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Chapter 2

Impact of Polypharmacy on Deglutition in Patients with Coronary and Cardiac Diseases

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Additional information is available at the end of the chapter

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1. Introduction

Dysphagia relates to swallowing problems due to physiological changes in aging people or such factors as diseases and medications [1]. Previous studies stated that world prevalence of dysphagia ranged between 16% and 22% [2]. Dysphagia can be classified into two types: oropharyngeal and esophageal. Oropharyngeal dysphagia includes cerebrovascular disorders (like stroke), central nervous system disorders (like Parkinson's disease), and others (like thyroid disorders). Esophageal dysphagia includes aging, alcoholism, diabetes mellitus (DM), cancers, and medications [3]. Several symptoms detected to determine the type of dysphagia (i.e. swallowing problems) included gastrointestinal symptoms (such as heartburn, indigestion, and gastro-esophageal reflux disease), respiratory symptoms (like cough), and musculoskeletal chest pain [4].

Many medications are known to induce dysphagia by affecting smooth and striated muscle via increasing the sensitivity of mucosa resulting in swallowing difficulty. There are two different ways in which this occurs. First, there is the normal adverse effect (or the indirect effect) due to pharmacological action and complications such as dysphagia induced by antibiotics as well as immunosuppressive and anti-cancer agents. Second, there is the direct effect of medications irritating the mucosa, which is more observed in the elderly [5]. The aortic arch is the area most susceptible to injuries induced by pills. Medications with a pH less than 3 (such as doxycycline and tetracycline) as well as certain slow-release anticholinergic dosage medications were more caustic resulting in moderate and severe injuries [6]. The severity of injuries depended on chronic irritation, high osmolarity, and the dissolution rate of dosage forms [7]. Medications that are known to induce dysphagia can be categorized into four groups [8]: (1) medications affecting smooth muscle such as theophylline and calcium channel

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blockers; (2) medications reducing esophageal sphincter pressure such as nitrates and atropine; (3) medications inducing xerostomia such as antihypertensive agents and antiarrhythmics; and (4) medications inducing esophageal injury such as aspirin and non-steroidal anti-inflammatory medications.

Polypharmacy is defined as patient use of five or more medications [9]. Polypharmacy contributes to the high incidence of adverse effects as a consequence of possible drug interactions between medications [10, 11]. Although some studies state that polypharmacy should be considered a significant predictor for dysphagia [2, 12], they have weaknesses in that they were either case reports or mainly dealt with specific dysphagia type. Thus, the aims of the current study are, first, to describe the incidence, severity, and predictors of dysphagia; second, to determine the relationship between polypharmacy and dysphagia; and, third, to describe the association between types of dysphagia (depending on concurrent symptoms) and polypharmacy.

2. Methodology

2.1. Study design

The cross-sectional design based on patients self-reporting was used in the current study to determine the incidence of dysphagia and its concurrent symptoms. The reason this study was carried out at the Cardiac Clinic of Penang General Hospital was because polypharmacy is more detectable in cardiac patients as a result of their treatment by chronic and multiple therapies. There were 576 cardiac outpatients involved in the current study. Approval for this study was granted by the Ministry of Health of Malaysia and consent forms were collected from patients. All patients involved in the current study were aged 18 years or above, used medications dispensed from the pharmacy of the hospital, and were able to understand and fill in the questionnaire form in Standard Malay (Bahasa Malaysia) or English.

2.2. Self-reporting questionnaire and assessment of polypharmacy

The self-reporting questionnaire used in the current study had the purpose of counting the incidence and severity of dysphagia and its symptoms. The validity of the questionnaire was established after conducting language, panel, and statistical validity, after conducting a pilot study, and after settling on an appropriate coefficient of reliability (Cronbach's α = 0.92). Statistical advanced logistic regression was used to measure the specificity and sensitivity of dysphagia and its symptoms, which had fixed in the questionnaire form. Patients were asked to answer “yes” or “no” to questions about the existence of dysphagia and its symptoms. Patients were also asked to report the severity of the symptoms as “mild”, “moderate”, or “severe”. Mild referred to symptoms that did not bother the patient who had no need for assistance. Moderate referred to patients who were bothered by symptoms but had no need for assistance. Severe referred to patients who were seriously bothered by these symptoms and had urgent need for assistance. Other information such as demographic data, medical

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history, and concurrent medications and diseases were taken from the progress files of patients.

The patients included in this study were classified into three groups: (1) patients taking no medications who were referred from other clinics for a follow-up; (2) patients already known to the department taking fewer than 5 medications and (3) patients known to the department taking 5 or more medications. All patients on medication had been in chronic therapy for at least one year.

2.3. Statistical analysis

The Statistical Package for the Social Sciences (SPSS) software program was used to analyze the results of the current study. The incidence and severity of dysphagia and its symptoms were measured descriptively. The correlation between dysphagia and its symptoms was tested using Spearman's rank correlation. Multiple logistic regression was used, first, to find out the effect of predictors' interaction on the incidence of dysphagia; second, to discover how polypharmacy impacted dysphagia; and, third, to determine the association between polypharmacy and type of dysphagia (oropharyngeal and esophageal). All the results of this study were considered significant if their p values were less than 0.05.

3. Results

3.1. Demographic characteristics and medical information

The highest incidence of disease was found in males with a mean age of 59.11±10.14 years. The most common diseases found in the current study were hypertension, DM, and ischemic heart disease (IHD). The medications used the most were statins, aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors (ACE-Is). Other demographic characteristics and medical information are illustrated in Table 1.

3.2. Severity of dysphagia types and its symptoms

The incidence (and percentage) of current patients complaining of dysphagia and its symptoms during therapy were 122 (21.2%), 177 (30.7%), 265 (46%), and 286 (49.7%) for dysphagia, indigestion, cough, and chest pain, respectively. Mild symptoms were the highest incidences followed by moderate and severe (as shown in Figure 1).

Spearman's rank correlation showed a positive significant (2-tailed, $p< 0.001$) relationship between dysphagia and its symptoms. The correlation coefficient between dysphagia and its symptoms was 0.322, 0.146, and 0.126 for indigestion, cough, and chest pain, respectively. This result showed that the incidence of esophageal dysphagia was more frequent than that of oropharyngeal dysphagia.

Demographic data and diseases		% (No.)	Medications	% (No.)
Gender (male)		74.3 (428)	Statins	87.8 (506)
Age (≤65)		68.9 (397)	Aspirin	67.4 (388)
Race	Malay	39.6 (228)	Beta-blockers	70.8 (408)
	Chinese	28.5 (164)	Calcium channel blockers	24.5 (141)
	Indian	29.7 (171)	ACE-Is	54 (311)
	Other	2.3 (13)	Angiotensin receptor blockers (ARBs)	10.6 (61)
Smoking		14.8 (85)	Trimetazidine	29.2 (168)
Alcohol consumption		9.4 (54)	Isosorbide dinitrate	23.1 (133)
Hypertension		65.8 (379)	Thiazides	6.8 (39)
DM		39.9 (230)	Furosemide	18.9 (109)
IHD		39.8 (229)	Spironolactone	6.3 (36)
Arrhythmia		3.3 (19)	Gliclazide	22.2 (128)
Renal disease		2.4 (14)	Metformin	25 (144)
Thyroid diseases		2.3 (13)	Digoxin	4.3 (25)
Myocardial infarction		2.3 (13)	Warfarin	5.6 (32)
			Clopidogrel	17.7 (102)
			Ticlopidine	11.3 (65)
			Prazosin	2.3 (13)

Table 1. Demographic characteristics and medical information of patients

3.3. Predictors of dysphagia

Gender, IHD, and statins were the most significant factors that must be involved in the regression model to insure the predictors of dysphagia could be determined (as shown in Table 2).

Categorical variables	χ^2	*df*	*p*
Gender	6.181	1	0.013
IHD	7.909	1	0.005
Statins	4.539	1	0.033

χ^2 = chi-square test; *df* = degrees of freedom; *p* = calculated probability

Table 2. Categorical variables included in the regression model

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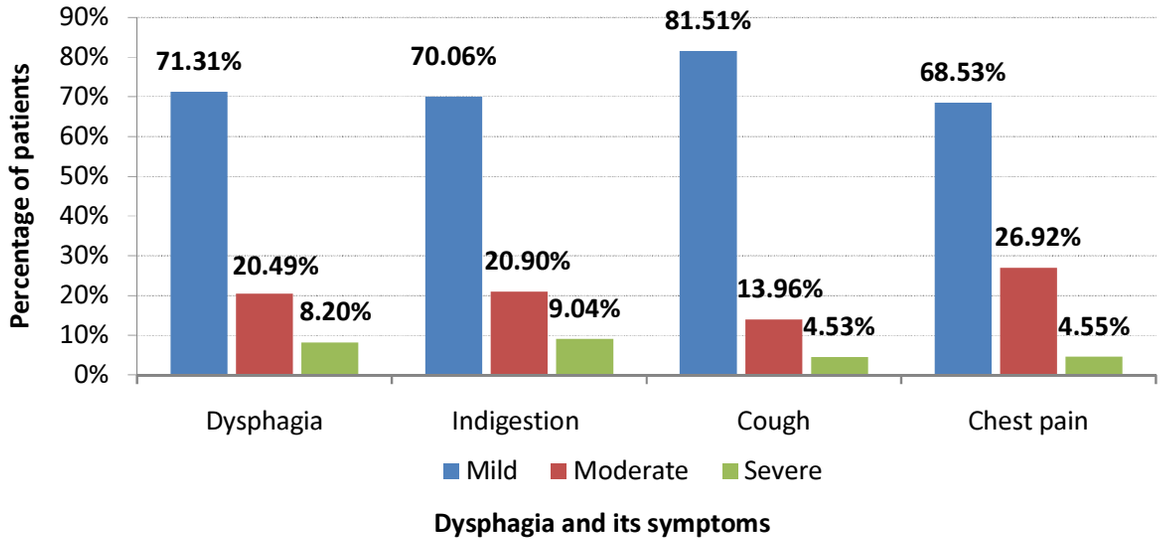

Figure 1. Incidence and severity of dysphagia and its symptoms

As a result of logistic regression, gender and IHD were found to be the significant risk factors involved in the high incidence of dysphagia. Female cardiac patients had incidences of dysphagia that were approximately 1.8 times higher than those of males. Patients with IHD had incidences of dysphagia that were 1.8 times higher than those without (as shown in Table 3).

Variable		*β*	*SE*	*OR*	*95% CI*	*p*
Gender	Female	0.575	0.233	1.777	(1.148, 2.750)	0.010
	Male (ref.)					
IHD	Yes	0.599	0.207	1.820	(1.212, 2.731)	0.004
	No (ref.)					

The reference category for the model is no dysphagia. The backward stepwise logistic regression test was used. The Hosmer and Lemeshow goodness-of-fit test with χ^2 (N = 576) = 3.365 and p =0.186

Table 3. Predictors of dysphagia in cardiac outpatients

3.4. Polypharmacy and its impact on dysphagia

Patients with polypharmacy (i.e. those using 5 or more medications) have a higher incidence (45.84%) of dysphagia than other patients (as shown in Figure 2).

Binary logistic regression showed that medication use was a risk factor in the incidence of dysphagia in cardiac outpatients. The incidence of dysphagia was about 2.8 and 3.2 times higher for patients taking 1–4 drugs and those taking ≥ 5 drugs (polypharmacy), respectively, than those taking no medications. However, the incidence of dysphagia in patients with polypharmacy was found to be higher than those taking fewer than 5 medications (as shown in Table 4).

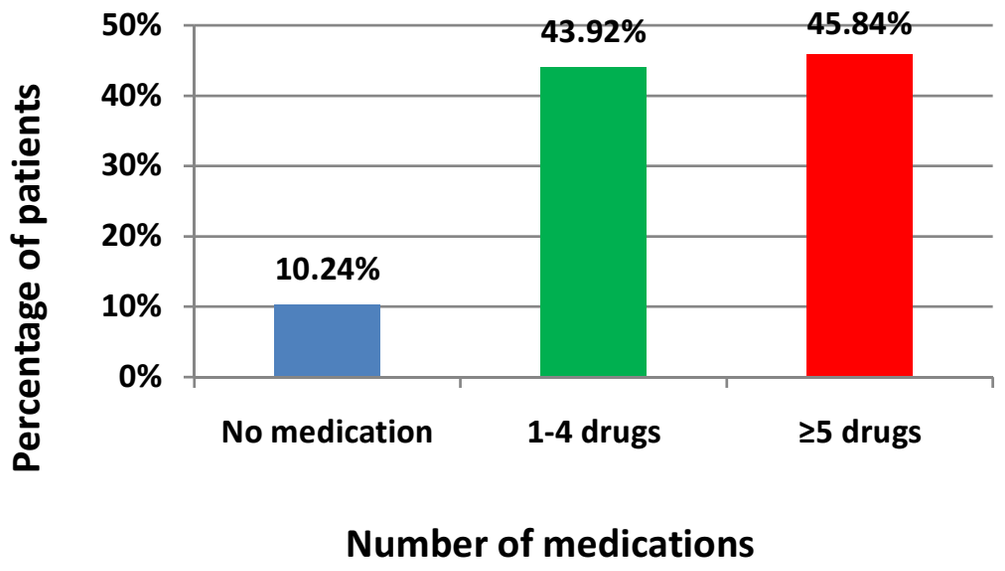

Figure 2. Percentage of medications used

Category	*β*	*SE*	*OR*	*95% CI*	*p*
1–4 drugs	1.144	0.491	2.842	(1.200, 8.223)	0.020
≥ 5 drugs	1.156	0.490	3.176	(1.216, 8.299)	0.018
No medications (ref.)					

The reference category for the model is no dysphagia.

Table 4. The association between polypharmacy and dysphagia

3.5. Predictor interaction and impact on dysphagia

The impact of predictor interaction on the incidence of dysphagia according to binary logistic regression showed gender and IHD to be two significant predictors. Patients taking 5 medications or more (i.e. polypharmacy) were more susceptible to the incidence of dysphagia, especially female patients and those with IHD.

Female cardiac patients taking 5 or more medications were about 2.2 times more prone to a high incidence of dysphagia than males taking no medications, while there was no significant impact on females taking fewer than 5 medications. This proved the impact polypharmacy has on females complaining of dysphagia (as shown in Table 5).

IHD patients taking 5 medications or more had a significantly higher (about 1.9 times) incidence of dysphagia than those free of IHD and taking no medications. However, no impact was found for IHD patients taking less than 5 medications (as shown in Table 6).

These tables show the impact of polypharmacy is going to increase the incidence of dysphagia when the interactions between predictors are taken into consideration. However, gender (female) was a higher predictor effect for dysphagia than the IHD predictor.

Category	*β*	*SE*	*OR*	*95% CI*	*p*
No. of drugs (gender)					0.012
1–4 drugs (female)	0.555	0.280	1.741	(1.006-3.015)	0.050
≥ 5 drugs (female)	0.770	0.306	2.159	(1.186-3.930)	0.012

The reference category is males taking no medications

The reference category for the model is no dysphagia

Table 5. Impact of polypharmacy and gender on dysphagia

Category	*β*	*SE*	*OR*	*95% CI*	*p*
No. of drugs (IHD)					0.022
1–4 drugs (IHD)	0.484	0.271	1.623	(0.954, 2.761)	0.074
≥ 5 drugs (IHD)	0.617	0.242	1.854	(1.154, 2.978)	0.011

The reference category is no medications and no IHD

The reference category for the model is no dysphagia

Table 6. Impact of polypharmacy and IHD on dysphagia

3.6. Polypharmacy and type of dysphagia

Dysphagia was classified according to symptoms of cardiac patients taking part in the study. Chest pain is the only symptom that showed a significant association with polypharmacy. Patients taking 5 or more medications had a significantly higher incidence of chest pain (about 2.1 times) than those without medications. Moreover, no significant effect was found for chest pain in patients taking fewer than 5 medications. Thus, polypharmacy has a greater effect on esophageal dysphagia than oropharyngeal dysphagia (as shown in Table 7).

4. Discussion

Many different results have been reported on the incidence of dysphagia in different areas of the world as a consequence of the number of diseases and medications that bring it about. Moreover, some studies have restricted themselves to different age groups; for example, some relate to childhood dysphagia while others relate to geriatrics [13]. Many physicians fail to take these symptoms into account either because they do not take dysphagia seriously or are unfamiliar with the factors that bring it about [14]. Siebens *et al* [15] and Croghan *et al* [16] found that morbidity and mortality were significantly higher in those with dysphagia than those without because of malnutrition and/or low quality of life [17]. Speyer *et al* [18] and Wallace *et al* [19] found that patients' self-reporting was the most effective tool for identifying dysphagia symptoms. This led to many studies being conducted on patients self-reporting with the aim of determining the incidence of dysphagia [20–22]. This was because patients were considered the main source of information to get at the data needed to conduct clinical

Indigestion	*β*	*SE*	*OR*	*95% CI*	*p*
1–4 drugs	-0.099	0.315	0.906	(0.488, 1.681)	0.754
≥ 5 drugs	0.130	0.311	1.139	(0.619, 2,079)	0.676
No medications (ref.)					
Cough					
1–4 drugs	0.040	0.291	1.041	(0.588, 1.842)	0.890
≥ 5 drugs	0.132	0.290	1.141	(0.647, 2.014)	0.648
No medications (ref.)					
Chest pain					
1–4 drugs	0.369	0.297	1.447	(0.808, 2.591)	0.214
≥ 5 drugs	0.748	0.296	2.113	(1.182, 3.777)	0.012
No medications (ref.)					

The reference category is no dysphagia.

Table 7. Association between polypharmacy and type of dysphagia

studies. Unfortunately, very few studies have reported on the risk factors relating to dysphagia.

There are a number of benefits stemming from the current study: first, establishing a new method to count the incidence of dysphagia by getting cardiac outpatients to fill in a validated, acceptable, and feasible questionnaire, especially because until now there has been no standard validated tool to report dysphagia and its symptoms capable of meeting clinical requirements [23]. Second, this study can be used to determine the type of dysphagia based on the types of symptoms by statistically correlating them into oropharyngeal and esophageal types; up until now all previous studies either depended on one type or using scales for the classification. Moreover, no study has ever been assigned to a specific clinical case such as the one here for cardiovascular diseases or investigated the interactions of dysphagia predictors.

The survey carried out by Barczi *et al* [24] stated the incidence of adult patients complaining of dysphagia ranged from 10 to 30%. The dysphagia incidence (21.2%) of the present study was in the normal range, which was considered to be a good level of incidence when other risks were taken into consideration; for example, the subjects involved in the current study were elderly cardiac patients complaining of serious diseases and using chronic multiple therapies. There is variance in the incidence of dysphagia symptoms such as cough, chest pain, and indigestion. Such differences have also been reported in previous studies [25, 26]. The reason for such differences is because the diseases affecting patients and the medications they take differ from one patient to another. Compared with other studies, cough had a higher incidence of dysphagia in the current study (46.7%), which was higher than incidence of dysphagia, and this case was similar to the compared results of Eslick *et al* [27] who reported dysphagia (16%), cough (27%) and chest pain (23%). Their study was based on different explanations of different mechanisms of dysphagia [28, 29]. The incidence of mild, moderate, and severe dysphagia in the present study was 71.31, 20.49, and 8.20%, respectively, which was similar to the results of Eslick *et al* who reported 65, 30, and 5% for mild, moderate, and severe, respectively [27].

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Dobrzycki *et al* found a significant association between IHDs and dysphagia, because the shifting of parasympathetic levels increases the incidence of gastric reflex and induces cardiac problems [30]. Similarly, cardiac patients in the current study considered IHDs to be the main risk factors of dysphagia, where the incidence of dysphagia increased approximately 1.8 times in patients complaining of IHDs. Alves *et al* found gender had a significant impact on the incidence of dysphagia by measuring swallowing parameters such as velocity, intervals, number, and volume capacity. The velocity at which females swallow was found to be slower than for males, the volume capacity of females was found to be less than males, and females were found to need more time to swallow [31]. There are two reasons for this. First, males have larger oral and pharyngeal cavities than females; hence, they find it easier to swallow. Second, some studies have reported that it takes longer for the esophageal sphincter to open in females than in males [32, 33]. However, the results of the current study are in agreement with previous studies regarding the relationship between gender and dysphagia; for example, there is a higher incidence (approximately 1.8 times) of dysphagia in females than in males.

The reason polypharmacy can be considered a significant risk factor to the high incidence of mortalities, morbidities, and serious adverse reactions, is because drug interactions increase the potential toxicity of medications, especially in elderly patients [34]. The incidence of polypharmacy detected varies widely between studies (22–82%) [35–39] as a result not only of the way in which medications are prescribed in different countries but also awareness about the risks of medications. The incidence of polypharmacy reported in the present study was considered good (45.84%) when compared with other studies. Moreover, none of these studies compared the incidence of dysphagia in healthy individuals and ill patients. Some patients in the current study were not taking any medications because they had came from other clinics for checking purposes only, making them a good standard group for comparison with those with polypharmacy and those without polypharmacy.

Previous studies have found that polypharmacy has an effect on the incidence of dysphagia and swallowing problems. However, these studies either were reports focused on types of dosage forms, or conducted at community pharmacies for primary care patients [4, 40, 41]. The present study has demonstrated significant clinical outcomes for the relationship between polypharmacy and dysphagia, and provided evidence to show that number of medications elevates the incidence of dysphagia in cardiac outpatients. In addition to these results, the interactions of predictors were also investigated with significant positive outcomes. Females with polypharmacy had a higher incidence of dysphagia than females without polypharmacy, due to females with polypharmacy being more susceptible to adverse reactions of medications [42]. Patients complaining of IHDs had a high incidence of polypharmacy, which elevates the incidence of adverse drug reactions including dysphagia [43]. Thus, the present study has shown that the incidence of patients with polypharmacy complaining of IHDs and reporting dysphagia is high. The present study has satisfied theories about the interactions between predictors and their impact on the incidence of adverse reactions. Few studies have investigated the synergistic effect of predictors on the incidence of dysphagia, which gives the current study importance in providing a new clinical viewpoint.

A final novel result concerns the classification of dysphagia induced by polypharmacy in cardiac outpatients. There has yet to be a study determining the effects of polypharmacy on the incidence of dysphagia, let alone the type of dysphagia. The present study found that chest pain had a greater association with polypharmacy than other symptoms. By correlating the symptoms of dysphagia, the study found that polypharmacy is likely to induce a higher incidence of esophageal dysphagia due to the significant irritation (e.g. of the mucosa) of medications and physiological changes with aging. Despite being unable to pinpoint a specific medication as the main causative agent for inducing a high incidence of dysphagia, the cumulative impact of polypharmacy was a prime candidate. Therefore, the current study suggests that the effect of total number of medications (polypharmacy) is greater than the effect of the medication itself, possibly due to the interactions and adverse reactions of medications.

5. Conclusion

Patients' self-reporting was considered the optimal method to gather information on adverse symptomatic effects like dysphagia. Polypharmacy, female patients, and IHDs are the main predictors for dysphagia. Despite these predictors being non-preventable, polypharmacy control can minimize the incidence and severity of dysphagia induced by medications. The authors of the present study recommend healthcare professionals (especially pharmacists) to do their utmost to reduce the number of prescribed medications (according to the guidelines of polypharmacy), because they are more aware than most of adverse drug reactions and drug interactions.

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