

Demographic, clinical and lifestyle predictors for severity of erectile dysfunction and biomarkers level in Malaysian patients

Raymond Mark¹, Hasniza Zaman Huri^{1,2*}, Azad Hassan Abdul Razack³

¹Department of Pharmacy, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, ²Clinical Investigation Centre, University Malaya Medical Centre, Lembah Pantai Kuala Lumpur, Malaysia, ³Departments of Surgery, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

The incidence of erectile dysfunction (ED) is rising worldwide and its prevalence is one of the main health concerns that affect overall men well-being in Malaysia. The cluster of demographic, clinical and lifestyle factors may have contributed to the severity of ED and changes in biomarkers level; nevertheless these have not been studied extensively. This cross sectional study involved a total of 276 patients with 138 was diagnosed with ED. The demographic, clinical, lifestyle factors and severity of ED were assessed using a set of questionnaire and the International Index of Erectile Function (IIEF-5). Meanwhile, Total Testosterone (TT) and Asymmetric dimethylarginine (ADMA) levels were determined using the enzyme-linked immunosorbant assay (ELISA). Binary logistic regression test was used to demonstrate the predictors of severity of ED, TT and ADMA levels. Significant predictors for worsening of severity of ED are self-employed [10.55 (0.43 – 257.06), p=0.004], pensioner [8.07 (0.19 – 352.45), p=0.026], non-government employee [1.16 (0.05 – 26.26), p=0.04] and TT [0.41 (0.25 – 0.69), p=0.001]. Nevertheless, pensioner [0.08 (0.01 – 0.87), p=0.038] and unemployed [0.04 (0.01 – 0.42), p=0.007], were the predictors that may influence the changes of TT levels. On the other hand, academic qualification (secondary) [4.51 (0.48 – 42.83), p=0.014] and intensity of physical activities (< 1 hour/day) [2.61 (0.65 – 10.48), p=0.008] were the predictors which were more likely to influence the changes of ADMA levels in ED patients. TT and ADMA levels were influenced by demographic and lifestyle factors whilst severity of ED was predicted by demographic and clinical factors in Malaysian ED population. These predictors may provide new knowledge on risk factors of severity of ED and help in management of ED. Thus, the predictive models could serve as a primary guidance to physicians to ensure ED being managed and treated more effectively.

Keywords: Erectile dysfunction/biomarker/clinical. Demography. Lifestyle. Men's Health. Malaysia

INTRODUCTION

According to National Institutes of Health (NIH) consensus panel, erectile dysfunction (ED) is defined as the inability of a man to obtain and/or maintain a penile erection that is sufficient for satisfactory sexual performance (NIH Consensus Conference, 1993; Shamloul, Ghanem, 2013). A recent study by Rahman showed that 69.5 % of Malaysians men with aged 40 to 79 years old reported had ED (Ab Rahman, Al-Sadat, Yun Low, 2011). Since it is not life threatening, men give less attention and left it untreated. Currently more than

150 million men worldwide are affected by this sexual disorder and this number could rise to 320 million by 2025 (Meller *et al.*, 2013; Nunes, Labazi, Webb, 2012). Erectile dysfunction which was previously known as impotence is common among men aged 40 and above (Pastuszak, 2014). Few epidemiology studies reported that the prevalence of erectile dysfunction varies according to age range, countries and ethnic groups. In Malaysia, Ab Rahman *et al.* (2011) and Fadzil *et al.* (2014) reported 69.5% and 62% of Malaysian aged 40 years and above have ED respectively and the incidence varies among the three main ethnic groups living in this country (Ab Rahman, Al-Sadat, Yun Low, 2011; Fadzil *et al.*, 2014).

ED was considered as organic and psychogenic origin. Increasing knowledge on erectile function postulates that demographic, clinical and lifestyle factors

*Correspondence: H. Z. Huri. Department of Pharmacy, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur. Phone: 603 79676659 / Fax: 603 79541904. E-mail: hasnizazh@um.edu.my

could play important roles in causing severe ED in an individual. However, these factors have not been well studied in Malaysian ED patients. The association of demographic factors with severity of ED can be seen with ethnicity (Momtaz *et al.*, 2014; Tan *et al.*, 2011) and current marital status (Oyekanmi *et al.*, 2012). Besides, the socioeconomic states such as occupation or employment status of an individual (Al Mogbel, 2014), academic qualification (Momtaz *et al.*, 2014) and household income (Martin *et al.*, 2014) have been found to have indirect association with severity of ED (Ab Rahman, Al-Sadat, Yun Low, 2011; Safarinejad, Hosseini, 2004). Apart from these, clinical factors such as biomarkers and type of comorbidities have been hypothesized to be strongly associated with severity of ED. Evidences signified that TT and ADMA were found to be the most prominent biomarkers associated with severity of ED. Studies have also shown that decreased levels of TT (Brooke *et al.*, 2014) and increased ADMA levels (Aktoz *et al.*, 2010) play a part in the expression of nitric oxide (NO) synthesis substantially leading to progression of severe ED. There are many convincing studies evidences that comorbidities such as type 2 diabetes mellitus (T2DM) (Tamler, 2009), coronary artery disease (CAD) (Grossmann, Gianatti, Zajac, 2010), hyperlipidaemia (Musicki *et al.*, 2010; Nikoobakht, Nasseh, Pourkasmaee, 2005), hypertension (Nunes, Labazi, Webb, 2012) and lower urinary tract symptoms (LUTS)/ benign prostatic hyperplasia (BPH) (Dutkiewicz *et al.*, 2012) as risk factors of ED and have been strongly associated with severity of ED. Practising good quality lifestyles are known to reduce the risk of severe ED. Besides that, lack of physical activity (Kařka *et al.*, 2013) has been well documented and proven to be associated with severity of ED (La Vignera *et al.*, 2013). In addition, studies have also shown that active and healthy lifestyles without smoking (Cao *et al.*, 2013) and alcohol (Lee *et al.*, 2010) significantly delay the progression of severe ED.

A biological marker or biomarker is defined as biochemical alterations that are measurable in human cells or fluids and can be used as an indicator for a biological process (Micheel, Nass, Omenn, 2012). Biomarkers are used in clinical settings to determine the status of a disease and also as an indicator of treatment response (Strimbu, Tavel, 2010). Amongst biomarkers that have been prominently associated with erectile dysfunction are ADMA, NO, advanced glycation end product (AGE), TT, oxytocin, interleukin 6, sphingosine-1-phosphate and more. Out of these, TT and ADMA which have an essential role in mechanism of erection were selected for this study. TT activates and increases the synthesis of

cyclic guanosine monophosphate (cGMP) by stimulating endothelial nitric oxide synthase (eNOS) synthase and increasing the expression of NO. NO is a crucial enzymes for erection. In addition, TT helps in the vasodilation of the penile arterioles around the corpora cavernosa and allows more blood inflow to maintain an erection (Isidori *et al.*, 2014). Meanwhile, the role of ADMA as an endogenous inhibitor of NO synthase decreases the bioavailability of NO, which eventually inhibits the relaxation of smooth muscle in penile tissues and leads to ED (Javaroni, Neves, 2012). Recent study shows that elevated ADMA level in serum is strongly associated with high prevalence of ED (Aktoz *et al.*, 2010), nevertheless ED is less prevalent in patients with high serum concentration of TT (Brooke *et al.*, 2014). Studies have been conducted on association of demographic, clinical and lifestyle factors with biomarker levels (TT and ADMA), however the potential predictors associated with these biomarkers levels in ED patients have yet to be identified, particularly in the Malaysian population.

There is scarcity of studies on severity of ED and biomarkers level in the Malaysian ED population. Most of the available studies on association of demographic, clinical and lifestyle factors with severity of ED and biomarkers cannot be generalized to the Malaysian population. Besides, the demographic, clinical and lifestyle factors have been studied as individual factors and linked to severity of ED. Nevertheless, to the best knowledge of the authors, no Malaysian studies have investigated the impact of combination of these factors with severity of ED and biomarkers level. It is essential to study these factors and their associations in order to identify the risk factors which influence the severity of ED and biomarker levels. Therefore, the present study was designed to assess the association of demographic, clinical and lifestyle factors with severity of ED and biomarker levels in Malaysian ED patients. This study also aimed to determine the predominant predictors that influenced the severity of ED and biomarker levels in Malaysian ED patients.

MATERIAL AND METHODS

Study design and setting

An unmatched case-control study was conducted in patients who attended ED, surgery, eye and medical clinics in a university hospital, University Malaya Medical Centre (UMMC) at Kuala Lumpur, Malaysia from September 2013 until April 2015. The study was conducted in accordance with the Declaration of Helsinki and was approved by the medical ethics committee of the

UMMC (MEC reference number 1010.18). Sample size was calculated from the published guidelines for testing individual predictors (VanVoorhis, Morgan, 2007). Based on the study, regression sample size for testing individual predictors is determined using formula, $N > 104 + m$, (where m is the number of predictors or independent variables). Convenience sampling was applied to select the subjects for this study (Huri *et al.*, 2016). A random selection of patients from the non-ED pool was included in the study (controls). Patients aged 40 years old and above (Pastuszak, 2014) who met the inclusion criteria were approached and briefed about the purpose of this study. Those who fulfilled the inclusion-exclusion criteria were selected and patient information sheet (PIS) was then given to them. Patients who voluntarily agreed to participate in this study were given a consent form to acknowledge the agreement to participate in this study. A face-to-face interview was conducted to complete a study questionnaire. An overview of the study methodology is illustrated in Figure 1.

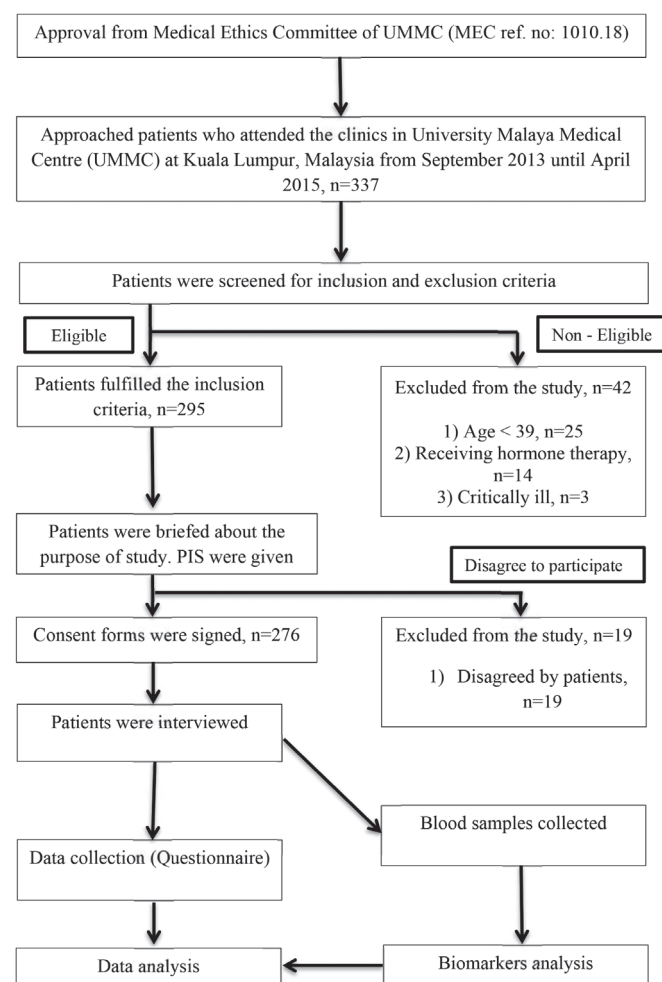


FIGURE 1 - Overview of study methodology.

Inclusion and Exclusion Criteria

- Inclusion Criteria (case)**
 - Adult male patients ≥ 40 years old (Pastuszak, 2014)
 - Patients who have IIEF-5 score ≤ 21 (Pastuszak, 2014)
- Inclusion Criteria (control)**
 - Adult male patients ≥ 40 years old
 - Patients who have IIEF-5 score > 21
- Exclusion Criteria (case)**
 - Patients that are critically ill who required medical treatment
 - Patients who are unwilling to participate in the survey
 - Patients who are diagnosed with psychiatry illness or mentally challenged.
 - Patients who underwent surgical treatment for ED
 - Patients who are admitted and required intervention in hospital
 - Patients who received non-pharmacological local therapy (herbal medications)
 - Patients who received hormone therapy for ED (hypogonadism)
 - Immunocompromised patients (HIV, AIDS and cancer patients)
- Exclusion Criteria (control)**
 - Patients that are critically ill requiring medical treatment
 - Patients who are unwilling to participate in the survey
 - Patients who are diagnosed with psychiatry illness or mentally challenged.
 - Patients who are admitted and required intervention in hospital
 - Immunocompromised patients (HIV, AIDS and cancer patients)

Questionnaire

Participants who gave their consent were provided with a study questionnaire which was adapted from few previous studies (Ab Rahman, Al-Sadat, Yun Low, 2011; Khoo, Tan, Low, 2008; Tan *et al.*, 2007). The questionnaire was divided into three parts. The first part (Part A) of the questionnaire assessed the socio-demographic characteristics such as age, ethnicity, marital status, occupation, academic qualification and monthly income. The second part of the questionnaire measured life style factors of patients which comprised of factors such as

physical activities (intensity and duration of physical activities), smoking history (intensity and duration of smoking) and alcohol consumption. Part C analysed detailed medical history (history of comorbidities) and sexual health (IIEF-5) of participants. The outline of the study questionnaire is as follow.

Part A: assessment of demographic factors

Socio-demographic characteristics were assessed in this first part of the questionnaire. Patient's age was calculated using year of birth as stated in hospital information system. Ethnic is classified into three major populations of Malaysia; Malays, Chinese and Indians. Marital status is categorized into married and others (never married or single, divorced, and widower). Occupation is classified into 5 categories; government employee, non-government employee, self-employed, pensioner and unemployed. Respondents' academic qualification is measured based on Malaysian education system which includes no formal schooling, primary education, secondary educations (PMR, SPM, STPM, A-Level, certificate) and tertiary/higher educations (Diploma, Bachelor degree and Postgraduate degree) (Ab Rahman, Al-Sadat, Yun Low, 2011; Momtaz *et al.*, 2014). Meanwhile monthly income is defined as low (< RM1000), medium (RM 1000 – RM 2999) and high (RM ≥ 3000) based on patients' salary in Malaysian Ringgit (MYR) (Ab Rahman, Al-Sadat, Yun Low, 2011; Momtaz *et al.*, 2014).

Part B: assessment of life style factors

This part of questionnaire evaluates life style factors of patients including items on physical activity, cigarette smoking history, and alcohol consumption. Physical activity was assessed on how often patients involved in activities which took hard physical efforts that made them breather harder than normal in the past 3 years.(Ab Rahman, Al-Sadat, Yun Low, 2011) Among the other questions asked to assess physical activities are:

- Over the last 3 years, how often did you do physical activities? For example heavy lifting, aerobic, carrying light loads, bicycling at a regular pace, or playing badminton.
- How many days per week were usually spent on doing these physical activities?
- How much total time did you usually spend on doing physical activities on one of those days?

The smoking history of patients was assessed. A patient was considered a smoker if he had smoked more

than one cigarette per day for at least one year; an ex-smoker if he had stopped smoking more than one year from the day of interview and a non-smoker if he had never smoked cigarette in his whole life (Chrysohoou *et al.*, 2013). Smokers were asked additional questions on how many cigarettes they smoked per day and the number of years they have been smoking. Based on the questionnaire responses, the respondents' status is classified as current smoker, non-smoker, and ex-smoker with varying intensity of smoking (number of cigarettes per day) and duration of smoking (years of smoking) (Gades *et al.*, 2005). Patients were evaluated based on consumption of drinks such as beer, wine, spirit, samsu, tuak, sake or others which contain alcohol (Ab Rahman, Al-Sadat, Yun Low, 2011). Response categories ranged from no (never drank alcohol in his life) to alcoholic (with an average of daily or weekly alcohol consumption) and ex-alcohol consumer (had stopped drinking alcohol more than one year from the day of interview) (Ab Rahman, Al-Sadat, Yun Low, 2011; Bacon *et al.*, 2006).

Part C: assessment of clinical factors and sexual health

Self-reported health conditions of patients on history of comorbidities were questioned in this questionnaire. The information on comorbidities was obtained from patients' medical records. Meanwhile, the list of PDE-5 inhibitors prescribed for ED patients was obtained from Pharmacy Information System, UMMC using patients' RN number. The severity of ED was measured using the International Index of Erectile Function-5 (IIEF-5) which is a self-evaluation questionnaire used for the assessment of male sexual function including screening and diagnosis of severity of ED (Pastuszak, 2014). Participants were asked to rate their ability to achieve and maintain an erection that is good enough for a satisfactory sexual intercourse without any treatment for the past 6 months. Response options ranged from very low, low, moderate, high and very high. Among the questions asked were as follow:

- How do you rate your confidence that you could get and keep an erection?
- When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
- During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
- During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

- When you attempted sexual intercourse, how often was it satisfactory for you?

Presence of ED is denoted by IIEF scores of equal or less than 21. Severity of ED is further categorised based on the IIEF scores: severe (5-7), moderate (8-11), mild to moderate (12-16), mild (17-21), and no ED (22-25). For analysis purposes, a binary variable was created based on IIEF-5 where scores from 12-21 is considered “less severe (Mild to Mild/Moderate)” and 5–11 is considered as “moderate to severe” ED. The IIEF-5 assessments were completed by consultant urologists in UMMC with a specialisation in ED.

Blood sampling and biomarkers analysis

Ten (10.0) ml of blood samples were collected in two SST tubes (BD vacutainer) and were immediately centrifuged at 4000 rpm for 15 min (Önder *et al.*, 2014). The supernatant (serum) was decanted into clean eppendorf centrifuge tubes and kept frozen in the -20°C freezer (Remi scientific, Malaysia, model: DW-YL270) until analysis. ADMA and TT levels were determined by using a commercially available enzyme-linked immunosorbant assay (ELISA) kit according to manufacturers' instructions (Uscn Life Science Inc, Wuhan, China). (Ali *et al.*, 2012; Griffeth, Carretero, Burks, 2013).

Statistical analysis

The data was analysed using Statistical Package for Social Sciences (SPSS) version 19.0 (IBM Corp. Released 2010, IBM SPSS Statistics for Windows, version 19.0. Armonk, NY: IBM Corp, USA). Descriptive statistics were used to summarize patients' demographic, clinical and lifestyle characteristics. Discrete variables were expressed as frequencies and percentages (N, %). On the other hand, continuous data was expressed as mean ± standard deviation. Chi-square test was used to analyse discrete variables, meanwhile one-way ANOVA was used to compare the means of continuous variables. To build the predictor model, all variables that showed significant association with both primary analysis (case & control group) and secondary analysis (severity of ED, TT and ADMA) were subjected to a binary logistic regression test (enter method) to determine their odds ratio (OR) and confidence intervals. The dependent variable of predictor models for severity of ED is categorised as scale 1: participants with IIEF scores of 12-21 and 2: participants with IIEF scores of 5–11. Plot receiver-operating characteristic (ROC) curve was used to determine the cut-off point for biomarkers levels (TT and ADMA). The ROC

analysis indicated cut-off point of TT is 9.55 nmol/L. The dependent variable for this modelling is TT with scale 1: high serum concentration level of TT, ≥ 9.55 nmol/L and 2: low serum concentration level of TT < 9.55 nmol/L. Meanwhile, an ADMA cut-off point of 0.665 $\mu\text{mol/L}$ yielded from ROC analysis. The dependent variable for this modelling is ADMA with scale 1: high concentration of serum ADMA, ≥ 0.665 $\mu\text{mol/L}$ and 2: low concentration of serum ADMA, < 0.665 $\mu\text{mol/L}$. Hosmer and Lemeshow test with $p > 0.05$ indicates that the entered data is suitable with the tested model. Nagelkerke R square (R^2) value shows the percentage of predictor's in influencing dependent variable. The ranking of predictors in the model were determined by the odds ratio (OR) values. Results with $p < 0.05$ were considered statistically significant.

RESULTS

Demographic, clinical and lifestyle characteristics of study population

A total of 337 patients were approached. Out of these, 42 respondents were excluded as they do not fulfil the inclusion criteria while 19 respondents disagreed to participate in this study. As a result, 276 patients who met the inclusion-exclusion criteria has participated in this study whereas 138 patients were reported having ED (IIEF scores ≤ 21) and categorised as the case group. The balance 138 patients who have IIEF > 21 were categorised as the control group. The association of demographic, clinical, biomarkers and lifestyle factors with erectile dysfunction; case and control (primary analysis) and ED severity subgroup (secondary analysis) were presented in Table I. Meanwhile, the association of demographic, clinical and lifestyle factors with biomarkers level (TT and ADMA) were shown in Table II.

Predictors of severity of ED, TT and ADMA level

Variables which gave significant result in both case & control (primary analysis) and severity group (secondary analysis) were subjected to this binary logistics regression analysis. The significant predictors for severity of ED in this study population were TT ($p = 0.001$) and occupation ($p = 0.03$). Based on the OR value, self-employed was ranked as first predictor which was 10.55 times most likely to increase severity of ED followed by pensioner (OR = 8.07) and non-government employee (OR = 1.16). Meanwhile, TT levels were 0.41 times more likely to worse severity of ED in Malaysian population. However in Malaysia, ADMA, academic qualification, monthly

TABLE I - Association of Demographic, Clinical, Biomarkers and Lifestyle factors with Erectile Dysfunction and Severity of ED

	Primary Analysis (Case and Control)			Secondary Analysis (Cases only)		
	Case n=138 (%) / Mean ± SD	Control n=138 (%) / Mean ± SD	p Value	Mild to Mild/Moderate n=105 (%) / Mean ± SD	Moderate to Severe n=33 (%) / Mean ± SD	p Value
Demographic factors						
Age	58.64 ± 9.23	54.80 ± 7.62	< 0.001 ^{d*}	54.99 ± 6.11	70.27 ± 7.76	< 0.001 ^{d*}
Ethnic						
Malay	68 (49.3)	64 (46.4)	0.890 ^a	52 (49.5)	16 (48.5)	0.951 ^a
Chinese	39 (28.3)	41 (29.7)		29 (27.6)	10 (30.3)	
Indian	31 (22.5)	33 (23.9)		24 (22.9)	7 (21.2)	
Marital Status						
Married	133 (96.4)	138 (100)	0.06 ^b	105 (100.0)	28 (84.8)	0.001 ^{b*}
Others	5 (3.6)	0 (0.00)		0 (0.0)	5 (15.2)	
Occupation						
Government Employee	36 (26.1)	65 (47.1)	< 0.001 ^{a*}	33 (31.4)	3 (9.1)	< 0.001 ^{b*}
Non-government employee	29 (21.0)	11 (8.0)		26 (24.8)	3 (9.1)	
Self Employed	21 (15.2)	7 (5.1)		17 (16.2)	4 (12.1)	
Pensioner	30 (21.7)	34 (24.6)		16 (15.2)	14 (42.4)	
Unemployed	22 (15.9)	21 (15.2)		13 (12.4)	9 (27.3)	
Academic Qualification						
Primary	11 (8.0)	9 (6.5)	0.006 ^{a*}	4 (3.8)	7 (21.2)	0.006 ^{b*}
Secondary	111 (80.4)	92 (66.7)		88 (83.8)	23 (69.7)	
Tertiary	16 (11.6)	37 (26.8)		13 (12.4)	3 (9.1)	
Monthly Household Income						
Low	30 (21.7)	30 (21.7)	< 0.001 ^{a*}	13 (12.4)	17 (51.5)	< 0.001 ^{b*}
Medium	65 (47.1)	24 (17.4)		51 (48.6)	14 (42.4)	
High	43 (31.2)	84 (60.9)		41 (39.0)	2 (6.1)	
Clinical factors						
Type 2 Diabetes Mellitus						
Present	70 (50.7)	73 (52.9)	0.810 ^c	51 (48.6)	19 (57.6)	0.482 ^c
Absent	68 (49.3)	65 (47.1)		54 (51.4)	14 (42.4)	
Hypertension						
Present	85 (61.6)	77 (55.8)	0.392 ^c	66 (62.9)	19 (57.6)	0.735 ^c
Absent	53 (38.4)	61 (44.2)		39 (37.1)	14 (42.4)	
Hyperlipidemia						
Present	65 (47.1)	56 (40.6)	0.332 ^c	46 (43.8)	19 (57.6)	0.237 ^c
Absent	73 (52.9)	82 (59.4)		59 (56.2)	14 (42.4)	
Coronary Artery Disease						
Present	80 (58.0)	72 (52.2)	0.397 ^c	58 (55.2)	22 (66.7)	0.338 ^c
Absent	58 (42.0)	66 (47.8)		47 (44.8)	11 (33.3)	
Lower Urinary Tract Symptoms/ Benign prostatic hyperplasia						
Present	42 (30.4)	35 (25.4)	0.421 ^c	26 (24.8)	16 (48.5)	0.076 ^c
Absent	96 (69.6)	103 (74.6)		79 (75.2)	17 (51.5)	
Biomarkers						
Total Testosterone (TT) (nmol/L)	11.58 ± 2.53	20.94 ± 2.89	< 0.001 ^{d*}	12.49 ± 1.96	8.70 ± 1.95	< 0.001 ^{d*}
Asymmetric dimethylarginine (ADMA) (μmol/L)	0.65 ± 0.16	0.50 ± 0.08	< 0.001 ^{d*}	0.61 ± 0.14	0.80 ± 0.12	< 0.001 ^{d*}
Life style Factors						
Physical activities						
Yes	48 (34.8)	83 (60.1)	< 0.001 ^{c*}	42 (40.0)	6 (18.2)	0.037 ^{c*}
No	90 (65.2)	55 (39.9)		63 (60.0)	27 (81.8)	

TABLE I - Association of Demographic, Clinical, Biomarkers and Lifestyle factors with Erectile Dysfunction and Severity of ED (cont.)

	Primary Analysis (Case and Control)			Secondary Analysis (Cases only)		
	Case n=138 (%) / Mean ± SD	Control n=138 (%) / Mean ± SD	p Value	Mild to Moderate n=105 (%) / Mean ± SD	Moderate to Severe n=33 (%) / Mean ± SD	p Value
Life style Factors						
Duration of physical activities						
No	90 (65.2)	55 (39.9)	< 0.001 ^{a*}	63 (60.0)	27 (81.8)	0.059 ^b
≤ 2 days/week	31 (22.5)	25 (18.1)		28 (26.7)	3 (9.1)	
> 2 days/week	17 (12.3)	58 (42.0)		14 (13.3)	3 (9.1)	
Intensity of physical activities						
No	90 (65.2)	55 (39.9)	< 0.001 ^{a*}	63 (60.0)	27 (81.8)	0.022 ^{b*}
< 1 Hour/day	15 (10.9)	41 (29.7)		11 (10.5)	4 (12.1)	
≥ 1 Hour/day	33 (23.9)	42 (30.4)		31 (29.5)	2 (6.1)	
Smoking						
Yes	81 (58.7)	57 (41.3)	0.006 ^{c*}	62 (59.0)	19 (57.6)	0.881 ^c
No	57 (41.3)	81 (58.7)		43 (41.0)	14 (42.4)	
Duration of smoking						
No smoking	57 (41.3)	81 (58.7)	< 0.001 ^{a*}	43 (41.0)	14 (42.4)	0.057 ^b
1 – 20 years	8 (5.8)	29 (21.0)		4 (3.8)	4 (12.1)	
21 – 40 years	42 (30.4)	18 (13.0)		37 (35.2)	5 (15.2)	
> 40 years	31 (22.5)	10 (7.2)		21 (20.0)	10 (30.3)	
Intensity of smoking						
No Smoking	57 (41.3)	81 (58.7)	< 0.001 ^{b*}	43 (41.0)	14 (42.4)	0.737 ^b
1 – 2 Cigarette(s)/day	3 (2.2)	23 (16.7)		2 (1.9)	1 (3.0)	
3 – 5 Cigarettes/day	68 (49.3)	25 (18.1)		51 (48.6)	17 (51.5)	
≥ 6 Cigarettes/day	10 (7.2)	9 (6.5)		9 (8.6)	1 (3.0)	
Alcohol consumption						
Yes	41 (29.7)	29 (21.0)	0.128 ^c	32 (30.5)	9 (27.3)	0.894 ^c
No	97 (70.3)	109 (79.0)		73 (69.5)	24 (72.7)	

Nominal data are reported as number (percentage), meanwhile interval data are expressed as mean±SD. ^aComputed using Pearson Chi Square. ^bComputed using Fisher's Exact Test. ^cComputed using Continuity Correction. ^dComputed using one way ANOVA test. *statistically significant (p<0.05).

TABLE II - Association of Demographic, Clinical, and Lifestyle factors with Biomarkers level (TT and ADMA), n= 138

	Total Testosterone ≤ 9.55 nmol/L n=33 (%)	Total Testosterone > 9.55 nmol/L n=105 (%)	p Value	Asymmetric dimethylarginine ≤ 0.665 μmol/L n=67 (%)	Asymmetric dimethylarginine > 0.665 μmol/L n=71 (%)	p Value
	Demographic factors					
Ethnic						
Malay	15 (45.5)	53 (50.4)	0.758 ^a	31 (46.3)	37 (52.1)	0.267 ^a
Chinese	11 (33.3)	28 (26.7)		17 (25.4)	22 (31.0)	
Indian	7 (21.2)	24 (22.9)		19 (28.4)	12 (16.9)	
Marital Status						
Married	28 (84.8)	105 (100.0)	0.001 ^{b*}	67 (100.0)	66 (93.0)	0.059 ^b
Others	5 (15.2)	0 (0.00)		0 (0.0)	5 (7.0)	

TABLE II - Association of Demographic, Clinical, and Lifestyle factors with Biomarkers level (TT and ADMA), n= 138 (cont.)

	Total Testosterone ≤ 9.55 nmol/L n=33 (%)	Total Testosterone > 9.55 nmol/L n=105 (%)	p Value	Asymmetric dimethylarginine ≤ 0.665 μmol/L n=67 (%)	Asymmetric dimethylarginine > 0.665 μmol/L n=71 (%)	p Value
Demographic factors						
Occupation						
Government Employee	3 (9.1)	33 (31.4)	< 0.001 ^{b*}	21 (31.3)	15 (21.1)	0.006 ^{a*}
Non-government employee	2 (6.1)	27 (25.7)		20 (29.9)	9 (12.7)	
Self Employed	5 (15.2)	16 (15.2)		11 (16.4)	10 (14.1)	
Pensioner	15 (45.5)	15 (14.3)		9 (13.4)	21 (29.6)	
Unemployed	8 (24.2)	14 (13.3)		6 (9.0)	16 (22.5)	
Academic Qualification						
Primary	7 (21.2)	4 (3.8)	0.002 ^{b*}	2 (3.0)	9 (12.7)	0.014 ^{b*}
Secondary	25 (75.8)	86 (81.9)		53 (79.1)	58 (81.7)	
Tertiary	1 (3.0)	15 (14.3)		12 (17.9)	4 (5.6)	
Monthly Household Income						
Low	16 (48.5)	14 (13.3)	< 0.001 ^{b*}	5 (7.5)	25 (35.2)	< 0.001 ^{a*}
Medium	14 (42.4)	51 (48.6)		33 (49.3)	32 (45.1)	
High	3 (9.1)	40 (38.1)		29 (43.3)	14 (19.7)	
Clinical factors						
Type 2 Diabetes Mellitus						
Present	20 (60.6)	50 (47.6)	0.270 ^c	31 (46.3)	39 (54.9)	0.397 ^c
Absent	13 (39.4)	55 (52.4)		36 (53.7)	32 (45.1)	
Hypertension						
Present	17 (51.5)	68 (64.8)	0.246 ^c	45 (67.2)	40 (56.3)	0.258 ^c
Absent	16 (48.5)	37 (35.2)		22 (32.8)	31 (43.7)	
Hyperlipidemia						
Present	18 (54.5)	47 (44.8)	0.434 ^c	29 (43.3)	36 (50.7)	0.483 ^c
Absent	15 (45.5)	58 (55.2)		38 (56.7)	35 (49.3)	
Coronary Artery Disease						
Present	21 (63.6)	59 (56.2)	0.580 ^c	35 (52.2)	45 (63.4)	0.249 ^c
Absent	12 (36.4)	46 (43.8)		32 (47.8)	26 (36.6)	
Lower Urinary Tract Symptoms/ Benign prostatic hyperplasia						
Present	14 (42.4)	28 (26.7)	0.134 ^c	16 (23.9)	26 (36.6)	0.150 ^c
Absent	19 (57.6)	77 (73.8)		51 (76.1)	45 (63.4)	
Sildenafil 100mg						
Yes	3 (9.1)	31 (29.5)	0.080 ^b	20 (29.9)	14 (19.7)	0.237 ^c
No	30 (90.9)	74 (70.5)		47 (70.1)	57 (80.3)	
Sildenafil 50mg						
Yes	19 (57.6)	43 (41.0)	0.140 ^c	29 (43.3)	33 (46.5)	0.837 ^c
No	14 (42.4)	62 (59.0)		38 (56.7)	38 (53.5)	
Tadalafil 20mg						
Yes	3 (9.1)	19 (18.1)	0.282 ^b	9 (13.4)	13 (18.3)	0.583 ^c
No	30 (90.9)	86 (81.9)		58 (86.6)	58 (81.7)	
Vardenafil 10mg						
Yes	5 (15.2)	4 (3.8)	0.058 ^b	4 (6.0)	5 (7.0)	0.799 ^b
No	28 (84.8)	101 (96.2)		63 (94.0)	66 (93.0)	
Vardenafil 20mg						
Yes	3 (9.1)	8 (7.6)	0.724 ^b	5 (7.5)	6 (8.5)	0.830 ^c
No	30 (90.9)	97 (92.4)		62 (92.5)	65 (91.5)	

TABLE II - Association of Demographic, Clinical, and Lifestyle factors with Biomarkers level (TT and ADMA), n= 138 (cont.)

	Total Testosterone		p Value	Asymmetric dimethylarginine		p Value
	≤ 9.55 nmol/L n=33 (%)	> 9.55 nmol/L n=105 (%)		≤ 0.665 μmol/L n=67 (%)	> 0.665 μmol/L n=71 (%)	
Life style Factors						
Physical activities						
Yes	2 (6.1)	46 (43.8)	< 0.001 ^{b*}	30 (44.8)	18 (25.4)	0.027 ^{c*}
No	31 (93.9)	59 (56.2)		37 (55.2)	53 (74.6)	
Duration of physical activities						
No	31 (93.9)	59 (56.2)	< 0.001 ^{b*}	37 (55.2)	53 (74.6)	0.055 ^a
≤ 2 days/week	1 (3.0)	30 (28.6)		19 (28.4)	12 (16.9)	
> 2 days/week	1 (3.0)	16 (15.2)		11 (16.4)	6 (8.5)	
Intensity of physical activities						
No	31 (93.9)	59 (56.2)	< 0.001 ^{b*}	37 (55.2)	53 (74.6)	0.006 ^{a*}
< 1 Hour/day	1 (3.0)	14 (13.3)		6 (9.0)	9 (12.7)	
≥ 1 Hour/day	1 (3.0)	32 (30.5)		24 (35.8)	9 (12.7)	
Smoking						
Yes	21 (63.6)	60 (57.1)	0.647 ^c	39 (58.2)	42 (59.2)	0.910 ^c
No	12 (36.4)	45 (42.9)		28 (41.8)	29 (40.8)	
Duration of smoking						
No smoking	12 (36.4)	45 (42.9)	0.019 ^{b*}	28 (41.8)	29 (40.8)	0.160 ^b
1 – 20 years	3 (9.1)	5 (4.8)		5 (7.5)	3 (4.2)	
21 – 40 years	5 (15.2)	37 (35.2)		24 (35.8)	18 (25.4)	
> 40 years	13 (39.4)	18 (17.1)		10 (14.9)	21 (29.6)	
Intensity of smoking						
No Smoking	12 (36.4)	45 (42.9)	0.104 ^b	28 (41.8)	29 (40.8)	0.189 ^b
1 – 2 Cigarette(s)/day	0 (0.0)	3 (2.9)		1 (1.5)	2 (2.8)	
3 – 5 Cigarettes/day	21 (63.6)	47 (44.7)		30 (44.8)	38 (53.5)	
≥ 6 Cigarettes/day	0 (0.0)	10 (9.5)		8 (11.9)	2 (2.8)	
Alcohol consumption						
Yes	11 (33.3)	30 (28.6)	0.761 ^c	21 (31.3)	20 (28.2)	0.825 ^c
No	22 (66.7)	75 (71.4)		46 (68.7)	51 (71.8)	

Nominal data are reported as number (percentage), meanwhile interval data are expressed as mean±SD. ^a Computed using Pearson Chi Square.

^b Computed using Fisher's Exact Test. ^c Computed using Continuity Correction. *statistically significant (p<0.05)

income, physical activity and intensity of physical activity were reported as insignificant predictors for severity of ED (Table III).

The only significant predictor which influenced TT level in Malaysian ED patients was occupation (p = 0.023). Specifically, pensioner (0.038) and unemployed (0.007) decreased the TT level by 0.08 and 0.04 times respectively (Table IV). On the other hand, intensity of physical activity (p = 0.018) and academic qualification (p = 0.047) were reported as the significant predictors which influenced ADMA level in Malaysian ED population. Spending less hours (inactive) for physical activities are 2.61 times most likely increasing ADMA level than active men (OR = 0.87). Meanwhile, men with secondary academic qualification are 4.51 times most likely to increase ADMA level than men with tertiary academic qualification level (OR = 1.88) (Table V).

DISCUSSION

Severity of ED was increased as the age increased. Mean IIEF-5 scores was higher in control group compared to case (ED patients). This finding was consistent with a survey conducted in Malaysia (Khoo *et al.*, 2008). Beside, half of the patients who participated in this study were reported having ED (n = 138). This prevalence is in accordance with two studies conducted in Malaysia previously which reported nearly two third of the study population were suffering from ED (Ab Rahman, Al-Sadat, Yun Low, 2011; Fadzil *et al.*, 2014). Occupation (p = 0.03) and TT levels (p = 0.001) are the significant predictors for worsening of severity level of ED in Malaysian population. Meanwhile, occupation (p = 0.023) is the only significant predictor which influencing TT level in Malaysian ED patients specifically, pensioner (0.038)

TABLE III - Predictors of Severity of ED (Binary Logistic Regression – Factors Associated with Severity of ED)

Predictors	OR	95% CI		p-value	
		Low	High		
Occupation ^a	Government			0.03*	
	Non-government	1.16	0.05	26.26	0.04*
	Self employed	10.55	0.43	257.06	0.004*
	Pensioner	8.07	0.19	352.45	0.026*
	Unemployed	4.04	0.31	52.25	0.071
TT	0.41	0.25	0.69	0.001*	
ADMA	320.75	0.77	133030.84	0.06	
Academic Qualification ^b	Primary			0.10	
	Secondary	0.02	0.00019	1.18	0.06
	Tertiary	0.01	0.00031	0.68	0.07
Monthly Income ^c	Low			0.21	
	Medium	36.86	0.60	2269.33	0.09
	High	10.73	0.22	521.76	0.23
Physical activity ^d	Yes			0.408	
	No	1.57	0.16	15.45	0.701
Intensity of Physical activity ^e	No			0.82	
	< 1 Hour/day	1.34	0.12	15.30	0.82
	≥ 1 Hour/day	1.07	0.88	1.26	0.86

Binary logistics regression test was done to obtain the OR and p value; *statistically significant (p<0.05); ^a Reference category: Government; ^b Reference category: Primary Education; ^c Reference category: Low Monthly Income; ^d Reference category: Yes (Actively involved in physical activity); ^e Reference category: No (Physical activity – Inactive).

TABLE IV - Predictors of Total Testosterone Level (Binary Logistic Regression – Factors Associated with TT level)

Predictors	OR	95% CI		p-value	
		Low	High		
Occupation ^a	Government			0.023*	
	Non-government	0.50	0.06	4.56	0.542
	Self employed	0.46	0.03	6.62	0.571
	Pensioner	0.08	0.01	0.87	0.038*
	Unemployed	0.04	0.01	0.42	0.007*
Academic Qualification ^b	Primary			0.108	
	Secondary	0.06	0.01	1.71	0.099
	Tertiary	0.33	0.02	6.10	0.458
Monthly Income ^c	Low			0.102	
	Medium	0.08	0.01	0.84	0.335
	High	1.26	0.15	10.82	0.835
Physical activity ^d	No			0.999	
	Yes	7.03	0.25	195.13	0.250
Duration Physical activity ^d	No			0.755	
	≤ 2 days/week	2.16	0.05	91.51	0.686
	> 2 days/week	2.65	0.95	50.51	0.686
Intensity Physical activity ^d	No			0.932	
	< 1 Hour/day	0.87	0.04	20.13	0.932
	≥ 1 Hour/day	0.48	0.04	52.39	0.827
Duration of smoking ^e	No smoking			0.628	
	1 – 20 years	1.40	0.39	4.99	0.608
	21 – 40 years	0.24	0.01	4.13	0.324
	> 40 years	1.46	0.31	7.00	0.635

Binary logistics regression test was done to obtain the OR and p value; *statistically significant (p<0.05); ^a Reference category: Government; ^b Reference category: Primary Education; ^c Reference category: Low Monthly Income; ^d Reference category: No (Physical activity - Inactive); ^e Reference category: No Smoking

TABLE V - Predictors of Asymmetric Dimethylarginine (ADMA) level (Binary Logistic Regression – Factors Associated with ADMA level)

Predictors	OR	95% CI		p-value	
		Low	High		
Occupation ^a	Government			0.109	
	Non-government	5.40	0.45	64.15	0.181
	Self employed	1.89	0.16	22.73	0.615
	Pensioner	6.23	0.51	76.70	0.153
	Unemployed	7.15	0.64	80.36	0.111
Academic Qualification ^b	Primary			0.047*	
	Secondary	4.51	0.48	42.83	0.014*
	Tertiary	1.88	0.48	7.40	0.341
Monthly Income ^c	Low			0.418	
	Medium	20.99	1.87	235.25	0.190
	High	1.85	0.52	6.60	0.367
Physical activity ^d	Yes				
	No	0.52	0.19	1.41	0.198
Intensity Physical activity ^e	No			0.018*	
	< 1 Hour/day	2.61	0.65	10.48	0.008*
	≥ 1 Hour/day	0.87	0.18	4.21	0.060

Binary logistics regression test was done to obtain the OR and p value; *statistically significant ($p < 0.05$); ^aReference category: Government; ^bReference category: Primary Education; ^cReference category: Low Monthly Income; ^dReference category: Yes (Actively involved in physical activity); ^eReference category: No (Physical activity - Inactive).

and unemployed (0.007) decreasing the TT level by 0.08 and 0.04 times respectively. On the other hand, intensity of physical activity ($p = 0.018$) and academic qualification ($p = 0.047$) were reported as the significant predictors which influencing ADMA level in Malaysian ED population.

Factors associated with severity of ED

Our study showed that occupation is significantly associated with the severity of ED and this finding is supported by few studies conducted previously in Malaysia and globally (AlMogbel, 2014; Aytaç *et al.*, 2000). This study envisions that patients' ED management is prone to be affected by occupation status. Particularly, self-employed men were 10.55 times more likely to have severe ED as compared to government employees. Besides that, pensioners (OR = 8.07) and non-government employees (OR = 1.16) were also more prone to have severe ED than government employees. A study conducted in 26 diabetes clinics in Israel involving 900 ED patients with diabetes mellitus showed severity of ED was significantly increased in unemployed ($p < 0.0001$) and blue-collar profession patients ($p = 0.0044$) (Kalter-Leibovici *et al.*, 2005). The term "blue-collar" and "white-collar" are occupational classifications that differentiate workers who perform manual labour and professional jobs respectively. Similar report was obtained from a study conducted by Aytaç *et*

al. (2000) that revealed a significant association between occupation or employment status with severity of ED. The result demonstrated that men in blue-collar professions were 1.55 times more likely to acquire severe ED when compared to men in white-collar occupation (O.R.=1.55, 95% C.I.=1.06–2.28) (Aytaç *et al.*, 2000). Furthermore, another study involving 312 Saudi diabetic patients reported that unemployed men were more likely to develop severe ED as compared to employees, and significant association was obtained between occupation and severity of ED ($X^2 = 29.069$, $df = 3$, $p = 0.001$) (AlMogbel, 2014). In our study, IIEF scores were reported to be higher among patients with better employment status with less workload and work stress. This explains that men with stable employment, who are also generously compensated have a greater sense of control over their wellbeing (Momtaz *et al.*, 2014). Besides that, ED was severe among patients with unstable employment as this could be due to financial constraints in treating ED. The costs associated with ED treatment can be a financial burden. Therefore, the ED treatment is unaffordable for some patients who have unsecured job coupled with high living expenses (Hackett, 2005). This situation explains the huge difference in severity of ED among patients in different categories of occupation. High workload and unemployment for a longer period of time can impact our health as well. Stress due to unemployment or work burden eventually affects erection

and impedes men's sexual life. A significant negative impact on sexual health was reported in a psychological study inspecting the association between sexual dysfunction and occupational stress (Štulhofer, Træen, Carvalheira, 2013). The study revealed that working longer hours and stress in accomplishing a work within a targeted time eventually affect sexual performance. This study also showed that men with a higher workload are 1.8 times more likely to have issues in sexual relationship than men with less work strain (Štulhofer, Traeen, Carvalheira, 2013). In addition, financial crisis faced by unemployed men causes their ED to be untreated over a long time. This could also lead to the risk of increasing ED severity. Approaching a therapist or a doctor is the best solution to alleviate severe ED. Besides that, discussing the problem with partners by expressing their feeling and expectations could help affected men to feel better.

This finding emphasized that there was a significant association between TT level and the severity of ED. From this study, it can be observed that TT ($p < 0.001$) was significantly associated with severity of ED. Furthermore, binary regression analysis indicated low TT level as a significant predictor which was more likely to cause severe ED, (OR=0.41). High level of TT might not heavily affect erectile function, however low TT level can have significant impact on the severity level of ED (Mikhail, 2006). This was proven in a few studies which explored significant effect of low TT level on the severity of ED (Brooke *et al.*, 2014; Liao *et al.*, 2012; Martínez-Jabaloyas *et al.*, 2006). TT plays a crucial role in the sexual function of men and several studies have investigated the relationship between TT levels with male sexual behaviours especially ED (Liao *et al.*, 2012; Tsujimura, 2013). According to a systematic study by Mikhail, low level of TT may have a major impact on erectile function (Mikhail, 2006). Study conducted on 1,776 Chinese men aged 20 to 77 years old showed that TT is significantly associated with severity of ED with an odds ratio of 1.02 after adjusting the confounding variable; age (OR: 1.02; 95% CI: 1.00–1.04) (Liao *et al.*, 2012). This finding was consistent with the evidence from a study by Brooke *et al.* (2014) involving 126 ED patients with type II diabetes which reported a significant positive correlation between IIEF-5 scores and TT ($r = 0.546$, $p = 0.001$), where the severity of ED decreases as TT level increases (Brooke *et al.*, 2014). Parallel to this finding, a prospective study by Kang *et al.* (2011) involving 134 men who visited urology clinics with the complaint of ED revealed a significant positive correlation between serum TT level and IIEF scores ($r = 0.124$, $p = 0.034$). This study also disclosed that TT levels below the normal range significantly increased the severity of ED (Kang *et al.*, 2011). TT acts as a vasodilator

for the penile arterioles. The vasodilation of the arteries around the corpora cavernosa allows more blood to flow in to help maintain the erection. Additionally, TT activates the NO synthase and increases the expression of NO and phosphodiesterase type 5, which are essential enzymes for erection (Blute *et al.*, 2008). Besides that, testosterone restores structural, biochemical and physiological changes and induces new DNA synthesis in the smooth muscle cells and blood vessels. In addition, testosterone also contributes to venous occlusion and helps men to maintain erection (Shabsigh, 2005). Investigation on TT level should be done in men who were having symptoms of ED. Undeniably, testosterone therapy can be considered as a recommended and effective treatment for men with severe ED.

Factors associated with Total Testosterone (TT) levels in Malaysian ED patients

The effect of demographic, clinical and lifestyle factors cause significant changes on binary regression model of TT level in ED patients. After all the significant variables of demographic, clinical and lifestyle factors are included into binary regression model, occupation ($p = 0.023$) remained as significant predictor. Findings revealed that pensioners (OR = 0.08, 95% CI = 0.01-0.87, $p = 0.038$) and unemployed men (OR = 0.04, 95% CI = 0.01-0.42, $p = 0.07$) are most likely to have low TT level as compared to government employees.

To the best of the author's knowledge, very few studies have been done on predictors of demographic factors on TT level in ED patients. However, some association studies have been conducted based on low TT level with occupation and found that lower social status is significantly associated with low TT level (Zitzmann, Nieschlag, 2001). Men with better employment status have higher TT level as compared to unemployed men and pensioners. This result was in accordance with multiple studies that had been conducted earlier, studying the significant impact of occupation on TT level. Men who have work stress are likely to have lower TT level. On the contrary, higher TT level helps in lowering stress and in giving more strength and inspiration to perform better at work (Greene *et al.*, 2014). It is a known fact that stress may have physiological effects on body and cause infertility by decreasing TT level. Besides that, high stress and low TT level result in common physical symptoms including erectile dysfunction. There are few studies evidencing that the stress hormone cortisol and TT level work against each other and a high stress level is strongly associated with low TT level. Increasing stress level due to heavy workload could affect gonadal hormones secretion which results in low TT levels (Nargund, 2015).

A meta-analysis study reported that cortisol level may have a significant effect on TT level (Geniole *et al.*, 2016). The notable psychological association between TT level and stress is not well known. It is most likely that the chemicals secreted in response to stress may regulate the TT production and control its level. This indicates that socioeconomic statuses as well as psychological stress influence men's endocrine system and in turn influences the TT level.

Factors associated with Asymmetric Dimethylarginine (ADMA) level in Malaysian ED patients

Academic qualification is presented as predictor which influences ADMA level in ED patients. The link between education and ADMA level is complex and is tied closely to income. Although no studies were established on the association of academic qualification with ADMA level yet, there were few theories and hypotheses which can illustrate how education can be associated with ADMA level in term of patients' health. Education can increase an individual's knowledge levels and sense of control over their life, which in turn would encourage them to embrace a healthier lifestyle. Educated men value their health highly. They constantly look for the guidance of a physician or an experienced health care provider about their health and these men are ready to communicate effectively with them. However, less educated people might be unaware of their health due to lack of knowledge on diseases and its symptoms, which compromises on their health. In addition, poor quality of doctor-patient communication contributes to the high percentage of health issue among this group (Verlinde *et al.*, 2012). Low morbidity rate was reported among educated men and they are less likely to have poor health. In contrast, the opposite result was observed for less educated men (Sallis, Carlson, 2015; Zimmerman, Woolf, 2014). Besides that, a few studies suggest that educated people have healthier behaviours. Those with higher education level were less likely to smoke, drink heavily, use illegal drugs or be overweight (Cutler, Lleras-Muney, 2010). In this study, the knowledge on chemical nature of biomarker (especially ADMA) is essential as it will help them to predict how it is produced and the mechanism of action in our body. This knowledge will help an individual to be aware of the biomarker level changes and to seek medical help in order to overcome the problem.

Meanwhile, increasing intensity of physical activities could help to decrease ADMA concentration level in ED patients. This finding is consistent with a study conducted by Mittermayer *et al.* (2005), which reported that

constant physical activity significantly decreases ADMA concentration ($p < 0.001$) (Mittermayer *et al.*, 2005). Even though the above mentioned study was conducted on non-ED population, the finding concluded that there is an association between intensity of physical activities and ADMA levels. Recently, Kevin (2011) showed that after a moderate to intense exercise, ADMA level decreased in patients from the initial level before they began the exercise (0.42 ± 0.02 and 0.43 ± 0.03 micromol/l). The ADMA level started to increase again after they discontinued their exercise (Kevin, 2011). A decrease in ADMA level was even recorded in an animal study after the rats were exposed to exercise training, although the result was statistically insignificant (Esfahani *et al.*, 2013). These studies concluded that ADMA level can be lowered by consistent physical activities. The mechanism to decrease ADMA level associated with physical exercise is crucial. ADMA is produced in substantial amount through methylation of protein-bound L-arginine by protein methyltransferase (PRMT) enzyme and the decomposition of these ADMA by DDAH activity appears to determine the ADMA level in our body (Teplan *et al.*, 2014). Intensive physical activities may affect antioxidant level through increased expression of the superoxide dismutase. The DDAH activity was reduced by the increased concentration of oxidants level and oxidative stress. Hence, the enhancement of antioxidant status through regular exercise might be related to the decrease in ADMA level in physically active individuals (Mittermayer *et al.*, 2005; Teplan *et al.*, 2014). Besides that, constant physical activity can initiate the endothelial NO-synthase (eNOS) expression through increased endothelial shear stress and arterial blood flow. As we discussed earlier, ADMA inhibits NO synthesis. However, increasing intensity of physical exercise elevate NO bioavailability. This explains that ADMA level is suppressed upon significant improvement in physical activities which resulted in increased concentration level of NO (Schlager *et al.*, 2011). Furthermore, ADMA could trigger the development of atherosclerosis by inhibiting NO production from amino acid L-arginine. Hence, decreased ADMA levels may enhance endothelial function in ED patients who were physically active (Böger, 2006). Since high ADMA level was related to ED (Paroni *et al.*, 2012), our findings demonstrate that physical activity does not only decrease ADMA level but could also contribute to improvement in erectile function.

In addition, food intake and diets may be associated with ED. It is noted that cleaning up our diet is the more natural ways to improve the erectile function. Foods as well as the environmental pollutants and chemicals that can cause ED should be avoided for a better men's sexual health (Esposito *et al.*, 2010). Research has demonstrated that

similar eating patterns that can cause cardiovascular diseases due to limited blood flow in the coronary arteries also block blood flow to the arteries around corpora cavernosa (La Favor *et al.*, 2013). Diets that lack of fruits and vegetables alongside with plenty of fatty, fried and processed foods can lead to decreased blood circulation throughout the body. According to Esposito, ED is disproportion to clean diet, which includes fruits, vegetables, whole grains, fish, heart-healthy fats including nuts and olive oil (Esposito *et al.*, 2010). Animal fat and cholesterol is particularly bad for our heart. In fact, many men do not realize that ED is one of the early signs of cardiovascular diseases whereas a good blood circulation is needed to achieve and maintain an erection.

Besides, consuming foods packed in cans or plastic would increase the possibility having severe ED. Bisphenol-A (BPA) is a chemical found in plastic products as well as on the linings in canned foods which can inhibit sex hormones (Vandenberg *et al.*, 2007; Rudel *et al.*, 2011). Few studies have found links associating BPA with ED and decreased sexual desire, as well as infertility (Li *et al.*, 2009; Li *et al.*, 2010). Other than this, soy and processed foods which were high in carbohydrates and excessive unhealthy fats have an estrogenic effect and can affect men's hormones as well. It contains substances that mimic estrogen, a female hormone that men have in smaller amounts. It is important to maintain the right balance between estrogen and testosterone to preserve the sexual health especially erectile function (Siepmenn *et al.*, 2011).

There are evidences that chronic heavy drinking can cause liver and nerve damage which can interfering with the normal balance of male sex hormone levels that can lead to ED. Alcohol may alter the endocrine system and has an inhibitory effect on hypothalamic pituitary testicular axis which has direct effect on testis. Alteration in gonadotropin releasing hormone receptor by alcohol may result in decrease of LH synthesis. Moreover, increased β -endorphin levels in heavy alcoholics may lead to testicular damage and diminish testosterone production (La Vignera *et al.*, 2013).

In conclusion, the purpose of this study was to examine the combination of demographic, clinical and lifestyle factors that could be associated with the severity of ED and biomarker levels in Malaysian ED patients. The binary regression result concluded occupation and TT as the significant predictors of severity of ED. Demographic and biomarker dominate clinical and lifestyle factors in determining predictors of severity of ED in Malaysian ED patients. It shows that Malaysian patients generally live a healthy lifestyle practising good ethics in term of physical activeness, smoking and alcohol consumption. Meanwhile, demographic and lifestyle factors predominate clinical

factors in influencing TT and ADMA levels. As per the present results, there is a reasonable need to investigate the TT level and occupational background of patients when they present with severe ED. Urologists or ED experts should examine patients' TT levels and add the necessary improvements in treating ED patients. Besides, urologists also need to educate ED patients and give priorities for their health issues regardless of their occupation background and help them to live a quality life. Identification of these predictors influencing severity of ED, TT and ADMA level may help to increase our knowledge on risk factors of ED. Thus, these predictors may serve as new indicators in providing primarily guidance to urologists or physician and ensuring ED can be managed and treated more effectively.

ACKNOWLEDGEMENT

The authors would like to thank University of Malaya, Malaysia (RP024A-14HTM) for financial and technical supports.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

- Ab Rahman AA, Al-Sadat N, Yun Low W. Prevalence of erectile dysfunction in primary care setting, Malaysia. *J Mens Health*. 2011;8(S1):S50-S3.
- Aktoz T, Aktoz M, Tatli E, Kaplan M, Turan FN, Barutcu A, et al. Assessment of the relationship between asymmetric dimethylarginine and severity of erectile dysfunction and coronary artery disease. *Int Urol Nephrol*. 2010;42(4):873-9.
- Al Mogbel TA. Erectile dysfunction and other sexual activity dysfunctions among Saudi Type 2 Diabetic patients. *Int J Health Sci*. 2014;8(4):347-59.
- Ali Z, Mishra A, Kumar R, Alam P, Pandey P, Ram R, et al. Interactions among vascular-tone modulators contribute to high altitude pulmonary edema and augmented vasoreactivity in highlanders. *PLoS One*. 2012;7(9):e44049.
- Aytaç IA, Araujo AB, Johannes CB, Kleinman KP, McKinlay JB. Socioeconomic factors and incidence of erectile dysfunction: findings of the longitudinal Massachusetts Male Aging Study. *Soc Sci Med*. 2000;51(5):771-8.

- Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. A prospective study of risk factors for erectile dysfunction. *J Urol*. 2006;176(1):217-21.
- Blute M, Hakimian P, Kashanian J, Shteynshluyger A, Lee M, Shabsigh R. Erectile dysfunction and testosterone deficiency. *Front Horm Res*. 2008. p. 108-22.
- Böger RH. Asymmetric dimethylarginine (ADMA): a novel risk marker in cardiovascular medicine and beyond. *Ann Med*. 2006;38(2):126-36.
- Brooke J, Walter D, Kapoor D, Marsh H, Muraleedharan V, Jones T. Testosterone deficiency and severity of erectile dysfunction are independently associated with reduced quality of life in men with type 2 diabetes. *J Androl*. 2014;2(2):205-11.
- Cao S, Yin X, Wang Y, Zhou H, Song F, Lu Z. Smoking and risk of erectile dysfunction: systematic review of observational studies with meta-analysis. *PLoS One*. 2013;8(4):e60443.
- Chrysohoou C, Panagiotakos D, Pitsavos C, Siasos G, Oikonomou E, Varlas J, et al. Low total testosterone levels are associated with the metabolic syndrome in elderly men: the role of body weight, lipids, insulin resistance, and inflammation; the Ikaria study. *Rev Diabet Stud*. 2013;10(1):27.
- Cutler DM, Lleras-Muney A. Understanding differences in health behaviors by education. *J Health Econ*. 2010;29(1):1-28.
- Dutkiewicz S, Skawiński D, Duda W, Duda M. Assessing the influence of Benign Prostatic Hyperplasia (BPH) on Erectile Dysfunction (ED) among patients in Poland. *Cent European J Urol*. 2012;65(3):135-138.
- Esfahani PS, Gharakhanlou R, Karimian J, Khazaei M, Feizi A, Safarzade A. Effect of resistance training on plasma nitric oxide and asymmetric dimethylarginine concentrations in type i diabetic rats. *Int J Prev Med*. 2013;4(Suppl 1):S78.
- Esposito K, Ciotola M, Giugliano F, Maiorino MI, Autorino R, De Sio M, Giugliano D, et al. Effects of intensive lifestyle changes on erectile dysfunction in men. *J Sexual Med*. 2009;6(1):243-250.
- Esposito K, Giugliano F, Maiorino MI, & Giugliano D. Dietary factors, Mediterranean diet and erectile dysfunction. *J Sexual Med*. 2010;7(7):2338-2345.
- Fadzil MA, Sidi H, Ismail Z, Hassan MRC, Thuzar K, Midin M, et al. Socio-demographic and psychosocial correlates of erectile dysfunction among hypertensive patients. *Compr Psychiatry*. 2014;55(Suppl 1):S23-S8.
- Gades NM, Nehra A, Jacobson DJ, McGree ME, Girman CJ, Rhodes T, et al. Association between smoking and erectile dysfunction: a population-based study. *Am J Epidemiol*. 2005;161(4):346-51.
- Geniole SN, Bird BM, Ruddick EL, Carré JM. Effects of competition outcome on testosterone concentrations in humans: An updated meta-analysis. *Horm and Behav*. 2016. [ahead of print].
- Greene FJ, Han L, Martin S, Zhang S, Wittert G. Testosterone is associated with self-employment among Australian men. *Econ Hum Biol*. 2014;13:76-84.
- Griffeth RJ, Carretero J, Burks DJ. Insulin receptor substrate 2 is required for testicular development. *PLoS One*. 2013;8(5):e62103.
- Grossmann M, Gianatti EJ, Zajac JD. Testosterone and type 2 diabetes. *Curr Opin Endocrinol Diabetes Obes*. 2010;17(3):247-56.
- Hackett GI. Patient preferences in treatment of erectile dysfunction: the continuing importance of patient education. *Clin cornerstone*. 2005;7(1):57-65.
- Huri HZ, Sanusi NDM, Razack AHA, Mark R. Association of psychological factors, patients' knowledge, and management among patients with erectile dysfunction. *Patient Prefer Adherence*. 2016;10:807.
- Isidori AM, Buvat J, Corona G, Goldstein I, Jannini EA, Lenzi A, et al. A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment-a systematic review. *Eur Urol*. 2014;65(1):99-112.
- Javaroni V, Neves MF. Erectile dysfunction and hypertension: impact on cardiovascular risk and treatment. *Int J Hypertens*. 2012;2012:627278.
- Kang JI, Ham BK, Oh MM, Kim JJ, Moon DG. Correlation between serum total testosterone and the AMS and IIEF questionnaires in patients with erectile dysfunction with testosterone deficiency syndrome. *Korean J Urol*. 2011;52(6):416-20.

- Kalka D, Domagała Z, Dworak J, Womperski K, Rusiecki L, Marciniak W, et al. Association between physical exercise and quality of erection in men with ischaemic heart disease and erectile dysfunction subjected to physical training. *Kardiol Pol.* 2013;71(6):573-80.
- Kalter-Leibovici O, Wainstein J, Ziv A, Harman-Bohem I, Murad H, Raz I. Clinical, socioeconomic, and lifestyle parameters associated with erectile dysfunction among diabetic men. *Diabetes care.* 2005;28(7):1739-44.
- Kevin R. Rapid communication-effect of exercise training on asymmetric dimethylarginine concentration in women aged 65-74 years with Type 2 Diabetes. *Endocrinol Metabol Syndrome.* 2011.
- Khoo EM, Tan HM, Low WY. Erectile dysfunction and comorbidities in aging men: An urban cross-sectional study in Malaysia. *J Sex Med.* 2008;5(12):2925-34.
- La Favor JD, Anderson EJ, Hickner RC, Wingard CJ. Erectile dysfunction precedes coronary artery endothelial dysfunction in rats fed a high-fat, high-sucrose, Western pattern diet. *J Sex Med.* 2013;10(3):694-703.
- La Vignera S, Condorelli RA, Balercia G, Vicari E, Calogero AE. Does alcohol have any effect on male reproductive function? A review of literature. *Asian J Androl.* 2013;15(2):221-5.
- Lee A, Ho L, Yip A, Fan S, Lam T. The effect of alcohol drinking on erectile dysfunction in Chinese men. *Int J Impot Res.* 2010;22(4):272-8.
- Li D, Zhou Z, Qing D, He Y, Wu T, Miao M, Zhu Q, et al. Occupational exposure to bisphenol-A (BPA) and the risk of self-reported male sexual dysfunction. *Human Reproduction.* 2009;25(2):519-527.
- Li DK, Zhou Z, Miao M, He Y, Qing D, Wu T, Zhu Q, et al. Relationship Between Urine Bisphenol-A Level and Declining Male Sexual Function. *J Androl.* 2010;31(5):500-506.
- Liao M, Huang X, Gao Y, Tan A, Lu Z, Wu C, et al. Testosterone is associated with erectile dysfunction: a cross-sectional study in Chinese men. *PloS One.* 2012;7(6):e39234.
- Martínez-Jabaloyas JM, Queipo-Zaragoza A, Pastor-Hernández F, Gil-Salom M, Chuan-Nuez P. Testosterone levels in men with erectile dysfunction. *BJU Int.* 2006;97(6):1278-83.
- Martin SA, Atlantis E, Lange K, Taylor AW, O'Loughlin P, Wittert GA. Predictors of sexual dysfunction incidence and remission in men. *J Sex Med.* 2014;11(5):1136-47.
- Meller SM, Stilp E, Walker CN, Mena-Hurtado C. The link between vasculogenic erectile dysfunction, coronary artery disease, and peripheral artery disease: role of metabolic factors and endovascular therapy. *J Invasive Cardiol.* 2013;25(6):313-9.
- Micheel C, Nass S, Omenn G. Committee on the Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials; Board on Health Care Services; Board on Health Sciences Policy; Institute of Medicine. Evolution of translational omics: Lessons learned and the path forward. *Evolution of Translational Omics: Lessons Learned and the Path Forward Institute of Medicine.* 2012; 300p.
- Mikhail N. Does testosterone have a role in erectile function? *Am J Med.* 2006;119(5):373-82.
- Mittermayer F, Pleiner J, Krzyzanowska K, Wiesinger GF, Francesconi M, Wolzt M. Regular physical exercise normalizes elevated asymmetrical dimethylarginine concentrations in patients with type 1 diabetes mellitus. *Wien Klin Wochenschr.* 2005;117(23-24):816-20.
- Momtaz YA, Hamid TA, Ibrahim R, Akahbar SAN. Racial and socioeconomic disparities in sexual activity among older married Malaysians. *Arch Gerontol Geriatr.* 2014;58(1):51-5.
- Musicki B, Liu T, Lagoda GA, Strong TD, Sezen SF, Johnson JM, et al. Hypercholesterolemia-induced erectile dysfunction: Endothelial nitric oxide synthase (eNOS) uncoupling in the mouse penis by NAD (P) H oxidase. *J Sex Med.* 2010;7(9):3023-32.
- Nargund VH. Effects of psychological stress on male fertility. *Nat Rev Urol.* 2015;12(7):373-82.
- NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. *JAMA.* 1993;270(1):83-90.
- Nikoobakht M, Nasseh H, Pourkasmaee M. The relationship between lipid profile and erectile dysfunction. *Int J Impot Res.* 2005;17(6):523-6.
- Nunes KP, Labazi H, Webb RC. New insights into hypertension-associated erectile dysfunction. *Curr Opin Nephrol Hypertens.* 2012;21(2):163-70.

- Önder A, Aycan Z, Koca C, Ergin M, Çetinkaya S, Ağladioğlu SY, et al. Evaluation of asymmetric dimethylarginine (ADMA) levels in children with growth hormone deficiency. *J Clin Res Pediatr Endocrinol.* 2014;6(1):22.
- Oyekanmi AK, Adelufosi AO, Abayomi O, Adebowale TO. Demographic and clinical correlates of sexual dysfunction among Nigerian male outpatients on conventional antipsychotic medications. *BMC Res Notes.* 2012;5:267.
- Paroni R, Barassi A, Ciociola F, Dozio E, Finati E, Fermo I, et al. Asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA) and L-arginine in patients with arteriogenic and non-arteriogenic erectile dysfunction. *Int J Androl.* 2012;35(5):660-7.
- Pastuszak AW. Current diagnosis and management of erectile dysfunction. *Curr Health Sex Rep.* 2014;6(3):164-76.
- Rudel RA, Gray JM, Engel CL, Rawsthorne TW, Dodson RE, Ackerman JM, Brody JG, et al. Food packaging and bisphenol A and bis (2-ethylhexyl) phthalate exposure: findings from a dietary intervention. *Environ Health Persp.* 2011;119(7):914.
- Safarinejad MR, Hosseini SY. Erectile dysfunction: clinical guidelines (2). *J Urol.* 2004;1(4):227-39.
- Sallis JF, Carlson JA. Population health: behavioral and social science insights physical activity: numerous benefits and effective interventions. Agency for Healthcare Research and Quality, Rockville, MD. Rockville, MD: Agency for Healthcare Research and Quality; 2015.
- Schlager O, Giurgea A, Schuhfried O, Seidinger D, Hammer A, Gröger M, et al. Exercise training increases endothelial progenitor cells and decreases asymmetric dimethylarginine in peripheral arterial disease: a randomized controlled trial. *Atherosclerosis.* 2011;217(1):240-8.
- Shabsigh R. Testosterone therapy in erectile dysfunction and hypogonadism. *J Sex Med.* 2005;2(6):785-92.
- Shamloul R, Ghanem H. Erectile dysfunction. *Lancet.* 2013;381(9861):153-65.
- Siepmann T, Roofeh J, Kiefer FW, Edelson DG. Hypogonadism and erectile dysfunction associated with soy product consumption. *Nutrition.* 2011; 27(7): 859-862.
- Strimbu K, Tavel JA. What are biomarkers? *Curr Opin HIV AIDS.* 2010;5(6):463.
- Štulhofer A, Træen B, Carvalheira A. Job-related strain and sexual health difficulties among heterosexual men from three european countries: the role of culture and emotional support. *J Sex Med.* 2013;10(3):747-56.
- Tamler R. Diabetes, obesity, and erectile dysfunction. *Gend Med.* 2009;6(Suppl 1):4-16.
- Tan H, Ng C, Low W, Khoo E, Yap P, Tan W. The Subang men's health research—a multiethnic community based study. *Aging Male.* 2007;10(2):111.
- Tan KC, Shiu SW, Wong Y, Tam X. Serum advanced glycation end products (AGEs) are associated with insulin resistance. *Diabetes Metab Res Rev.* 2011;27(5):488-92.
- Teplan V, Mahrova A, Pit'ha J, Racek J, Gürlich R, Teplan Jr V, et al. Early Exercise Training After Renal Transplantation and Asymmetric Dimethylarginine: Effect Obesity Kidney Blood Press Res. 2014;39(4):289-98.
- Tsujimura A. The relationship between testosterone deficiency and men's health. *World J Mens Health.* 2013;31(2):126-35.
- Vandenberg LN, Hauser R, Marcus M, Olea N, Welshons WV. Human exposure to bisphenol A (BPA). *Reproduct Toxicol.* 2007;24(2):139-177.
- VanVoorhis CRW, Morgan BL. Understanding power and rules of thumb for determining sample sizes. *Tutor Quant Methods Psychol.* 2007;3(2):43-50.
- Verlinde E, De Laender N, De Maesschalck S, Deveugele M, Willems S. The social gradient in doctor-patient communication. *Int J Equity Health.* 2012;11(1):1-14.
- Zimmerman E, Woolf SH. Understanding the relationship between education and health. Institute of Medicine of the National Academies; 2014.
- Zitzmann M, Nieschlag E. Testosterone levels in healthy men and the relation to behavioural and physical characteristics: facts and constructs. *Eur J Endocrinol.* 2001;144(3):183-97.

Received for publication on 16th October 2017
 Accepted for publication on 29th January 2018