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Quality of Life of Patients with Familial Hypercholesterolaemia: Contributing factors for Malaysians.

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Abstract
Familial hypercholesterolaemia (FH) causes severe complications including cardiovascular diseases (CVDs) and stroke, leading to poor quality of life (QoL). Despite the availability of advanced treatment, data on QoL and its contributing factors is sparse. Hence, this study aimed to describe the pattern of QoL among FH patients and investigate its association with sociodemographic factors and illness characteristics. Hundred FH patients were assessed using Pro forma questionnaires and World Health Organization QoL questionnaire (WHOQOL-BREF). Significant contributing factors including level of education, income, and the presence and type of CVDs. These findings may help to inform more effective interventions for FH patients.

Keywords: Familial hypercholesterolaemia; quality of life; sociodemography; cardiovascular disease

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1.0 Introduction

1.1 Familial hypercholesterolaemia

Familial Hypercholesterolaemia (FH) is the most common inherited lipid disorder, which causes severe elevation of low-density lipoprotein cholesterol (LDL-C) (Varghese, 2014). Unlike secondary dyslipidaemia, which elevated LDL-C is caused by external factors such as high-fat diet, or from other disease such as hypothyroidism, liver disease or chronic renal failure (Jacobson et al., 2014; Vodnala, Rubenfire, & Brook, 2012), FH is a primary dyslipidaemia where the disease is acquired since birth by genetic mutations in genes involved in cellular transportation and catabolism of LDL-C, such as LDL-receptor (*LDLR*), apolipoprotein B (*APOB*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*) and low-density lipoprotein receptor adaptor protein 1 genes (*LDLRAP1*) (Al-Khateeb, 2016). FH patients will have their LDL-C level elevated (>5 mmol/L) since childhood (Wiegman et al., 2015). Early exposure to elevated LDL-C will accelerate the atherogenesis and cause the premature manifestation of coronary heart disease (CAD) as early as in their 30s (Nordestgaard et al., 2013). Worldwide, the prevalence of FH is around 1: 500-200, while it is more common in the Malaysian population with an estimated frequency of 1:100 (Vallejo-Vaz et al., 2018). If untreated, FH patients will suffer reduced life expectancy by up to 30 years compared those without FH (Alonso, Mata, & Mata, 2005).

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1.2 Quality of life of FH patients

People who live with life-shortening diseases are generally associated with poor quality of life (QoL), whether physically, psychologically or socially (Megari, 2013). If FH is identified in children, the QoL of parents is also affected (De Jongh et al., 2003). However, with the introduction of multitude range of lipid-lowering medications and recent advancement in the clinical and molecular method for early detection of FH have greatly improved the life year gained of FH patients (Wiegman et al., 2015, Hagger et al., 2018a)). If FH is detected and treated with a statin in young age, an FH patient may even live almost as long as those without FH (Vuorio, Docherty, Humphries, Kuoppala, & Kovanen, 2013). FH patients who received lipid-lowering treatment and successfully achieved their treatment target were generally enjoying better QoL (Mortensen, Madsen, Kruse, & Bundgaard, 2016). In accordance with an increase of global awareness and collaborative study of FH (Watts et al., 2016), Malaysia has updated the national guideline for the management of dyslipidaemia by taking FH into account of treatment (Rajadurai et al., 2018). Regardless of the treatment received, however, different sociodemographic background patients' knowledge and perception on the disease may lead to different quality of life in each patient (Hagger et al., 2018b) The data of QoL among Malaysian FH patients, and QoL influencing factors in these patients are still scarce.

1.3 Aims

Recognising the limited data on QoL and its contributing factors, this study aimed to: i) describe the general perceptions of QoL and health status, and their correlation with four domains of QoL (physical health, psychological, social relationship and environment); ii) investigate the association between sociodemographic factors (gender, age, marital status, educational level, level of income) and QoL of FH patients; and, iii) compare the QoL of FH patients with different illness characteristics [presence and types of cardiovascular disease (CVD), and treatment received].

2.0 Methodology

2.1 Study design, setting and data collection

This study was a cross-sectional study which recruited participants from the Specialist Lipid and Coronary Risk Prevention Clinics in a Teaching Hospital in Malaysia. Convenient sampling was used, and the participants aged 18 years or more who were patients diagnosed with FH according to Dutch Lipid Clinic (DLC) criteria were enrolled. The DLC criteria is a validated set of criteria based on the patient's family history of premature cardiovascular disease (CVD) in their first-degree relatives, personal coronary heart disease (CHD) history, their untreated LDL-c levels and physical signs such as tendon xanthomata or arcus cornealis prior to the age of 45. Prior to the commencement of the study, written informed consent was granted from all participants. The study was approved by the Institutional Research Ethics committee (600-RMI (5/1/6).

2.2 Assessment tools

Sociodemographic background and illness characteristics were assessed using self-reported pro forma questionnaires. Sociodemographic variables include information regarding gender, age, marital status, level of education and their total household income per month. Information gathered in relation to their illness characteristics including the presence of CVDs, type of CVDs (including coronary heart disease, angina, stroke atherosclerosis and peripheral vascular disease) treatment for FH, and risk factors for coronary artery disease (including smoking status, high blood pressure, depression and high stress).

The assessment of Quality of Life (QoL) was based on a questionnaire measuring the quality of life by the World Health Organization (WHOQOL –BREF). It has been well validated and commonly used by researchers in Malaysia (Bandar, Jani, & Karim, 2014; Hasanah, Naing, & Rahman, 2003). It comprises the initial two questions which examine participants' overall perception of quality of life (Q1) and general perception of their health (Q2). The subsequent items assess the four major domains of QoL; physical (D1), psychological (D2), social relationship (D3), and environment (D4). 'Physical' domain measures the quality and satisfaction of the participants on activities of daily living; dependence on medicinal substances and medical aids; energy and fatigue; mobility; pain and discomfort; sleep and rest; and work capacity. 'Psychological' domain asks about satisfaction on bodily image and appearance; negative feelings; positive feelings; self-esteem; spirituality, religion and personal beliefs as well as thinking, learning, memory and concentration. 'Social relationship' domain relates to questions on the personal relationship, social support and sexual activity. The last domain is 'environment' which evaluates the financial resources, freedom, physical safety and security; health and social care; accessibility and quality; home environment; opportunities for acquiring new information and skills; participation in and opportunities for recreation, leisure activities, physical environment (pollution/noise/ traffic /climate) and transport.

2.3 Analysis

Statistical Package for the Social Sciences (SPSS) version 24 was used to analyse the data. Descriptive data were presented in the form of mean scores, frequencies and percentages. Cronbach's alpha (internal consistency index) was used to estimate the reliability of the QoL (Cronbach›s alpha values of ≥0.70 was considered as acceptable). The correlations between four domains of WHOQOL-BREF were analysed using Pearson's correlation. Paired *t*-test was used to compare the difference between score means of different domains. For possible associations between respondent characteristics and QoL, the independent t-test was used. Two-tailed tests were used and p values below 0.05 were considered statistically significant.

3.0 Results

3.1 Sociodemography

A total of hundred participants (37% male and 63% female), predominantly in the late forties (mean: 49.8 ± 11.4 years old) and ever married individuals (92%) participated in the study. They were mainly from a lower socioeconomic position with which 55% of the participants have a total household income less than RM3000 a month and 52% of studied participants attained only up to the level of secondary education (See Table 1).

Table 1: Background sociodemographic and illness characteristics of the participants

Variable		N	%
Sociodemography			
Age	Mean =49.8 ± SD=11.40)		
Gender			
Female		37	37.0
male		63	63.0
Marital status			
Ever married		92	92.0
Unmarried		8	8.0
Education			
Pre-university and university		48	48.0
Secondary		44	44.0
Primary and below		8	8.0
Total household income per month (RM)			
<3000		55	55.0
3001-10000		36	36.0
>10000		9	9.0
Illness Characteristics			
Cardiovascular disease			
Yes		41	41.0
No		59	59.0
Types of CVD			
Coronary heart disease		35	85.4
Angina		8	19.5
Atherosclerosis		4	9.8
Stroke		4	9.8
Peripheral vascular disease		1	2.4
Currently received treatment for FH			
Yes		69	69.0
No		31	31.0
Present of risk factor			
Smoker		13	13.0
High blood pressure		40	40.0
Depression		8	8.0
High stress		8	8.0

3.2 Illness Characteristics

Of the total participants who have FH, 41% have CVDs; mainly coronary heart disease (n=35; 85.4%), angina (n=8; 19.5%), atherosclerosis (n=4; 9.8%), stroke (n=4; 9.8%) and one participant has peripheral arterial disease. About two-thirds (69%) of the participants received lipid-lowering agents. More than a third (40%) of the participants had hypertension, 13% were smokers and 8% reported feeling stressed up and complained of feeling depressed (See Table 1 above).

3.3 Description of Quality of Life

Table 2 below shows the inter-correlations between the general perception of QoL, health status and the other four domains of QoL as described by the participants. There are statistically significant correlations between all domains. The Cronbach's alpha coefficient for internal consistency of WHOQOL-BREF was acceptable (0.857) for all 26 questions. The paired t-test showed significant differences between all four different domains of WHOQOL-BREF (see Table 3).

See Figure 1 and Figure 2 for general perceptions of QoL and health status respectively. Majority of FH patients in this study reported acceptable general perception on QoL with about 83% (n= 83) of FH patients described their QoL as 'good' or 'very good' and about 70% (n=68) of them described their health status as 'satisfied' or 'very satisfied'.

3.4 QoL and sociodemography

The 'social interaction' domain of FH female patients was better than male patients (mean score ± SD: 17.3±2.1 vs 16.3±2.4 respectively; p=0.04). 'Physical domain' of QoL was lower in patients with secondary education compared to those with pre-university and university level (14.4±2.4 vs 16.6±2.2 respectively; p<0.001). FH patients with the highest income of more than RM10,000 had the poorest 'physical' and 'psychological' domains of QoL compared to those with lower income (p=0.004 and p=0.027 respectively (See Table 4 above).

Table 2: Correlation coefficients in two overall question and four domains of WHOQOL-BREF

	Q1	Q2	D1	D2	D3	D4
Q1	1	0.388** **(<0.001)**	0.512** **(<0.001)**	0.549** **(<0.001)**	0.257* **(<0.001)**	0.397** **(<0.001)**
Q2		1	0.664** **(<0.001)**	0.495** **(<0.001)**	0.472** **(<0.001)**	0.442** **(<0.001)**
D1			1	0.691** **(<0.001)**	0.599** **(<0.001)**	0.604** **(<0.001)**
D 2				1	0.581** **(<0.001)**	0.635** **(<0.001)**
D3					1	0.499** **(<0.001)**
D4						1

All tests are measured by Pearson Correlation with 2-tailed statistical significance
**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

Table 3: Differences between domains

				95% Confidence Interval of the Difference				
	Mean	SD	Std. Error Mean	Lower	Upper	t	df	*p* value*
Pair 1: D1 - D2	-0.45	1.90	0.19	-.833	-.073	-2.37	98	**0.020**
Pair 2: D1 - D3	-1.11	2.18	0.22	-1.544	-.676	-5.07	98	**<0.001**
Pair 3: D1 - D4	-0.28	2.19	0.22	-.723	.156	-1.28	97	0.203
Pair 4: D2 - D3	-0.66	2.09	0.21	-1.074	-.240	-3.13	98	**0.002**
Pair 5: D2 - D4	0.17	1.99	0.20	-.233	.564	0.82	97	0.411
Pair 6: D3 - D4	0.82	2.35	0.24	.354	1.294	3.48	97	**0.001**

*Paired t-test

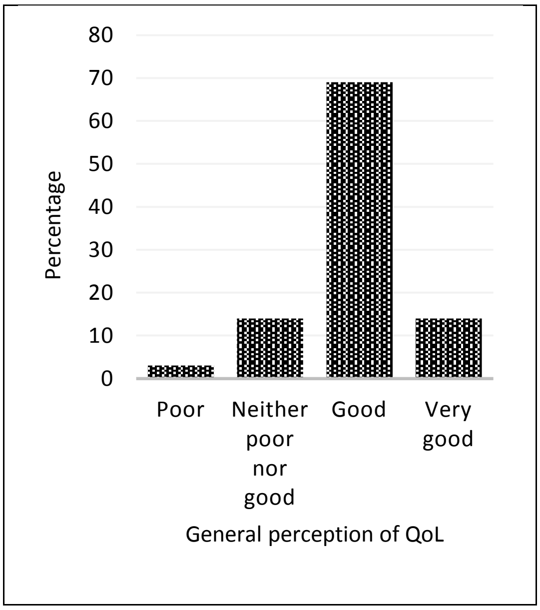

Fig 1: Percentage of the general perception of QoL

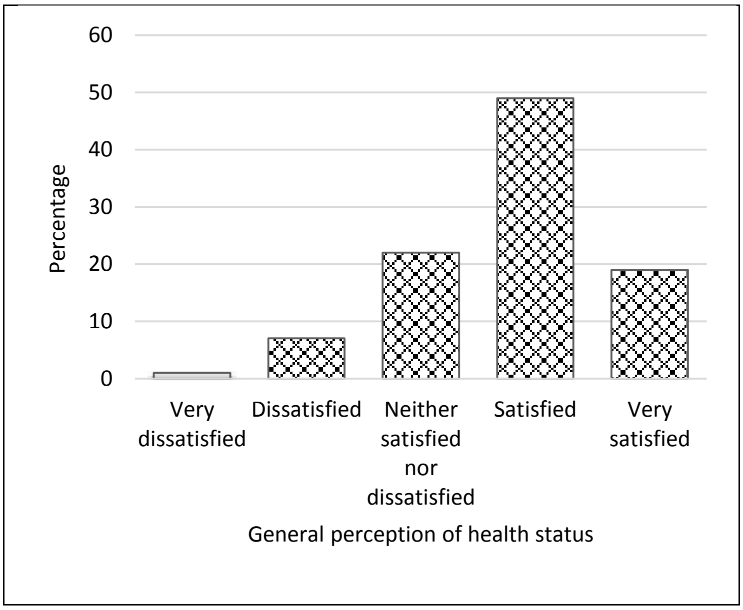

Fig 2: Percentage of the general perception of health status

3.5 QoL and illness characteristics

FH patients with CVD compared to those without, had significantly lower scores in physical (14.6±2.7 vs 16.2±2.2, p<0.001) and psychological domains (15.3±2.3 vs 16.5±2.1, p=0.012) of QoL. FH patients with multiple compared to a single type of CVD (of either CAD, angina, atherosclerosis or stroke, or in any combination) had significantly lower scores in the psychological domain of QoL (15.4±2.32 vs 16.8±1.88 respectively, p=0.010). See Table 5 for the pattern of QoL and illness characteristics of FH patients.

Table 4: Comparison of the WHOQOL-BREF mean scores in four domains according to sociodemographic variables

Sociodemography		**D1** **Mean± SD**	**D2** **Mean± SD**	**D3** **Mean± SD**	**D4** **Mean± SD**
Age					
	Pearson correlation	0.021	0-.029	0.063	0.128
	P value	0.838	0.780	0.535	0.210
Gender					
	Female	15.6±2.56	16.3±2.25	17.3±2.11	16.0±2.43
	male	15.5±2.53	15.8±2.28	16.3±2.35	15.7±2.34
	P value	0.801	0.337	**0.040**	0.444
Marital status					
	Ever married	15.5±2.58	16.0±2.32	16.7±2.30	15.8±2.42
	Unmarried	15.9±2.09	15.9±1.65	16.3±2.44	15.7±1.78
	P value	0.699	0.939	0.703	0.914
Education					
	Pre-university and university	16.6±2.18	16.5±2.15	16.8±2.43	16.2±2.31
	Secondary	14.4±2.43	15.5±2.25	16.2±2.11	15.4±2.24
	Primary and below	15.1±2.76	15.1±2.82	18.3±2.14	15.6±3.31
	P value	**<0.001***	0.075	0.071	0.216
Income (RM)					
	<3000	16.8±2.44	17.6±1.89	17.0±2.65	17.1±2.50
	3001-10000	16.3±2.53	16.2±2.28	17.1±2.08	16.2±2.49
	>10000	14.8±2.36	15.5±2.23	16.2±2.37	15.3±2.18
	P value	**0.004****	**0.027*****	0.189	0.056

*Post hoc test showed mean physical domain of pre-university and university significantly higher than secondary (p<0.001)

** Post hoc test showed mean physical domain of ≤ RM3000 significantly higher than the group of RM 3001-10, 000 (p<0.010)

*** Post hoc test showed mean phycological ≤ RM3000 significantly higher than those earn >RM10000 (p<0.036)

Table 5: Pattern of QoL and the illness characteristics

	Presence of CVDs **Mean (SD)**			**Types of CVD** **Mean (SD)**			**Lipid-lowering drugs for FH Treatment** **Mean (SD)**		
QoL Domain	*CVD (+)* *(n = 41)*	CVD (-) *(n = 59)*	p value	Multiple (n=35	Single (n=32)	*p-value*	Yes (n=69)	No (n=31)	p value
D1	14.6(2.70)	16.2(2.18)	**0.001**	14.8(2.86)	16.0(2.18)	0.060	15.3(2.59)	16.0(2.37)	0.490
D2	15.3(2.29)	16.5(2.14)	**0.012**	15.4(2.32)	16.8(1.88)	**0.010**	15.8(2.17)	16.3(2.46)	0.249
D3	16.5(2.25)	16.7(2.36)	0.685	16.6(2.53)	17.0(1.70)	0.561	16.7(2.28)	16.4(2.37)	0.995
D4	15.5(2.63)	16.0(2.16)	0.307	15.9(2.53)	15.9(2.10)	0.985	15.9(2.41)	15.5(2.28)	0.953

4.0 Discussion

Majority of FH patients in this study described acceptable general perceptions of QoL and health status. This is in keeping with the findings of a smaller scale study by other local researchers who used SF-36 to describe QoL among their 60 FH patients (Khoo, Page, Liew, Defesche, & Watts, 2016). Unlike those study, we were able to determine the important contributing factors that influence QoL including the level of education, level of income and the presence and type of CVD. The findings may inform clinicians in providing effective management to FH patients so that they have the optimum QoL.

Education is not merely about academia and pedagogy. In the context of quality of life, education underpins not only economic growth but transmits knowledge through generations, participation in social affairs, and how one perceived and reacted on the world they lived in (Powdthavee, Lekfuangfu, & Wooden, 2015). Level of education determines health literacy which is important for access and utilisation of health care, patient-provider relationship, and self-care (Paasche-Orlow & Wolf, 2007). Hence, it is not surprising that this study found that FH patients who were more educated felt more satisfied with their physical aspects of QoL. Furthermore, as described by previous researchers through education, the QoL of FH patients can be optimised even without monetary channels (Powdthavee et al., 2015). For examples, QoL in terms of satisfaction on physical aspects described by the educated FH patients in this study as feeling contented on their routine activities of daily living, medications and treatment, general energy, work capacity, mobility, ease from pain and discomfort; as well as the pattern of their sleep and rest.

This study supports the notion that QoL is not always about money (Diener & Seligman, 2018). It is interesting to highlight that our study found a paradox that FH patients with the highest income of more than RM10, 000, had the poorest physical and psychological domain of QoL, whereas those living in poverty (income less than RM3000) had both domains the highest. Again, the non-pecuniary aspects of life may play an important role in determining the level of QoL in our FH patients. According to a study that examined a model of income and quality of life, good QoL relies more on social relationships and enjoyment at work rather than love for money (Tang, 2007). In the context of FH patients, perhaps those who are poor may have strong resilience and use effective and adaptive coping to overcome the challenges they experienced having the FH and its cardiovascular complications (Stewart & Yuen, 2011). In contrary, those who are rich may feel stressed up and overwhelmed with dissatisfaction at their state, image and appearance of being ill, preoccupied with negative feelings about the illness and having reduced self-esteem following a loss of functionality after being diagnosed with FH and its CVD complications (Lapadatu & Morris, 2019). The presence of CVDs (either coronary heart disease, angina, atherosclerosis or stroke) had given a significant impact on the physical and psychological domain of QoL among our FH patients. Previous local researchers also supported our findings that those with multiple disease comorbidities such as those with hyperlipidemia, stroke and heart disease had poorer QoL than those who without (Sazlina, Zaiton, Afiah, & Hayati, 2012).

'Social interaction', one of the important domains of QoL represents the quality of a personal relationship, intimacy and social support. In this study, we found female FH patients had a better quality of life in terms of social interaction than male FH patients. It is tempting to speculate that one reason for this finding is that typically, women who are experiencing stress (such as illness) have externalizing type of coping style of becoming more forward for help-seeking, sharing their feelings and venting out their emotions to others when dealing with stress (Liddon, Kingerlee, & Barry, 2018). On the other hand, male prefers to keep their illness to themselves and less interacting with others, perhaps because of feeling ashamed, silly and taking effort to normalize symptoms (Galdas, Cheater, & Marshall, 2005).

5.0 Limitation and Conclusion

The strength of this study is that it is able to suggest several important contributing factors that influence the QoL of FH patients. The findings may inform clinicians especially those providing services for FH patients to plan more effective interventions for their patients so that they have the optimum QoL despite having FH and its complications. Despite our promising findings, some further considerations need to be highlighted. First, given the difficult genetic testings that have to be done before FH is diagnosed, a small number of samples recruited may reduce the power of the study and one might argue the generalizability of the findings. Hence, a larger number of samples is recommended for future research. It is important to comment that using self-report questionnaires to define the existence of illness such as CVDs, angina, hypertension and stroke may result in bias in reporting. A qualitative interview to assess other possible underlying elements of QoL is also recommended. It is also suggested that clinically diagnosed variables be used for future research.

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