

Cardiac and coronary artery study on sudden death cases in Hospital Canselor Tuanku Muhriz

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ABSTRACT

Background: Sudden death (SD) is defined as an unexpected natural death within an hour onset of symptoms or unwitnessed death that occurs within 24 hours, which accounts for most cardiovascular deaths in Malaysia. This study aimed to evaluate the extent of histopathological changes in the heart and to study the demographic trend in SD cases in Kuala Lumpur, Malaysia.

Methods: Specimens from all SD cases were received from 2017 to 2018 by the Forensic Unit, Hospital Canselor Tuanku Mukhriz (HCTM) were studied. The specimens were the left ventricular myocardium and left anterior descending artery (LAD), which were fixed in 10% formalin with haematoxylin and eosin staining. The tissues were graded histologically based on changes such as arterial occlusion, myocardial infarction, and/or thrombus formation. **Results:** Out of 545 medicolegal deaths, only 25 cases (4.6%) had samples available for analysis. Among these 25 patients, 24 (96%) were male patients and only one (4%) was a female patient. The available samples were from patients aged between 30 to 79 years old. In terms of ethnicity, Malays (40%) were the most numerous, followed by patients of Chinese and Indian ethnicities. The majority of the SD cases had a body mass index (BMI) that ranged between underweight (56%) and obese (40%). Besides, there were 10 (40%) cases of coronary artery with atheroma and 15 (60%) cases of myocardial infarction. The most common presentation of atherosclerosis was grade III and IV, and acute MI was the most common presentation at death, followed by healed infarcts and old infarcts.

Discussion and Conclusion: Our findings reflect worsening risk factor levels in cardiovascular diseases, compounded by demographic trends. Further studies on biomarkers specific for cardiac diseases are warranted to understand imminent sudden cardiac death.

Keywords: Autopsy; cardiac death; coronary artery; forensic pathology; sudden death

INTRODUCTION

Sudden death (SD) is defined as natural death that occurs within 24 hours, in the presence or absence of onset of symptoms. Sudden cardiac death (SCD) is defined as an unexpected death that occurs within one hour, with or without the onset of symptoms (Nisha et al., 2011). Epidemiological reports have proven that both types of deaths are strongly associated with age, sex, lifestyle, ethnicity, and family medical history (Mozaffarian et al., 2015). Hence, demographic factors should be taken into consideration in an autopsy to assist in the determination of the cause of death.

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Several factors have been linked with the aetiology of SD, and cardiac disease is the major cause of incidence worldwide (Tezcan et al., 2003). Several diseases are related to cardiac abnormalities such as myocardial infarction (MI), cardiomyopathy, myocarditis and congenital disabilities. MI is known as an irreversible necrosis of myocardial tissue resulting from decreased blood flow in arteries, which leads to an insufficient oxygen supply. In Malaysia MI is one of the leading causes of death, accounting for 20.1 % of all deaths (Chai et al., 2015). The risk factors of MI depend on age, sex, lifestyle, ethnicity and family history. With increased age, there is a higher risk of having MI. It was reported that men are at more at risk of MI at the age of 65, while for women, it is 71.8 years old (Mozaffarian et al., 2015). This is due to physiological changes in women, such as hormonal changes, unhealthy lifestyle, and reduction of metabolic rate (Hemingway et al., 2001; Wong et al., 2012).

Besides age, sex plays a vital role in the pathogenesis of MI. A report by the National Centre for Health Statistics in 2012 stated that readmission due to cardiac disease in women was higher than in men at the age of 65 and above (Statistics, 2012). Women are believed to have a higher risk of MI compared to men, as women will experience endothelial dysfunction and deposition of fat in the blood vessel during menopause. Moreover, reduced estrogen level is believed to be the primary cause of MI in menopausal females (Mozaffarian et al., 2015). The function of estrogen is not only to regulate prostaglandin production, but also increases vascular permeability (Williams 1978) and induces nitric oxide production, which will promote vasodilation. According to a study by INTERHEART, the Indian population in Asia has a higher risk of cardiac disease at a young age compared to other races in Middle and South America. This is because they share a history of diabetes, which is closely linked to the aetiology of cardiac diseases (Jha et al., 2003; Rodriguez et al., 2014).

MATERIALS AND METHODS

The study was conducted at the Forensic Unit of Hospital Canselor Tuanku Muhriz (HCTM), Kuala Lumpur from 2017 to 2018. A cross sectional study design was used by using retrospective data. An ethics approval (JEP-2018-062) was granted by the UKM Ethical Committee.

The inclusion criterion was all subjects with cardiac abnormalities. Infants, children, other causes of death, and incomplete postmortem reports were excluded. The age range of subjects was 30-79 years old, based on the retrospective data. The BMI classification was based on a previous study done in Malaysia, which divided subjects into 4 categories: <18.5kg - Underweight; 18.5-22.9 kg - Normal; 23-27.4kg - Overweight; and 27.5 - Obese (Azhari et al., 2017). There were 25 cases in total of heart and vessel samples of the left anterior descending artery (LAD) and left ventricular myocardium (LV).

Histopathological analysis

The sampled were fixed in 10% formalin, and underwent tissue processing using an automated tissue processor (Leica TP1020, Germany), which comprised of three processes: 1) dehydration, 2) clearing, and 3) impregnation. The processed tissue samples were then embedded in paraffin wax to form blocks (Leica EG1160, Germany) that were later sectioned using a rotary microtome (Leica RM2135, Germany). The sectioned blocks of tissue were then attached to slides and proceeded to haematoxylin and eosin (H&E) staining in order to visualize the morphology of the tissue. All histological sections were examined under a microscope for the presence of atheroma, MI and thrombus.

Atherosclerosis was graded based on the criteria by Siraj Ahmed & Begum (2013). The classification was based on the percentage of occlusion of plaque covering the artery lumen, subdivided into 5 different grades as shown in Table 1. MI was classified as acute, healing and old infarcts (Arai, 2015). Acute myocardial infarction (AMI) was featured by the absence of nuclei due to karyolysis and inflammatory cell infiltration. Meanwhile, fibroblasts and macrophages were present in

healing infarcts, while fibrosis and fibroblast were predominant in old infarcts.

Table 1: Atherosclerosis grading system based on percentage occlusion of plaque

Grade	Occlusion (%)
Grade 0	Normal
Grade I	1 – 25
Grade II	26 – 50
Grade III	51 – 75
Grade IV	76 – 100

Statistical analysis

Statistical analysis was performed using SPSS Version 22.0. The tests used were descriptive analysis and Spearman correlation with $p \leq 0.05$ considered significant.

RESULTS

The collected data exhibited 1740 deaths in 12 months, which comprised of 545 (31.3%) medicolegal and 1195 (68.7%) non-medicolegal cases. Of the 545 cases, 138 SD and 55 (40%) had cardiac abnormalities. After considering inclusion and exclusion factor, 25 cases between the age range of 30 to 79 years old were sampled. It was observed that the number of SD cases was the highest among the 60 to 69 years old subjects ($n = 9$), and this was followed by a decreasing trend in the other age groups: 40 to 49 ($n = 6$) and 50 to 59 ($n = 6$), 70 to 79 ($n = 3$) and 30 to 39 years of age ($n = 1$) (Table 2). It was evident that the highest risk was exhibited by the 60 to 69 years old age group compared to the 70 to 79 years old age group, probably because of the good management in hospitals that the older subjects were given.

Table 2: Age and sex distribution in sudden death cases

Age (years)	Male	Female	Total
30 – 39	1	0	1
40 – 49	5	1	6
50 – 59	6	0	6
60 – 69	9	0	9
70 – 79	3	0	3
Total	24 (96%)	1 (4%)	25 (100%)

Interestingly, one subject ($n = 1$) in the 50 to 59 years old age group had a normal BMI, but this age group also had the highest number of both overweight and obese subjects ($n = 4$) (Table 3).

Table 3: Age and BMI in sudden death cases

Age (years)	Normal (18.5 – 22.9)	Overweight (> 23 – 27.4)	Obese (> 27.5)
30 – 39	0	4	2
40 – 49	0	3	3
50 – 59	1	4	4
60 – 69	0	3	0
70 – 79	0	0	1
Total	1 (4%)	14 (56%)	10 (40%)

Malaysia has three main ethnic communities i.e., Malays, Chinese and Indians. By ethnicity, the Malays ($n = 10$) had the highest cardiac case-fatalities, followed by Chinese ($n = 8$), other ethnicities ($n = 6$) and Indians ($n = 1$). This could be due to the Malays and Chinese being the

dominant populations in Malaysia, thus proportionately contributing to the higher numbers.

Table 4: Sudden cardiac death by ethnicity

Ethnicity	Number of cases
Malay	10
Chinese	8
Indian	1
Others (Indonesian, Bangladeshi, Libyan)	6
Total	25 (100%)

Table 5: Severity of atherosclerosis in LAD

Atherosclerosis grading system	Number of cases
Grade 0 (Normal)	2
Grade 1	4
Grade 2	3
Grade 3	11
Grade 4	5
Total	25 (100%)

Note: LAD – left anterior descending artery

In this study, the samples were graded for atherosclerosis according to the percentage of occlusion in the artery. (Table 5, Figure 1). Of all samples, atherosclerosis grade III was the most prevalent (n = 11), followed by grade IV (n = 5), grade I (n = 4), grade II (n = 3), and grade 0 (n = 2). Although the number of grade III samples was the highest, it was possible that the fewer number of grade IV samples was due to the subjects not surviving the severest form of the disease. Grade 0 to II (mild to moderate) were the least in the sample population, as some may go undiagnosed at the early stages due to missed or having no symptoms at all.

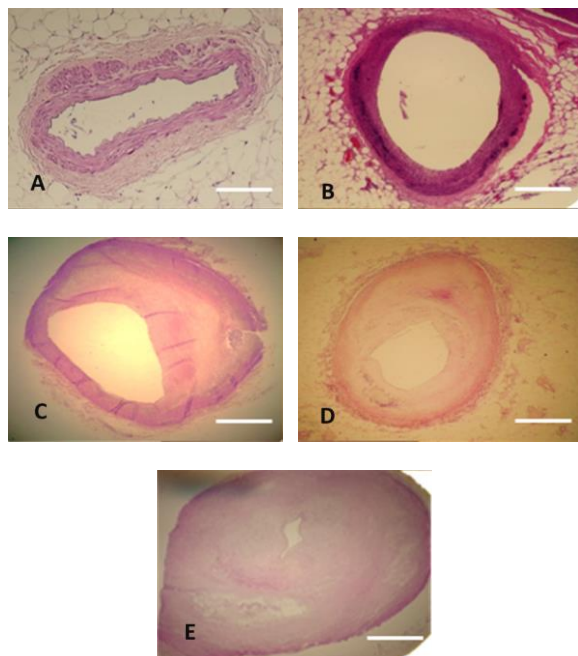


Figure 1: Photomicrographs (40x magnification) of the left anterior descending artery (LAD) for different stages of atherosclerosis. A: Normal, B: 20% occlusion, C: 50% occlusion, D: 60% occlusion, E: 95% occlusion. Scale bar (100 μm) (Soo et al. 2019)

The samples that presented plaques and narrowing of the lumen were visualised with H&E stain, and observed under a light microscope. It can be seen that as the plaque size increased, the lumen size was bound to decrease (Figure 1).

The results showed that AMI (n = 15; 60%) was the most common presentation in the samples, followed by healing infarcts (n = 9; 36%) and old infarcts (n = 1; 4%). (Table 6, Figure 2) This indicated that AMI was the most typical presentation at the time of death, while the other presentations which were the healing infarcts and old infarcts were the least to present at death.

Table 6: MI grading system in sudden cardiac deaths

MI Grading System	Number of cases
MI	15
Healing Infarct	9
Old Infarct	1
Total	25 (100%)

Note: MI - Myocardial infarct

Table 7: Distribution of BMI and atherosclerosis in sudden cardiac death.

	Grade 0	Grade I	Grade II	Grade III	Grade IV
Normal	0	0	0	0	1
Overweight	1	2	3	1	6
Obese	2	1	0	4	4
Total	3	3	3	5	11

Note: BMI – Body Mass Index

By distribution of atherosclerosis in different types of BMI, the most prevalent grade of atherosclerosis was grade IV (n = 11), in particular, among the overweight (n = 6) and obese (n = 4) subjects (Table 7). Generally, all five stages of atherosclerosis were found in the overweight and obese subjects. This suggested that excess body fat was associated with a significantly increased risk of ischaemic heart diseases due to atherosclerosis.

The Spearman’s correlation analysis showed that atherosclerosis displayed weak correlations with age and BMI. (Table 8). In contrast, MI and thrombosis showed strong correlations with age and BMI (p < 0.05). Interestingly, though atherosclerosis and MI increased with advancing age, thrombosis showed a decreasing trend. This could be due to the age factor, whereby thrombosis might not have time to develop to be demonstrated in the elderly. Also, as the BMI increased, the incidence of atherosclerosis and MI decreased, while it increased for thrombosis. No plausible theories could be offered at this stage on this phenomenon and more empirical studies have to be done to provide an explanation.

Table 8: Spearman’s correlation analysis between atherosclerosis, MI and thrombosis with age and BMI.

	Atherosclerosis	MI	Thrombosis
Age	r = 0.26	r = 0.87*	r = -0.53*
BMI	r = -0.262	r = -0.87*	r = 0.53*

Note: MI – Myocardial infarct, BMI – Body Mass Index, r – Coefficient correlation *p < 0.05

DISCUSSION

The present study showed that men exhibited a higher risk of SD related to cardiac abnormalities compared to women, as also reported by other studies (Siraj Ahmed & Begum, 2013; Wong et al., 2018). This mortality trend could be attributed to the presence of estrogen in women that prolongs life expectancy by increasing vascular permeability and production of nitric oxide that promotes vasodilation in the heart (Nevzati et al., 2015). Conversely, the reduction of estrogen levels upon menopausal age will increase the risk of cardiac abnormalities among women (Mozaffarian et al., 2015). The literature has demonstrated the relationship between age and cardiac abnormalities (Mozaffarian et al., 2015; Hemingway et al., 2001; Wong et al., 2012). There is a high risk of cardiac defects that comes with advancing age. Men may be more vulnerable to cardiac defects at a younger age than women for reasons of physiological changes in men, such as physical activity, dietary intake and metabolic rate (Hemingway et al., 2001; Wong et al., 2012).

While the Chinese ethnicity formed the majority of SD cases at HCTM, the Malays recorded the highest casualties from SCDs in this study. However, in the literature, it was reported that Indians had a

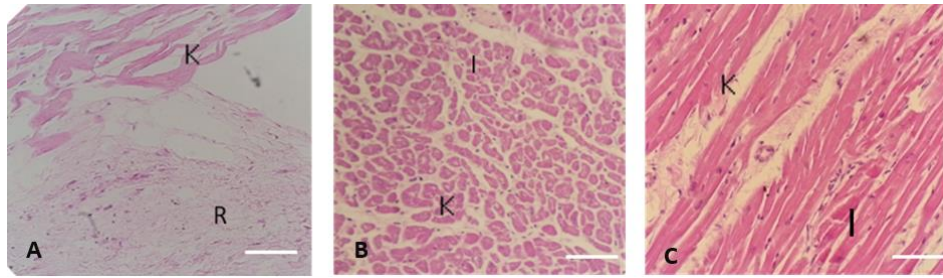


Figure 2: Photomicrographs (40x magnification) of H&E stained myocardium. A: Contraction bands with extravasation of red blood cells, B: Absence of nuclei due to karyolysis of nucleus with inflammatory cell infiltration, C: Presence of fibroblast and inflammatory cells with transition to scarring. Scale bar (100 μ m). (K – karyolysis, I – inflammatory cells, R – Extravasation of red blood cells) (Siraj Ahmed & Begum 2013)

higher risk of cardiovascular mortality, followed by Chinese and Malay ethnicities (Haque et al., 2016). A research done by INTERHEART proved that the Indian ethnicity exhibited a higher risk of having cardiovascular diseases (CVD) compared to other ethnicities in Asian countries (Statistics, 2012).

Also, we observed an increasing trend between BMI and atherosclerosis, whereby cases diagnosed with high BMI were correlated with grade III and IV atherosclerosis (Table 7), which correlated well with a previous research (Mongraw-Chaffin et al., 2015). Besides, a local study demonstrated that obesity is one of the risk factors of CVD in Malaysia (Cheah et al., 2011). Generally, the number of overweight and obese subjects were evident in all age groups except among the elderly. This indicated that younger subjects were more likely to be obese as compared to the elderly due to fast food consumption and poor physical activities with high usage of technology and gadgets nowadays (Bhavani et al., 2019). Overweight and obese children are more likely to stay obese into adulthood and to develop non-communicable diseases such as diabetes and cardiovascular diseases at a younger age (Cote et al., 2013).

It was stipulated that MI and thrombosis are common complications that may arise with advancing age, although the present study found that thrombosis was more common in the young than in the elderly. As the BMI increased, both atherosclerosis and MI displayed a lower prevalence. Conversely, the incidence of thrombosis increased as the BMI increased, and this could be attributed to the increased dynamics of blood flow in obese patients, hence contributing to blood clots and obstructions in small vessels. Nevertheless, one has to be cautious with the results as there were insufficient samples due to incomplete autopsy reports in this study.

CONCLUSION

In conclusion, the most common cardiac abnormalities were atherosclerosis grade III and IV with AMI as the most frequent presentation at death. The most prevalent age group to develop sudden death related to cardiovascular diseases was between 50 till 59 years old. Overweight individuals associated with SDs accounted for 56% of the overall BMI data. Hence, there was a strong association between histological changes of the heart and coronary arteries with demographic factors in this study. As shown in this study, demographic factors such as ethnicity, BMI, gender and age may play a role in SD cases. A comprehensive study is needed to include specific biomarkers for SCDs to increase the prediction of such deaths in the future.

DISCLOSURES

The authors declare that there is no conflict of interest.

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