysm rupture. Familiarity with atypical manifestations and constant vigilance may allow earlier and accurate diagnosis, management and possibly a favourable outcome.

### *Thoracic Aortic Aneurysms*

Norbert Ortner first described hoarseness due to left recurrent laryngeal nerve paralysis in 1897. Various cardiopulmonary and thoracic arch aorta pathologies associated with left recurrent laryngeal nerve palsy have been described over the last 100 years and has been known as cardio-vocal syndrome. Zaharudin et al. presented seven cases of Ortner's syndrome due to thoracic aortic aneurysm with compression of the left recurrent laryngeal nerve and resultant hoarseness.<sup>22</sup> Unilateral vocal cord palsy secondary to thoracic aortic aneurysm is a rare presentation in the aortic aneurysm spectrum. A direct compression of the enlarging thoracic aneurysm on the left recurrent laryngeal nerve causes neuronal injury of the nerve, which manifests as hoarseness. In Malaysia, Jaafar et al. presented a case report of rare unilateral vocal cord palsy in a 60-year-old healthy gentleman caused by a large thoracic aortic aneurysm.<sup>23</sup> Another local case report described a similar case of an 80-year-old man with a two-year history of voice hoarseness secondary to left vocal cord paralysis.<sup>24</sup> The CT scan had revealed a saccular thoracic aneurysm compressing the left recurrent laryngeal nerve. These unique presentations have a sinister underlying pathology, which might be delayed or misdiagnosed.

Thoracic aneurysms were found to not only affect the recurrent laryngeal nerve but occasionally compresses the phrenic nerve as well, causing hemidiaphragm paralysis as another feature in patients. A case report by Akhtar et al., described a patient with chronic chest pain, dysphagia, and voice hoarseness.<sup>25</sup> The chest radiograph revealed lobular enlargement of the superior mediastinum and elevated right hemi-diaphragm while contrast-enhanced computed tomography of the thorax revealed a giant partially thrombosed aneurysm originating from the ascending aorta and extending into the aortic arch.

Acute injury and blunt trauma to the thoracic aorta is also life threatening and can potentially lead to different types of aortic injury such as the formation of false aneurysms or pseudoaneurysms. In Malaysia, Yusof et al., reported two cases of pseudoaneurysms due to acute traumatic aortic injury from motor vehicle accidents. Chest radiograph is the initial radiological investigation in chest trauma as it is able to help identify emergency situations of haemothorax and pneumothorax. However, CT scans are the preferred imaging modality to exclude or confirm thoracic injury.<sup>26</sup> Another rare case of pseudoaneurysm was reported locally which was associated with an aorto-oesophageal fistula. The patient had presented with chest pain and haematemesis one week after swallowing a fish bone. Oesophagogastroduodenoscopy and computed tomographic angiography findings were consistent with oesophageal perforation, proximal descending aortic pseudoaneurysm, and aorto-oesophageal fistula. Thoracic endovascular aortic repair was performed but patient died from severe mediastinal sepsis. It was concluded that early surgical intervention and broad-spectrum antibiotic therapy are crucial in preventing life-threatening mediastinal infection.<sup>27</sup>

Other associated conditions include pulmonary atelectasis, which may be caused by endobronchial lesions or by

extrinsic compression of the bronchus. Although the thoracic aorta is closely associated with the bronchus, pulmonary atelectasis due to an aortic aneurysm is rare. Most patients are asymptomatic, and the aneurysms are often detected on imaging for other indications. Yap et al., reported a case of a 76-year-old hypertensive patient who had pulmonary atelectasis due to an extrinsic compression from a descending thoracic aortic aneurysm, indicating these cases do exist within the Malaysian context.<sup>28</sup> Other relatively uncommon symptoms include dysphagia lusoria in the event of vascular causes. A local case report described a patient presenting with dysphagia caused by a saccular aneurysm of the descending thoracic aorta.<sup>29</sup>

### *Other Aneurysms*

An unruptured right sinus of Valsalva aneurysm leading to severe obstruction of the right ventricular outflow tract is uncommon. A similar sample case in Malaysia was reported to have presented initially with exertional dyspnoea. Surgery should be considered for extremely large aneurysms or for progressive enlargement of the aneurysm on serial evaluation.<sup>30</sup>

Other types of aneurysms include mycotic aneurysms, which have an association with infection. *Burkholderia pseudomallei* in particular, associated with mycotic aneurysm is a rare presentation and is found in 1-2% of cases related to high rates of morbidity, mortality, and relapse. Ding et al. reported a case of a 56-year-old man with a history of abdominal pain and high-grade fever who was found to have a left non-dissecting infrarenal mycotic aortic aneurysm by abdominal computerised tomography scan.<sup>31</sup> These rarely observed cases are occasionally present within the Malaysian community.

### *New Investigations*

Modern clinics and hospitals require accurate prediction tools. A local study reviewed the importance and trends of data mining methods and frameworks on hemodynamic predictions in abdominal aortic aneurysm (AAA).<sup>32</sup> These explorations enable the potential for statistical prediction of rupture potentials of aneurysmal patients and provide an alternate solution for substituting computational modelling. Other innovative techniques are observed when Hosseini et al., proposed a technique for automatic segmentation of abdominal aortic aneurysms, which integrates information of the morphological properties of aortic lumen to segment the aorta.<sup>13</sup> Exploitation of such automatic techniques enables greater precision in pre and post-treatment evaluation of the disease.

However, on a molecular level, prior studies have shown the correlation between MMP-9 concentration levels with AAA suggesting the probability of its utility as a biomarker in AAA disease. Affirul et al., from the Universiti Kebangsaan Malaysia conducted a prospective controlled trial to identify the correlation between MMP-9 concentration levels with AAA disease and assess its function as a biomarker in the local hospital setting.<sup>33</sup> They discovered no correlation of MMP-9 levels with age, gender, or other risk factors. It was concluded that the utility of MMP-9 as a diagnostic test is limited due to low sensitivity and specificity. An elevated

MMP-9 has limited use to predict the presence of AAA while a normal MMP-9 level is insufficient to determine the absence of AAA.

## MANAGEMENT & TREATMENT

### *Open Repair*

Abdominal aortic aneurysms (AAA) repairs are routine operations with low mortality in the developed world. There were few studies on the operative management of AAA in the Asian population as vascular surgery was a relatively new field in Asia.<sup>34-35</sup> Yii et al., conducted a study to review the outcomes of all the AAA patients seen by a single surgeon in Borneo on completion of training with no previous experience in the condition. A total of 151 patients with AAA repair from a prospective database between 1996 and 1999 in the state of Sarawak was analysed. It was concluded that highly motivated and adequately trained surgeons, despite having little previous experience, could repair AAA with a safe approach.<sup>36</sup> Prior to this in Sarawak, there had been no attempted elective AAA repair and no patient with ruptured AAA survived an attempted repair.

The author then proceeded to conduct an audit of AAA surgeries and evaluated the application of the Portsmouth Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (P-POSSUM) in the Sarawak for standard of care.<sup>37</sup> Eighty-five consecutive surgical patients with AAA from a prospective vascular database from 1996 to 2001 were analysed. No significant difference was found between the predicted and observed rates of death for elective, urgent and emergency AAA repairs. The observed rates of death were also comparable to P-POSSUM predicted rates of death in the various risk range groups, thus validating its easy use and applicability as a comparative vascular auditing tool in Asia.

In the northern region of Malaysia, a prospective study of all infra-renal abdominal aortic aneurysm (AAA) repairs in Penang between 1997 to 2000 was carried out.<sup>38</sup> Most infrarenal AAA repairs were performed as emergency operations compared to electives. Mortality rate was 31.5% and the primary reason was the lack of operating time available for urgent operation and for treatment of concurrent disease states. Pulmonary complications were commoner than cardiac complications possibly related to the urgent nature of the operation, smoking or history of pulmonary tuberculosis.

In adverse cases, the repair of an AAA in a renal transplant recipient poses many different challenges due to warm ischaemia to the grafted kidney. Naresh et al., presented a case of an elderly patient who had a previous renal transplant with AAA. To reduce the effects of ischaemia on the transplanted kidney, an axillo unifemoral bypass was performed prior to the aneurysm repair, thus allowing continued perfusion to the transplanted kidney. AAA repair in a renal transplant patient is a safe procedure if renal protection is employed. Despite the many methods used, there has been no single technique, which has been proven superior to the others due to the small numbers of studies and the design of comparative studies would be impossible.<sup>39</sup>

### *Endovascular Aneurysm Repair*

Endovascular aneurysm repair (EVAR) was first introduced as a minimally invasive procedure as an alternative to the conventional open surgical repair and has become an acceptable treatment option for patients with infra-renal aortic aneurysms (AAA).<sup>40</sup> This surgical approach makes local anaesthesia possible as an anaesthetic technique and eliminates the potential risk of mortality and morbidity of general anaesthesia.<sup>41</sup> Syed et al., reported on four cases of infra-renal abdominal aortic aneurysm in Hospital Kuala Lumpur, Malaysia who underwent EVAR with local anaesthesia and controlled sedation.<sup>42</sup> This study demonstrated that EVAR with LA had an excellent outcome in terms of safety, reduced length of post-operative stay, reduced ICU admission, reduced postoperative monitoring and postoperative morbidity. Similarly, another local case report described a patient presenting with ruptured AAA, eight months after treatment for a ruptured thoracic aortic aneurysm.<sup>43</sup> Due to the patient's compromised respiratory system, he underwent endovascular aneurysm repair (EVAR) under local anaesthesia (LA). This case showed the importance of a comprehensive knowledge of available treatment options and the discernment to choose the most suitable option for each patient is essential to reduce post-operative mortality and morbidity. A single institutional review of 16 patients from 2009 to 2014, who had endovascular stent grafts inserted for pseudo-aneurysms of the thoracic aorta, abdominal aorta and iliac arteries in Hospital Kuala Lumpur showed that endovascular stent graft repair for pseudo-aneurysm is a more viable option compared to open surgery; it is less invasive, has lower operative morbidity and fair outcomes.<sup>44</sup>

However, some patients may not be suitable for such techniques on the basis of unfavourable aortic anatomy. The main limitation to a successful EVAR procedure is due to the presence of an unsuitable infra-renal aortic neck, which mainly includes the presence of thrombus or severe calcification in the neck.<sup>45</sup> The problems mentioned above, which restrict the endovascular repair of AAA, could be solved by using a fenestrated stent-graft. Similar to conventional endovascular repair, imaging modalities play an important role and helical CT angiography has been regarded as the preferred imaging modality in both pre-operative planning and post-operative follow-up.<sup>46</sup>

### *Thoracic Endovascular Aneurysm Repair*

Conventional open repair for thoraco-abdominal aortic aneurysms is often associated with high rates of morbidity and mortality. Spinal cord ischemia, renal failure and bowel ischemia are some examples of complications that may follow after the procedure. With the recent advocacy of endovascular stent technologies, many novel approaches have been defined to reduce these complications, namely fenestrated stent grafts and hybrid procedures. Such procedures are observed in Malaysia where Kumaraguru et al., performed a hybrid procedure on a case of pseudoaneurysm of the descending thoracic aorta in Hospital Kuala Lumpur.<sup>48</sup> Another study was also conducted on the thoracic endovascular aneurysm repair (TEVAR) procedure but advocated controversy in their emergency approach to mycotic aneurysms.<sup>49</sup> Mycotic descending thoracic aneurysm

with aortobronchial fistula is a rare condition associated with high mortality. The risk of graft infection should be considered as well as the unknown long-term effects of the endovascular stent procedures.

Other than aneurysms, TEVAR has been shown to be effective to treat traumatic blunt injuries to the thoracic aorta in Malaysia. Blunt trauma to the thoracic aorta occurs typically in a high-velocity or high-impact motor vehicle accident where the isthmus is the most common location for rupture, followed by the ascending aorta or aortic arch and the distal thoracic aorta. Shaari et al., reported a series of five local patients with traumatic blunt injury to the thoracic aorta, secondary to high-velocity MVA who underwent TEVAR and thoracic stent graft procedures in the Vascular Unit, HKL from 2008-2011. TEVAR offers better post-operative recovery as it is minimally invasive, which essentially does not require a large incision such as with thoracotomy. This is advantageous in trauma patients with concomitant injuries such as pulmonary contusion, where a thoracotomy wound could prolong their recovery time.<sup>50</sup>

Despite the known benefits of TEVAR, the incidence of infection following TEVAR is present but low. In Malaysia, the first and only case report of post-thoracic endovascular aortic repair was described with *Streptococcus viridans* graft infection.<sup>51</sup> The patient underwent TEVAR for dissecting thoracic aneurysm with spinal ischaemia and had an eventful recovery in the intensive care unit. Three months later, he presented with persistent chest discomfort and fever and computed tomography of the thorax revealed evidence of graft infection with *Streptococcus viridans* according to the blood culture. Caution and care should be considered in the event of such a rare complication post-operatively.

#### *Conservative Treatment*

Salmonella septicaemia is expected to result in Salmonella aortitis in affecting the elderly as they have a higher incidence of atheromatous plaques. Complete excision of the affected aorta is the key to curative treatment, however, surgical procedures are associated with significant mortality rates and risks of recurrent infection.<sup>52</sup> Abu Bakar et al. reported a local case of mycotic aneurysm secondary to Salmonella with paraortic and psoas abscess that was treated conservatively and remained stable six months post-discharge.<sup>53</sup> In the event surgery is refused such as this, long-term antibiotics may improve survival in patients as an alternative treatment.

#### *Other Treatment*

Pseudo-aneurysms of the internal iliac artery is a rare condition that may typically present with pain over the lower abdomen which may radiate to the back. Guru et al., demonstrated another treatment method other than open and endovascular repairs to treat such a case.<sup>54</sup> Initial attempts to embolise the pseudoaneurysm had revealed a connection between the pseudoaneurysm and the interanal iliac vein where foam was being dislodged into the venous system. Subsequently, a vascular plug was used and found that post-procedure, there was no more flow into the right internal iliac artery pseudoaneurysm.

Hussein et al., also presented a case of pseudo-aneurysm but involving the infra-renal aorta revealed by computed tomography scan. The patient underwent repair of the pseudoaneurysm with an in situ silver-coated bifurcated Dacron graft. The postoperative recovery was uneventful and he remained well up to 12 months of follow-up. This is the first and only case in Malaysian literature where an in situ silver-impregnated vascular graft was successfully used in treating a tuberculous pseudoaneurysm.<sup>55</sup>

Last but not least, Eng et al., introduced another treatment method for a case of a patient with both large aneurysm of the aortic arch and severe coronary artery disease. The technique involved a combination of repair of the aortic arch aneurysm and a coronary artery bypass grafting via a modified clamshell incision using deep hypothermic circulatory arrest and retrograde cerebral perfusion. The results were favourable where the patient made an uncomplicated postoperative recovery, indicating the potential for future considerations of this approach in Malaysia.<sup>56</sup>

## **AORTIC DISSECTION**

Aortic dissection is a common vascular disease, which has high morbidity and mortality if it presents with acute onset. It is characterised by the separation of the aortic wall layers into true and false lumens, which may lead to serious complications including aortic rupture, myocardial ischemia, hypotension/shock, end organ ischemia and death.<sup>57</sup> The condition can be classified into Stanford type A dissection, which involves the ascending aorta and Stanford type B dissection, which only involves the descending aorta.<sup>58</sup> Factors which may predict a complicated Stanford type B dissection and the need for TEVAR include larger flow through the false lumen and the size and site of the entry site.<sup>59</sup>

#### *Pathophysiology*

It has been known that the progression of Stanford type B aortic dissection is closely associated with vascular geometry and hemodynamic parameters. A local study was carried out at the University of Malaya to investigate the impact of an additional re-entry tear on the flow, pressure and wall shear stress distribution in the dissected aorta. It was shown that the presence of an additional re-entry tear provided an extra return path for blood back to the true lumen during systole, and an extra outflow path into the false lumen during diastole. The presence of this additional path leads to a decrease in the false lumen pressure, particularly at the distal region. Meanwhile, the presence of this additional tear causes no significant difference on the time average wall shear stress distribution except at regions adjacent to re-entry tear.<sup>60</sup>

#### *Case Reports*

The presence of more than one arterial dissection in a young patient without atherosclerosis is extremely rare. Kosai et al., reported a Malaysian case of spontaneous multiple acute arterial dissections occurring in an adult male patient.<sup>61</sup> Stanford B aortic dissection and a separate dissection extending from the bifurcation of the right common iliac artery to the right common femoral artery was revealed on

computed tomographic angiography. A two-stage hybrid procedure involving a combination of open and endovascular surgery was performed. The rarity and danger of this condition warrants a high index of suspicion for early diagnosis and prompt intervention.

Another rare presentation includes a case of delayed ascending aortic dissection following coronary artery bypass surgery, which is a lethal complication. A local case was reported to have a delayed acute Stanford A aortic dissection following an off-pump coronary artery bypass surgery in a pre-existing chronic type B disease.<sup>62</sup> Such a case of an iatrogenic acute aortic dissection poses a significant challenge and dilemma in choosing the best technique for coronary revascularisation in this group of patients.

Ruptured dissecting aortic aneurysm tend to commonly occur in men within the 40-70 years age group, and most commonly is associated with atherosclerosis. Uncommon causes are previous heart surgery, connective tissue disorders and aortitis. Despite its rarity, *Clostridium* spp aortitis progresses very rapidly with a significant mortality rate, typically occurring within 48 hours of infection. Subramaniam et al., reported a local case of sudden death due to clostridial aortitis causing ruptured aortic dissection in an adult female.<sup>63</sup> This case demonstrated the essential features of infectious aortitis caused by *clostridium* spp, which requires a high index of suspicion for rapid diagnosis and management.

#### Investigation

Early diagnosis, characterisation of the type of dissection and identification of intimal tear is vital for patient management. CT angiography, with multi-slice CT imaging technique, is the method of choice for the diagnosis of aortic dissection. There is a substantial additional value of 3D visualisation, using virtual intravascular endoscopy, for the assessment of aortic dissection when compared to the conventional 2D views. It is expected that the intraluminal findings will assist radiologists to accurately diagnose and treat patients with suspected aortic dissection.<sup>64</sup>

False lumen patency has been recognised as the main determinant of aneurysmal dilatation and rupture, whereas complete thrombosis has been proven to improve disease outcomes. Naim et al., conducted a study to use the evolution of vortical structures throughout a cardiac cycle and its interaction with the wall shear stress to demonstrate the potential mechanism for the formation of thrombus and predict its location in an aortic dissection.<sup>65</sup> A three-dimensional patient-specific Stanford type B aortic dissection domain was generated from computed tomography angiographic images. The formation and thickening of thrombus was predicted to very much likely occur at the posterior false lumen wall, distal to the entry tear region. It was also concluded that the percentage of flow entering the false lumen increased with a correlating increase in the false lumen size, leading to a downward shift of the areas of thrombus formation along the false lumen wall.

#### Management

Acute aortic dissection is a life-threatening condition, warranting prompt diagnosis and treatment. Its management incorporates multidisciplinary expertise from the medical, surgical and intensive care. If left untreated, the mortality rate of acute ascending aortic dissection exceeds 50% within 48 hours and 80% within two weeks, with a 5-year survival rate of 19%. The most common cause of death in untreated acute aortic dissection, regardless of aetiology, is aortic rupture. Despite its high-risk nature, the condition has been fairly managed within Malaysia as shown by Ramzisham et al. who reported the successful management of cases at the two extreme ages of acute aortic dissection.<sup>66</sup> While type A aortic dissection patients are usually treated surgically, the optimal treatment strategy for type B aortic dissection is generally by conservative medical treatment of blood pressure control. More recently, TEVAR has been used for complicated Stanford Type B dissections with satisfactory results. Although aortic diameter measured by CT angiography has been utilised as a guide to predict dilation in aortic dissection, hemodynamic parameters, geometrical factors, and the composition of the aorta wall are recognised to significantly affect disease progression. Due to the limitations of cardiac imaging modalities, numerical simulations have been extensively used for the prediction of disease progression and therapeutic outcomes.

A Malaysian comprehensive overview on the applications of numerical simulations in aortic dissection has been presented, focusing on biomechanical factors leading to tear initiation and progression, as well as prediction of treatment outcomes.<sup>67</sup> Both idealised geometry and patient-specific models have been developed, with the help of various medical imaging modalities. Vessel wall properties and complicated geometrical and biomechanical factors are found to be closely correlated with tear initiation and progression. With various surgical treatments such as endovascular stent graft placement, bypassing the dissected aorta, fenestration and dynamic pressure will be substantially reduced.

#### CONGENITAL AORTIC CONDITIONS

A right-sided aortic arch is a rare anatomical variant present in about 0.1% of the adult population.<sup>68</sup> It often results from the persistence of the right fourth aortic arch and involution of the left and can be associated with an aberrant left subclavian artery arising from Kommerell's diverticulum. It is usually asymptomatic and diagnosed incidentally during adult age.

Coarctation of the aorta (CoA) is a congenital anomaly presenting by the combination of upper body hypertension and weak or absent femoral pulses, which accounts for 5%-8% of all congenital heart defects. If left untreated, most patients with significant CoA will have varying degrees of morbidity (e.g. hypertension, stroke, collateral formation and ventricular hypertrophy), possibly even mortality.<sup>69</sup> Surgery has been the mode of therapy for children born with congenital CoA.<sup>70</sup>

*Case Report*

In Malaysia, Mubarak et al., presented an incidental case of a right-sided aortic arch revealed by chest radiograph. Computed tomography of the thorax revealed a right-sided aortic arch with aberrant left subclavian artery originating from Kommerell's diverticulum. The patient was generally asymptomatic and there was no particular association with cardiac anomalies. However, some minor symptoms are likely to be due to atherosclerotic changes of the anomalous vessels, dissection, and aneurysm with compression of adjacent structures causing dysphagia and dyspnoea. In this reported case, there were no symptoms related to the vascular variations and therefore no surgery was indicated.<sup>71</sup>

*Investigation*

The advocacy of multi-slice computed tomography has revolutionised the performance of body CT and allowed the development of CT angiography (CTA). The newer generation of multi-detector scans has allowed for faster scanning times with no respiratory mis-registration at peak vascular opacification following peripheral contrast injection. The volume of data obtained from these scans can be further manipulated to generate two-dimensional and three-dimensional images with no increase in radiation. Hence, CTA has gained popularity and importance as the alternative diagnostic tool especially where conventional angiography is inadvisable. A case report by Harun et al., described a case of an infant with coarctation of the aorta and hypoplastic aortic arch, in which CT angiography was used to pinpoint the diagnosis.<sup>72</sup> It was concluded that spiral CT angiography is proven to be a reliable method in demonstrating anomalies of the aorta in a paediatric patient. It is also a practical clinical test that may be an alternative to cardiac catheterisation, especially in delineating extracardiac vascular structures.

*Management*

Surgical intervention has been recognised as the gold standard of treatment for children born with coarctation of the aorta. However, a local case report demonstrated stenting during catheterisation as an alternative nonsurgical treatment option for patients with CoA.<sup>73</sup> Angiography and measurement of pressure gradients were performed before and after stent implantation to ensure good treatment outcomes. The patients' treatment outcomes were good, with a significant reduction in pressure gradients across the narrowed segments. It is anticipated that the therapeutic treatment of CoA through the use of stents during interventional cardiac catheterisation represents a new paradigm of treatment for older patients with CoA, a condition that previously required surgical management. With increased expertise, improved techniques and better devices, it is envisaged that stenting for CoA will become a desired treatment option in suitable patients in the future.

Increased morbidity and shortened life span of infants born with coarctation suggest that the congenital abnormality should be treated early. Unfortunately, studies in many institutions have shown that the diagnosis of CoA is often missed. Long-term follow-up of adult patients following surgical intervention for CoA reveals ongoing risks; hence, less invasive endovascular therapy becomes an alternative

approach. Hafil et al., performed a literature review to compare the results of endovascular therapy with surgical techniques to repair adult with coarctation of the aorta.<sup>74</sup> Surgical therapy was associated with a very low risk of restenosis and recurrence, whereas endovascular therapy had a much higher incidence of restenosis and the need for repeated interventions. Surgical therapy was concluded to be superior compared to other modes of interventional therapy for adult with CoA, and it remains as current mode of therapy for adult with CoA.

**OTHER ACUTE AORTIC CONDITIONS***Case Report*

Mid-aortic syndrome is a rare clinical condition that is characterised by coarctation involving the distal thoracic or abdominal aorta and its major branches.<sup>75</sup> Renovascular hypertension is the main symptomatic presentation of this disease among children and adolescents. Yubbu et al., reported a case of a young female child with recurrent abdominal pain and symptomatic hypertension. Due to significant left ventricular systolic dysfunction and uncontrolled hypertension, percutaneous balloon angioplasty was performed to treat the coarctation. This is the first reported case of mid-aortic syndrome in Malaysia.<sup>76</sup> Penetrating atherosclerotic ulcer (PAU) is another rare condition that contributes to part of the acute aortic syndrome spectrum. Its incidence ranges from 5-10% within that spectrum, with the majority of cases detected as incidental findings. It is notably an uncommon presentation of aortic disease but potentially critical and dangerous if delayed or misdiagnosed. This is attributed to the fact that it may progress to complications such as intramural hematoma, aortic dissection or even rupture. It is characterised by the ulceration of the aortic wall as a result of atherosclerotic plaque along the wall of aorta. Boo YL et al., described a case of PAU complicated with IMH, which is a rare presentation but vital for early detection.<sup>77</sup> This recent case report has demonstrated similar rarity of the condition in Malaysia where the literature evidence remains low.

*Investigation*

Acute cardiac tamponade is a known complication of acute aortic intramural haematoma (IMH) and dissection, which are categorised under the spectrum of acute aortic syndrome. In acute IMH, weakening of the aortic wall from spontaneous haemorrhage into the aortic media commonly leads to outward aortic rupture or inward intimal dissection extending to the aortic root, with subsequent progression to haemopericardium and acute cardiac tamponade. Therefore, the recognition of the CT signs of acute cardiac tamponade on CT is of paramount importance as early cardiothoracic intervention directly relates to reduced morbidity. Poh et al., presented a local case of a patient with Stanford Type A intramural haematoma complicated by haemopericardium and acute cardiac tamponade.<sup>78</sup> This case emphasised the role of CT in the diagnosis of acute cardiac tamponade in complicated proximal acute aortic syndrome and highlighted the CT signs associated with this life-threatening condition.



For mid-aortic syndromes, the gold standard for evaluation is angiography, but magnetic resonance angiography is more frequently being used as an alternative due to its high level of diagnostic accuracy.<sup>76</sup>

#### Management

The aim of management for mid-aortic syndrome is to reverse hypertension, preventing the associated long-term complication, and preserving end-organ function. In most cases, it can be effectively treated with a combination of medical, endovascular and/or surgical interventions.<sup>76</sup>

Moorthy et al., also reported a local case of complete resolution of type B aortic intramural hematoma with only medical treatment.<sup>79</sup> The computed tomography scan had revealed crescentic thickening of the posterior wall of the descending thoracic aorta (type B intra-mural hematoma) and a left-sided pleural effusion. The patient was treated conservatively with bed rest, aggressive control of high blood pressure, and analgesia. The follow-up computed tomography scans at six months and 18 months later revealed complete resolution of the intramural hematoma and no recurrence.

### OTHER AORTIC DISEASES

#### Case Reports

Rohana et al., described a case of aortic thrombus that was detected late with resultant failure of thrombolytic therapy.<sup>80</sup> With early treatment using low dose streptokinase, most early detected umbilical arterial catheter (UAC) associated thrombi could be lysed rapidly with a low incidence of adverse effects. Unfortunately, in the case patient, the diagnosis of an aortic thrombus was delayed due to an omission of the routine abdominal ultrasound screening following removal of her UAC. As a consequence, despite prolonged treatment using high doses of multiple thrombolytic agents, the thrombus failed to lyse. In conclusion, this case illustrated the importance of early abdominal ultrasonography in detection of the presence of an aortic thrombus shortly after removal of UAC and prompt treatment using low dose streptokinase.

Another rare aortic condition is primary aorto-duodenal fistula, which is a rare and life-threatening cause of upper gastro-intestinal bleed. In this case report, a patient presented acutely with several episodes of haematochezia and pulseless lower limbs bilaterally.<sup>81</sup> Primary aorto-duodenal fistula with peripheral vascular disease was diagnosed after an urgent CT angiogram was performed. She received treatment by left axillo-bifemoral bypass, resection of the fistula, Rouxen-Y gastro-jejunostomy, pyloric exclusion and controlled duodenal fistula the following day.

Asymptomatic simultaneous thrombosis of abdominal aorta and inferior vena cava is a rare complication in advanced malignancy. Faisham et al., reported an incidental finding of this clinical condition in a patient who presented with advanced stage of malignant fibrous histiocytoma of soft tissue and pathological fracture.<sup>82</sup> The thrombosis of the abdominal aorta and inferior vena cava are rare complications of malignant fibrous histiocytoma. Major

vascular surgical intervention was avoided in this patient in view of poor prognosis. However, conventional treatment with anticoagulants for asymptomatic obstruction of aorta and inferior vena cava in advanced disease is still considered adequate.

A final case report presented a case of pulmonary artery aneurysm associated with severe aortic stenosis and an aortic root dilatation occurring in a patient who presented with dyspnoea and chest pain.<sup>83</sup> Pulmonary artery aneurysms are rare, and there are no current definitive guidelines on its management. There are controversial opinions on whether such aneurysms should be managed conservatively or surgically. This case concluded that concomitant pulmonary artery repair with other cardiothoracic surgery can be performed safely, even in patients with moderate surgical risks.

### SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

This review of the research studies conducted in Malaysia contributes towards the general overview of knowledge, understanding and management of patients with aortic disease in the country. The literature of Malaysian studies and evidence demonstrates that research in the area has been performed but perhaps not at an optimum level. There is no national database or registry on aortic disease in the country. It is inevitable that there is a need for increased awareness of this disease and the benefits of its treatment.

The reported incidence of aortic diseases in Malaysia is similar to that in Western developed countries.<sup>10,84</sup> It is inevitable that there is a need for increased awareness of this disease and the benefits of its treatment. Interventions and swift measures should be taken to identify strategies to improve patient awareness,<sup>85</sup> which may include patient education through clinic consultations and setting up specialist aortic disease clinics for robust care.

Good results have been reported for AAA surgery in Malaysia.<sup>36</sup> However in some parts of the country, the majority of cases were emergency operations with high mortality.<sup>38</sup> Greater efforts must be made towards better awareness of the condition amongst physicians and patients for earlier diagnosis so that more of these operations can be done electively with better results.

The surgical treatment of aneurysms of the descending thoracic and abdominal aortas have moved towards endovascular techniques (TEVAR & EVAR) in recent times.<sup>86</sup> However, in Malaysia, only limited number of such procedures have been performed, suggesting that greater efforts must be made to improve training and provision of facilities for these procedures.<sup>44</sup> Although these procedures have been performed in Malaysia, there are very limited publications of the outcomes of these.

### SECTION 3: FUTURE RESEARCH DIRECTION

There is a lack of research on aortic disease in Malaysia as this review only identified 60 studies in a time frame of 16

years. In the last two years, only six papers on aortic diseases was published in Malaysia of which, four were case reports. More importantly, those with prevention strategies and evidence-based treatment themes have not been the main focus in the research studies. Such studies are needed to determine their feasibility and effectiveness in reducing the burden of aortic disease load in the country, and improving its prognosis once diagnosed. Studies are also needed to better understand why prevention strategies and treatments are not as effective in this country and identify opportunities for its improvement.

The different incidence of aortic diseases in the different ethnic groups is interesting and warrants further studies to determine if genetic factors may be responsible for aortic diseases.<sup>11</sup>

Several risk factors for aortic diseases have been identified including ethnicity, older age group, males, smoking, hypertension and respiratory disorders, amongst others.<sup>10</sup>

Further studies to better define the risk factors for aortic disease is needed for a screening program for the at-risk population.

There is an absence of data on the long-term outcomes following both open and endovascular aortic repair in the country. Although such data is available from the western countries, it is important that the long-term outcomes in this country are also identified to ensure that our patients are benefiting from these invasive treatments. According to the UK EVAR trials, endovascular procedures were associated with a significantly lower operative mortality. However, no significant differences were seen in total mortality or aneurysm-related mortality in the long term.<sup>86</sup> Quality and evidence-based research are needed to evaluate and improve the current practice in Malaysia and also identify whether current guidelines are being adhered to. To this end, the recent launch of the National Thoracic and Cardiovascular Surgical Database (NCTSD) Registry should hopefully take into consideration with regards to aortic disease data and its surgical management.

It is also vital for the review of studies conducted in the country in order to identify the different types of presentations and how they are investigated and treated locally. This provides an overall understanding and acknowledgement of Malaysia's academic contribution to the field. It also opens the opportunities for the sharing of input on an international platform when comparing studies with other nations. With the support of the Ministry of Health, it is hoped that clinical practice in the treatment of aortic disease would soon improve. With established centres with the good facilities and expertise, positive results comparable to those in centres in the Western countries could be achieved.<sup>85</sup>

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