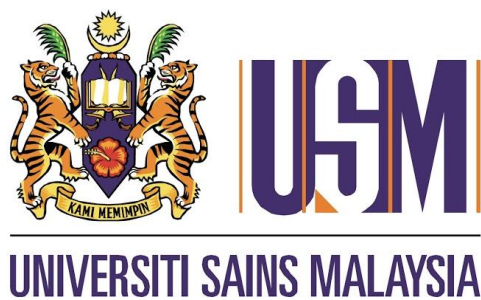


**A STUDY ON PREDICTIVE RISK OF ASYMPTOMATIC GALLSTONES  
AMONG DIABETIC GROUP OF PATIENTS IN HUSM**

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**DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE  
REQUIREMENT FOR THE DEGREE OF MASTER OF  
MEDICINE (GENERAL SURGERY)**



**UNIVERSITI SAINS MALAYSIA**

**2017**

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## ACKNOWLEDGEMENTS

Immeasurable appreciation and deepest gratitude for the help and support are extended to the following persons who in one way or another have contributed in making this study possible:

- Dr Maya Mazuwin Yahya (Consultant Breast and Endocrine Surgeon, Department of Surgery, USM) my supervisor, for all her guidance from the beginning of this research, until completion of this dissertation.
- Dr Ikhwansani Mohamed (Fellow in Hepatobiliary Surgery, Department of Surgery, USM) my co supervisor, who maintained my interest for this research. Without his guidance and help, this dissertation would not have been possible.
- Dr Khairil Amir Sayuti (Radiologist, Department of Radiology, USM) who guide me through the aspect of radiology as a new source of knowledge for me. His support, comments suggestions and initial provisions that benefited much in the completion of this study.
- All the lectures/surgeons of Department of Surgery USM, especially Dr Zaidi Zakaria (Head of Department, Consultant Colorectal Surgeon) who had shared his wise wisdom, vast knowledge and unconditional support throughout this study.

- All the staffs in Medical Record Office HUSM, for the permission to grant access as part of my dissertation.
  
- Cik Siti Nur Farliza Zaharudin from Statistic Department, for her support, patience and guidance on statistical analysis.
  
- My colleagues and course mates, for their suggestions, concerns and cooperation throughout this study.
  
- My family, for their continuous support and understanding, especially my lovely wife Dr Norhayaty Samsudin, jovial son, Ahmad Rayyan Syahmi and playful daughter, Nur Atikah Sofia, for all the sacrifices made.

***Chapter 1:***

***Introduction***

***Literature review***

***Rationale of the study***

## **ABSTRAK:**

### **KAJIAN TENTANG RISIKO JANGKAAN PENYAKIT “ASYMPTOMATIC GALLSTONES” DI KALANGAN PESAKIT KENCING MANIS DI HUSM**

#### **Latar Belakang:**

Penyakit batu hempedu dan kencing manis adalah penyakit yang biasa di hadapi di dalam masyarakat moden masa kini. Kebanyakan pesakit batu hempedu menghidapinya secara diam atau tiada simptom yang berkaitan. Penyakit kencing manis adalah faktor risiko yang telah di kenalpasti seiring dengan faktor risiko yang lain. Komplikasi penyakit batu hempedu adalah lebih tinggi di dalam pesakit yang menghidap kencing manis.

#### **Matlamat dan Objektif:**

Matlamat kajian ini adalah untuk mengenal pasti hubungan di antara faktor risiko penyakit batu hempedu dengan pembentukan batu hempedu. Pengenalpastian ini akan membantu untuk menjalankan program penyaringan kepada pesakit berisiko tinggi yang tiada simptom batu hempedu. Oleh itu, rawatan yang sewajarnya dapat di mulakan dari peringkat awal dan komplikasi penyakit batu hempedu akan dapat di kurangkan.

#### **Pesakit dan Kaedah Kajian:**

Kajian retrospektif ini di jalankan di Hospital Universiti Sains Malaysia dari Ogos 2013 sehingga Disember 2014. Seramai 143 pesakit telah di kenalpasti menghidap penyakit batu hempedu tanpa simptom. Pesakit di kenalpasti selepas melalui ujian ultrabunyi yang mana di jalankan bukan di atas indikasi untuk penyakit batu hempedu. 73 pesakit di golongan dalam kumpulan kencing manis manakala 70

pesakit pula di golongkan dalam kumpulan kawalan. Di dalam kumpulan kencing manis, seramai 37 pesakit ialah lelaki dan 70 pesakit ialah perempuan. Di dalam kumpulan kawalan, pesakit perempuan ialah 47 orang manakala pesakit lelaki ialah 23 orang. Data retrospektif di kumpulkan dan di analisis menggunakan perisian SPSS Versi 22. “Statistical significance” untuk “continuous variables” di perolehi menggunakan ujian T-test dan Pearson Correlation manakala hubungan di antara pembolehubah di perolehi menggunakan Simple dan Multiple Logistic Regression.

**Keputusan:**

Prevalens untuk pesakit “asymptomatic gallstones” ialah 50.3% di dalam kumpulan kencing manis manakala untuk kumpulan bukan kencing manis ialah 49.7%.

Bagi kumpulan kencing manis, umur min ialah 59 tahun (SD 8.9). Kebanyakan daripada mereka berada di dalam kumpulan umur 50 sehingga 59 tahun (44%) dan 60 tahun dan ke atas (41.7%). Taburan pesakit ialah 50% bagi setiap jantina di dalam kumpulan kencing manis. Di dalam subset lelaki, (n=36) jumlah pesakit meningkat seiring dengan umur iaitu (40 sehingga 49 tahun 8.3%, 50 sehingga 59 tahun 44.4%, dan lebih daripada 60 tahun (47.2%). Di dalam subset lelaki peratus tertinggi ialah di dalam kumpulan umur 50 to 59 tahun (44.4%). Kumpulan umur 40 to 49 tahun ialah 19.4% dan lebih daripada 60 tahun pula ialah 36.1%.

Taburan kaum mengikut kumpulan kajian menunjukkan kaum Melayu di dalam kumpulan diabetes ialah 88% manakala di dalam kumpulan bukan-kencing manis ialah 91.5%.

Min untuk body mass index (BMI) di dalam kumpulan kencing manis ialah 28.24 kg/m<sup>2</sup> (SD 6.9). Kebanyakan pesakit ialah di dalam kategori obes iaitu 40% di susuli oleh kategori and “overweight” seramai 34.7%.

Kebanyakan pesakit tidak mempunyai sejarah penyakit “gallstones” di dalam keluarga. (kumpulan kencing mani 83%, bukan-kencing manis 80%)

Di kalangan pesakit perempuan di dalam kumpulan kencing manis pula di dapati min anak ialah 5 orang. 75% mempunyai anak lebih dari 3 tau lebih manakala 25% dari mereka mempunyai kurang dari 3 orang anak.

Di dalam kumpulan bukan-kencing mansi, umur min ialah 52.68 tahun (SD 15.00). Kebanyakan pesakit berada di dalam kumpulan lebih daripada 60 tahun (33.8%), 28.2% di dalam kumpulan umur 50-59 tahun, 23.9% di dalam kumpulan 30 to 39 tahun dan 14.1% di dalam kumpulan 40 to 49 tahun. Seramai 66.2% ialah jantina perempuan manakala 33.8% ialah lelaki. Subset lelaki menunjukkan taburan tertinggi ialah di dalam kumpulan umur lebih dari 60 tahun (54.2%). Di dalam subset perempuan, kumpulan umur 50 sehingga 59 tahun pula adalah tertinggi sebanyak 36.2%. Kumpulan umur 30 sehingga 39 tahun dan lebih daripada 60 tahun adalah sama iaitu 23.4%.

Min jumlah anak adalah 4 orang (SD 2). 70% mempunyai anak seramai 3 atau lebih orang manakala 30 peratus wanita di dalam kumpulan ini mempunyai anak kurang dari 3 orang.

Di dalam kumpulan kencing manis, HbA1c dan tempoh menghidap penyakit kencing manis (n=72), mempunyai perbezaan yang signifikan (p-value= 0.024, r = 0.291).

Perubahan yang signifikan juga di dapati di dalam umur (t statistics 3.13 (df)=141, p=0.002) dan jumlah anak (t statistics (df)= 2.07 (81), P-value =0.042) di antara kumpulan kencing manis dan bukannya kencing manis.



Ujian Multiple logistic regression menunjukkan risiko untuk menghidap penyakit kencing manis di kalangan pesakit batu hempedu adalah 1.4 kali apabila umur meningkat sebanyak setahun. (95% CI: 0.02, 1.08 p value = 0.003).

**Rumusan:**

Kajian ini menunjukkan umur dan jumlah anak mempunyai perbezaan yang signifikan di antara kumpulan pesakit kencing manis dan bukan-kencing manis. Di dalam kumpulan pesakit kencing manis, tahap HbA1c dan tempoh menghidap kencing manis menunjukkan perbezaan yang signifikan. Risiko untuk menghidap penyakit batu hempedu dan kencing manis adalah meningkat 1.4 kali setiap tahun.

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**Kata kunci: penyakit batu hempedu tanpa simptom, kencing manis, umur, perempuan, jumlah anak**

## **ABSTRACT:**

### **A study on Predictive Risk of Asymptomatic Gallstone Among Diabetic Group of Patients in HUSM**

#### **Background:**

Gallstones disease and diabetes mellitus is a common disease in the modern society. There is no epidemiological data published about gallstone disease in Malaysia. Western data showed that about 20 to 25 million people or 10 to 15% of adult population had gallstone disease (Stinton *et al.*, 2010). Many of them about 50 to 70% are asymptomatic at the time of diagnosis (Sakorafas *et al.*, 2007). In Malaysia, the recognition of importance to manage this disease had led Ministry of Health Malaysia to produce the clinical practice guidelines in 1997. Diabetes mellitus is well-known risk factors for developing gallstones (Méndez-Sánchez *et al.*, 2005c). In Malaysia, prevalence of diabetes mellitus had increased from 15% in 2011 to 17.5% in 2015 based on recent National Health and Morbidity Survey (Health, 2015). The morbidity from the complications of acute biliary disease and post operative is higher in diabetic patient compared to non diabetics (Agarwal *et al.*, 2015).

#### **Aims and objectives:**

Aim for this retrospective study is to identify relationship between risk factors to the development of gallstones disease. The objectives of this study are to find prevalence of the asymptomatic gallstones disease and to find the association of risk factors; age, gender, BMI, parity, family history, HbA1c and duration of diabetes mellitus between the diabetic and non-diabetic patient. Identification of risk factors will help to conduct a screening in diabetic patient. Thus, appropriate treatment will be commenced early and the complications of gallstones disease will be reduced.

**Patients and methods:**

This cross sectional study was conducted at Hospital Universiti Sains Malaysia from August 2013 until December 2014. 143 patients who are asymptomatic from gallstone disease were recruited. They were identified from ultrasound abdomen examination, which they underwent for other causes and accidentally found to have gallstones. 73 patients were in diabetic group while 70 patients in control group. In diabetic group, 37 patients were male and 36 patients were female. In control group, 47 patients were female and 23 patients were male. The retrospective data was collected by a single researcher and analysed in SPSS Version 22. Statistical significance for continuous variables was obtained with T-test and Pearson Correlation while correlation between variables was obtained using Simple and Multiple Logistic Regression.

**Result:**

The prevalence of the asymptomatic gallstones patient for this study is 50.3% for the diabetic group and 49.7% for the non-diabetic group.

For the diabetic group, the mean age for the patients was 59 years old (SD 8.9). Majority of them were in the group age of 50 to 59 years old (44%) and 60 years and above (41.7%). There was equal 50% for each gender in diabetic group. The male subset (n=36) showed increasing numbers of patients along with the age (40 to 49 years old 8.3%, 50 to 59 years old 44.4%, more than 60 years old 47.2%). In female subset, the percentage is highest in 50 to 59 years old group (44.4%). The 40 to 49 years old was 19.4% and more than 60 years old group was 36.1%.

The races in diabetic this study showed that Malays were 88% in diabetic group while 91.5% in non-diabetic group.

The mean body mass index (BMI) for the diabetic group was 28.24 kg/m<sup>2</sup> (SD 6.9). Most of them was in obese group about 40% and followed by overweight group about 34.7% of patients. Most of the diabetic group patients do not have family history of gallstones (82%).

Among the female patients in the diabetic group, the mean parity was 5 (SD 2) children. 75% of them had 3 or more children while 25% of them had less than 3 children.

In the non-diabetic group, the mean age was 52.68 years old (SD 15.00). They were more in age group of more than 60 years old (33.8%), 28.2% in the 50-59 years old group, 23.9% in the 30 to 39 years old group and 14.1% in the 40 to 49 years old group. About 66.2% of them were female gender while 33.8% of them were male gender. The male subset of non-diabetic group showed that the highest distribution is in more than 60 years old group (54.2%). It was followed by 30 to 39 years old group (25%), 50 to 59 years old group (12.5%) and 40 to 49 years old group (8.3%). In female subset, the 50 to 59 years old group was highest about 36.2%. Age group of 30 to 39 years old and more than 60 years old were similar of 23.4% and the least was 40 to 49 years old group about 17%.

Mean BMI of this group was 26.32 kg/m<sup>2</sup> (SD 6.9). The BMI is mostly in the obese group (36.6%) and 31% in the overweight group.

Many of them did not have family history of gallstone disease in the family (80.3%). The mean parity among the female patients was 4 children (SD 2). 70% of the female patients had 3 or more than children while 30% of them had less than 3 children.

In term of HbA<sub>1c</sub> and duration of Diabetes Mellitus in the diabetic group (n=72), there significant changes between HbA<sub>1c</sub> and duration of Diabetes Mellitus

(p-value= 0.024, r = 0.291).

There were significant differences of age (t statistics 3.13 (df)=141, p=0.002) and parity (t statistics (df)= 2.07 (81), P-value =0.042) between diabetic and non-diabetic group.

Multiple logistic regression showed that those who were getting older by 1 year has 1.4 times the odds of having DM (95% CI: 0.02, 1.08) among patients with Gallstones (p value = 0.003).

**Conclusion:**

The study showed that age and parity had significant changes between diabetic and non-diabetic group. HbA1c and duration of illness had significant changes in diabetic group. Risk of concurrent gallstones and diabetes mellitus is 1.4 times in increasing age by 1 year.

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**Keyword: asymptomatic gallstones, diabetes mellitus, age, female, parity**

**CHAPTER 1**  
**INTRODUCTION &**  
**LITERATURE REVIEW**

Gallstone disease is a common upper gastrointestinal problem seen in our medical practice. Gallstones and the complications pose considerable workloads to the surgeons and gastroenterologist. Malaysia Society of Gastroenterology and Hepatology was published the Consensus on Management of Gallstones in 1997 to help in the appropriate treatment. In Malaysia, there are no formal data to see the prevalence of this disease. Patients will present to the health facilities with spectrum of symptoms. They will seek medical attention usually with specific symptoms such as right hypochondriac pain. Some of the patient's experienced biliary colic that is tolerable. Thus the patients ignore the pain or they took analgesic by themselves. The patients may ignore the recurrence symptoms of abdominal pain until the pain is intolerable or they developed the complications. The complications are usually acute cholecystitis, acute cholangitis or gallstones pancreatitis. Some of the patients have non-specific symptoms. The symptoms are not related to gallstones disease. However, the recurrence and chronicity of the problem may prompt the further investigation that will reveal gallstones. This is another spectrum of gallstone disease.

Gallstone disease is a result of interactions between the environment and genetic factor in the patients. Gallstone disease also follows the trend of modifiable and non-modifiable factors in developing the disease. These aspects will affect our perspective on how to tackle and manage this disease in holistic approach.

Epidemiology perspective of gallstone disease and its importance:

The prevalence of this disease is an 8.3% in a Swedish population in 2009 (Halldestam *et al.*, 2009). The percentage is yielding an incidence for newly developed gallstones of 1.39 per 100 person-years. The other study at the Asia showed similar prevalence rate. In China, urban population in the industrialized area of China showed increasing trend of gallstones disease from 1.1% in 20s to 11% in 60s of age (Zeng *et al.*, 2012). Both study in different continent show that average prevalence is about 10% of the population. This showed that gallstones patients usually started in the middle age group. Thus the percentage is covered part of the population of that age group. Second view is that westernized diet in most of the countries. Our country may follow the similar suit. Urbanisation and industrialisation had shift Malaysian diet towards 'westernised' dietary pattern and food consumption (Tee, 1999) . Urbanites lifestyle are more hectic compared to the rural population. Thus urban population consumed more cooked, processed, ready to eat and fast foods. Fast food restaurants, coffee shops and convenience stores which may operate 24-hours are abundant in the urban. Furthermore, the price is considered affordable by the urban residents. This is supported by rapid expansion of the meat and poultry industry which influenced food consumption of meat as shown in Korea (Son, 2003).

Many of the gallstones patients are in silent or asymptomatic state. Asymptomatic cholelithiasis, defined by the Rome Group for the Epidemiology and Prevention of Cholelithiasis (GREPCO) when the gallstones are detected in the absence of gallstone-related symptoms, such as history of biliary pain or gallstone-related complications such as acute cholecystitis, cholangitis, or pancreatitis (Attili *et al.*, 1995). The detection is during the imaging or surgery for the other indication other than gallstones (Rege, 2009). About 50 to 70 percent of patients is

asymptomatic during the diagnosis of gallstones (Sakorafas *et al.*, 2007). It is estimated about 2% will have biliary complications every year. About 10% of them will develop symptoms or complications that require treatment within 5 years (Halldestam *et al.*, 2004). Complication of this disease will lead to sepsis and eventually morbidity and mortality. This reflect to the healthcare cost. The managing cost is amounting up \$6.5 billion in United States (Shaffer, 2005). This is from the need for antibiotics, procedures such as cholangiogram and also surgery be it laparoscopic or open surgery. Morbidity of this disease can be discussed in term of operative complication. Occurrence of recurrent inflammation of gallblader will produce difficult anatomy. Subtotal cholecystectomy is an option to removed the gallbladder. This will not devoid of having bile duct injury, subhepatic collection and also surgical site infection (Elshaer *et al.*, 2015). These complication will cause reduced quality of life and even reduce life span due to concurrent possible sepsis. Management of the disease will cause a considerable financial burden to the health care sector. In a Pakistani study showed that recurrent admission for the gallstone disease patient is incurred financial burden to the hospital. Thus they suggest for early detection and cholecystectomy to prevent this cost (Waqas *et al.*, 2014). While a study in Taiwan shows that a screening program towards detection of gallstones disease is a good direction to save the health budget (Chen *et al.*, 2013). Thus we could see that the importance of tackling the silent group of patient in term of continuous or active medical intervention to reduce or lessen the effect supposed they convert into symptomatic group.

Diabetes mellitus and gallstones disease:



Diabetes is identified as one of the risk factor towards developing gallstone disease. Diabetes also is a major public health issue. The macrovascular and microvascular complications in diabetics are challenge for the healthcare provider to cope. The magnitude of complications is extended if the patients had gallstones. In term of prevalence, a recent National Health and Mortality Survey in 2015 showed that 17.5% Malaysians are diabetics (Health, 2015). This increase is in steady rise trends as compared to the previous NHMS survey in 2006 which show the prevalence was at 14.9% (Letchuman *et al.*, 2010). However no national data is available to show the prevalence of diabetics and concurrent gallstone disease. A study in Italy had shown that about 25% of diabetics were having gallstones (Pagliarulo *et al.*, 2004). The number is higher than patients without diabetes. There is possibility of Malaysian having this numbers. This area is a possible to study in national setting. When zoom in into local view, state of Kelantan is among the highest prevalence diabetes in Malaysia. The prevalence range was 14.2 to 19.8% with Kelantan state had 18.5%. The staggering issues surrounding this group of patients are diabetecs has increase risk of mortality, cardiovascular events, and renal failure when they are going for cholecystectomy. Insulin-treated diabetics have more co-morbidities and poorer outcomes (Karamanos *et al.*, 2013). The other condition that associated with gallstones in diabetic patient are acute pancreatitis, gallbladder carcinoma and cardiac problem. As an overall view, the cycle of morbidiy, mortality, social impairment due to disease and cost for managing the patients will continue. Thus the importance of gallstones disease among diabetics the other issue to tackle.

Symptoms or late complications rather than objective findings of gallstone disease had actually lead to the diagnosis. Asymptomatic gallstones have been treated expectantly. Surgical operation, however, is reserved for a certain criteria (Malaysia,

1997). Surgical treatment of laparoscopic cholecystectomy is a gold standard for the gallstone disease. The complication and morbidity from this treatment is low. The recent study is on the area of asymptomatic gallstone patient who need the transplant surgery, bariatric surgery, paediatric age group and immunosuppressed group.

Rationale of study:

A study by Ross and Jayakumar in 1987, was conducted in HUSM to know the prevalence of asymptomatic gallstones without looking for association with diabetes mellitus (Ross and Jayakumar, 1987). As time evolved, diabetes is known to be the risk factor for development of gallstones. This study is aimed to produce local data in regards with subject studied. HUSM as the tertiary hospital may become a good area for conducting this study. Diabetes mellitus also had a high incidence of diabetes mellitus in Kelantan. The outcome of study is hoped to contribute data for improvement in health management in diabetic patient such as screening. As gallstone disease with diabetes will increase the morbidity and mortality to the sufferers. In long term, it is hoping to reduce the healthcare cost and socioeconomic effect and improving productivity to the nation and patient.

### **Literature review**

Search engine Google Scholar and PubMed was used to find the suitable articles. Keyword of asymptomatic gallstones, diabetes, parity, family history, obesity and gender were used. There are several research to study the relationship between risk factors of gallstones in diabetic group of patients. The studies were conducted in Asia, Africa and Europe.

El Mehdawi et al performed a case control study on 161 randomly selected diabetic patients and 166 age and sex matched non-diabetic patients. Patients were asked regarding the history of gallbladder stones disease and history of cholecystectomy. He studied the frequency of gallbladder stones among diabetes by ultrasound examination and the associated risk factors. The frequency of gallstones among diabetics is 40% as compared to 17.5% in non-diabetics. Female patients who were diabetics and having gallstones were significantly affected than male ( $p=0.011$ ). The patients with gallstones were significantly older ( $p=0.007$ ) and had higher body mass index ( $p=0.027$ ). Duration of diabetes mellitus did not influence significantly the frequency of patients with gallstones (Elmehdawi *et al.*, 2009).

Al Bayati et al conducted a case-control study to find the frequency of gallstones in diabetic and study the association with risk factors. He recruited 100 diabetes type 2 patients as diabetic group and 100 comparable patients without diabetes as control group. Gallstones are found in 33% of diabetics and 17% of non-diabetic patients. There was no significant association in age and family history of gallstones between diabetics and non diabetic patients. Body mass index overweight and above, increased duration of diabetes, increased HbA1c and multiparous are significantly associated in diabetic with gallstones (Al-Bayati and Kodayer, 2012b).

Olokoba with his colleagues do a study to determine the factors predisposing patients with Type 2 diabetes mellitus to gallstones disease. They recruited 100 test patients and 100 age and gender matched control group. The findings are 15% diabetic patients had gallstones as compared to 7% in control group ( $p=0.014$ ). The incidence was increased with the age group of patients. Age, body mass index and BMI are significantly higher in diabetic group with gallstones. The duration of

diabetes is higher in gallstone patients compared to without gallstones (Olokoba *et al.*, 2006).

Chapman et al study the prevalence of gallstone disease and associated risk factors in 308 diabetics and 318 control patients. Diagnosis of gallstone disease was made either by ultrasound confirmation or the history of cholecystectomy. There was higher prevalence of gallstone disease, which is significantly associated in diabetics (32.7%) compared to controls (20.8%) ( $p < 0.001$ ). Female gender with gallstones was significantly associated with diabetics compared to control ( $p < 0.001$ ). Among the risk factors, after multiple logistic regression was applied, male with diabetics and gallstones were having increase age and HDL as risk factor and female with diabetics and gallstones had aging, diabetes, fatter and decreased alcohol as the risk factor. This study had found that only diabetes mellitus female patients with diabetes as independent risk factor.

A study by Raman and collageues showed 32% diabetic and 6.7% healthy patients had gallstones. They had enrolled 50 diabetic type 2 patients and 30 healthy patients. The study looked into neuropathy and it is significant in diabetic patient with gallstones. They found that Mean duration of diabetes was significantly longer in those patients (Raman *et al.*, 2002).

Liu et al had done a large study by using national dataset. The study involved 615532 diabetic patients and 614871 control patients. They found that 9.87% diabetics and 7.83% control patients had gallstones with significant association ( $p = 0.014$ ). The diabetic group had significantly higher in female gender. Patients from urban area are prone to have the disease (Liu *et al.*, 2012).

The studies show that prevalence of gallstones patients with diabetic was 10 to 40 percent. This is higher when compared to non-diabetic, which was 6 to 20 percent.

The patient selection had possibility of including asymptomatic gallstones patient because of the diagnosis is made on ultrasound findings and past history of cholecystectomy. However, the numbers are comparable when reviewed with findings of Italian study (Pagliarulo *et al.*, 2004). He found that asymptomatic gallstones patient with diabetes was 25% of the population.

***Chapter 2:***

***Documents submitted to for ethical approval***

***Ethical approval letter***

**DISSERTATION PROPOSAL**  
**A STUDY ON PREDICTIVE RISK OF**  
**ASYMPTOMATIC GALLSTONES AMONG DIABETIC GROUP OF**  
**PATIENTS IN HUSM**

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## 1. INTRODUCTION

Asymptomatic gallstone is a spectrum of gallstone disease. This condition is defined as absence of typical presentation for gallstone disease such as right hypochondriac pain in a person who has gallstone and the gallstones are accidentally found during imaging investigation or during surgery for other reason other than gallstone(Rege, 2009). It is estimated that 50 to 70 percent of patients who had gallstones is in silent state (Sakorafas et al., 2007). A study conducted in HUSM in 1987 showed prevalence of asymptomatic gallstone in age group more than 29 years old is 11.8% in male and 13.7% in females (Ross and Jayakumar, 1987). The numbers are estimated to raise over years due to abundance food places that increase the risk factors.

There are studies to predict the natural history of asymptomatic gallstones. 1 to 2 % of asymptomatic patients will develop complications every year (Friedman, 1993). A study showed 28.4 % patients developed symptomatic gallstones in about 3 years (Thwayeb et al., 2013). In a longer 20 years observation, 10 to 25% of patients will develop symptomatic gallstones (Sakorafas et al., 2007). Symptomatic gallstone disease could give rise to mild condition such as biliary colic or severe condition such as acute cholangitis that could to sepsis and mortality (Brasca et al., 2002). The cost for managing gallstones diseases is \$6.5 billion in United States and this disease has become epidemic in certain parts of the world (Shaffer, 2005). The trend also increases in the Asian. Gallstones also associated with development of gallbladder cancer especially when having diabetes mellitus (Lai et al., 2012) and asymptomatic

gallstones patients prone to have biliary events if they have coronary artery disease (Lee et al., 2013).

Gallstone is form by solids from a bile solution in gallbladder. The organic compounds in bile are bilirubin, bile salts, phospholipid and cholesterol. Gallstone is usually classified as cholesterol and pigment stone. Pigment stone are further divided into black or brown. In Asia, pigment stone are more common whereas in Western countries, cholesterol stone are more common. The pathophysiology of stone formation is due to supersaturation of bile with cholesterol in cholesterol stone and supersaturation of calcium bilirubinate in black stone. The brown stone is formed from bile stasis and contamination in biliary infection (Oddsdottir et al., 2010).

The factors that related to prevalence of gallstones are age, gender and ethnic background. Certain condition may predispose to development of gallstones such as obesity, diabetes mellitus, pregnancy, dietary factors, Crohns disease, terminal resection, gastric surgery, hereditary spherocytosis, sickle cell disease, thalasaemia (Al-Jiffry et al., 2003).

Diabetes mellitus is recognized as one of the risk factors for developing gallstones (Méndez-Sánchez *et al.*, 2005). According to Third National Health and Mortality Survey (NHMS III) in 2010, it is estimated 3.4 millions or 14.9% Malaysians are diabetics. Malay ethnicity is at the second highest suffered from diabetes (Letchuman et al., 2010). Kelantan population is mainly consisting of Malay about 95% and the prevalence of diabetes in Kelantan also high about 11.4% in her 1.6 million population. There are almost 200 patients admitted to surgical ward HUSM for the gallstone disease in 2013.

There are several studies showed the relationship between risk factors of gallstones in diabetic group of patients. Various study conducted in Asia, Africa and

Europe found that diabetic patient who had gallstones ranges between 10 to 40% compared to 6 to 20% in non-diabetic patient (Chapman *et al.*, 1996; Raman *et al.*, 2002; BB, 2007; Elmehdawi *et al.*, 2009; Al-Bayati and Kodayer, 2012; Liu *et al.*, 2012).

El Mehdawi et al performed a study on 161 randomly selected diabetic patients and 166 age and sex matched non diabetic patients. He studied the frequency of gallbladder stones among diabetis and the associated risk factors. The frequency of gallstones among diabetics is 40% as compared to 17.5% in non diabetics. Females are significantly affected than male. The patients with gallstones were significantly older and had higher body mass index. Duration of diabetes mellitus and type of treatment does not influence the frequency of gallstones.

Al Bayati et al conducted a study to find the frequency of gallstones in diabetic and study the relationship with risk factors and nature of disease. He enrolled 100 patients as diabetic group and 100 patients as control group. Gallstones are found in 33% of diabetics and 17% of non diabetic patients. There was no significant relation in age and family history of gallstones between diabetics and non diabetic patients. BMI, increased duration of diabetes, increased HbA1c and multiparous are higher in diabetic with gallstones.

Olokoba with his collageus do a study to determine the factors predisposing patients with Type 2 diabetes mellitus to gallstones disease. They recrutes 100 test patients and 100 age and gender matched control group. The findings are 15% diabetic patients had gallstones as compared to 7% in control group. Age and BMI are significantly higher in diabetic group with gallstones. The duration of diabetes is higher in gallstone patients compared to without gallstones.

Chapman et al study the prevalence of gallstone disease and associated risk factors in 308 diabetics and 318 control patients. There are higher prevalence of gallstone disease in diabetics (32.7%) compared to controls (20.8%). Among the risk factors, female gender, increased age, body mass index, triglycerides, LDL cholesterol, decreased HDL cholesterol, alcohol intake, family history of gallstone disease and female parity more than 3 are associated with gallstone disease.

A study by Raman and colleagues showed 32% diabetic and 6.7% healthy patients had gallstones. They enrolled 50 diabetic patients and 30 healthy patients. The study looked into neuropathy and it is significant in diabetic patient with gallstones. Mean duration of diabetes was significantly longer in those patients.

Liu et al had done a large study by using national dataset. The study involved 615532 diabetic patients and 614871 control patients. They found that 9.87% diabetics and 7.83% control patients had gallstones. The diabetic group had significantly higher in female gender. Patients from urban area are prone to have the disease.

Female, increased age and body mass index are usual factors that most associated with gallstones. Being a female, the parity more than 3 are also associated. Family history with gallstones may contribute to the gallstones. While in diabetics, study showed that duration of diabetes had impact to the disease. The pathophysiology of diabetic and gallstone formation are impairment of gallbladder motility (Stone et al., 1988; Gaur et al., 2000) and hyperinsulinaemia may cause increasing of hydroxyl-3 methylglutaryl-coenzyme-A reductase (Nepokroeff et al., 1974).

Diagnostic imaging studies in gallstone disease that is easy and widely available is ultrasonography. Ultrasound is initial investigation of patients suspected

to have biliary tree disease. Trans-abdominal ultrasound can confirm the presence of stone in gallbladder. This investigation has sensitivity and specificity of more than 90% (Ralls et al., 2002; Oddsdottir et al., 2010).

Management of asymptomatic gallstone is expectant management (Sakorafas et al., 2007). Prophylaxis cholecystectomy is advocated in certain condition such as in organ transplantation patient, chronic hemolytic anaemia, location consideration and risk for gallbladder cancer. Diabetic is recommended for cholecystectomy in elderly age because of the natural inflammatory process (Johnson et al.).

## **2. STUDY OBJECTIVES**

### **RATIONALE OF THE STUDY**

This study is aimed to know the local data regarding presence of asymptomatic gallstones in patients who has underwent ultrasound pertaining to hepatobiliary area. In 1987, a study conducted in HUSM to know the prevalence of asymptomatic gallstones without looking for diabetes mellitus (Ross and Jayakumar, 1987). As time evolved, diabetes is known to associate with development of gallstones. Hence this study will produce updated data regarding the condition. The incidence of diabetes in Malaysia is increasing in trend. The 2015 National Health and Morbidity Survey showed that 17.5% Malaysians are diabetics. This is increased from 15% from NHMS 2011. Kelantan state had 18.5% of diabetics (Health, 2015). The outcome of this study is to improve the care in diabetic patient screening. This is because gallstone disease with diabetes will increase the morbidity and mortality to the sufferers (Agarwal *et al.*, 2015). Early detection will reduce the healthcare cost

and socioeconomic effect and overall improving productivity to the nation and patient.

## **STUDY HYPOTHESIS**

### **Null hypothesis**

- There is no association between the state of control and duration of diabetes mellitus in diabetic group of asymptomatic gallstone patients
- There is no association between diabetic and control patients with age, gender, body mass index, family history of gallstones and parity for females

## **STUDY OBJECTIVES**

### **General objective**

- To study the prevalence of asymptomatic gallstones disease in Hospital Universiti Sains Malaysia and the association with various risk factors.

### **Specific objectives**

1. To determine the prevalence of asymptomatic gallstone patient in diabetic and control group
2. To describe the socio-demographic data in asymptomatic gallstone patient in diabetic and control group.
3. To determine the association between state of control and duration of diabetes mellitus in diabetic group.

4. To determine the association between asymptomatic gallstones patients with age, gender, body mass index, family history of gallstones and parity for females.

### **3. RESEARCH METHODOLOGY**

#### **STUDY DESIGN**

Cross sectional and case record review

#### **STUDY AREA**

Hospital Universiti Sains Malaysia Kubang Kerian Kelantan

#### **REFERENCE POPULATION**

All patients who were underwent ultrasound pertaining to hepatobiliary area.

#### **SOURCE POPULATION**

All patients who were underwent ultrasound abdomen or hepatobiliary in Radiology Department HUSM from 1<sup>st</sup> August 2013 until 31<sup>st</sup> December 2014.

#### **SAMPLING FRAME**

All patients who had gallstones finding from the ultrasound

#### **SAMPLING METHOD**



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## **INCLUSION CRITERIA**

### **Diabetic group and control group**

1. For diabetic group, the patient is diagnosed as Type 2 Diabetes mellitus and had follows up in Specialist Outpatient Clinic HUSM
2. For control group the patients are not diagnosed as diabetes mellitus by the random blood sugar or fasting blood sugar.
3. Patients who underwent ultrasound abdomen or hepatobiliary at the Radiology Department HUSM from 1<sup>st</sup> August 2013 until 31<sup>st</sup> December 2014 for the other indication than gallstones.
4. Ultrasound showed accidental finding of gallstones.

## **EXCLUSION CRITERIA**

### **Diabetic group and control group**

1. Normal ultrasound finding
2. Age less than 30 years old

## **DATA COLLECTION, RESEARCH METHODOLOGY, STATISTICAL ANALYSIS AND RESEARCH TOOLS**

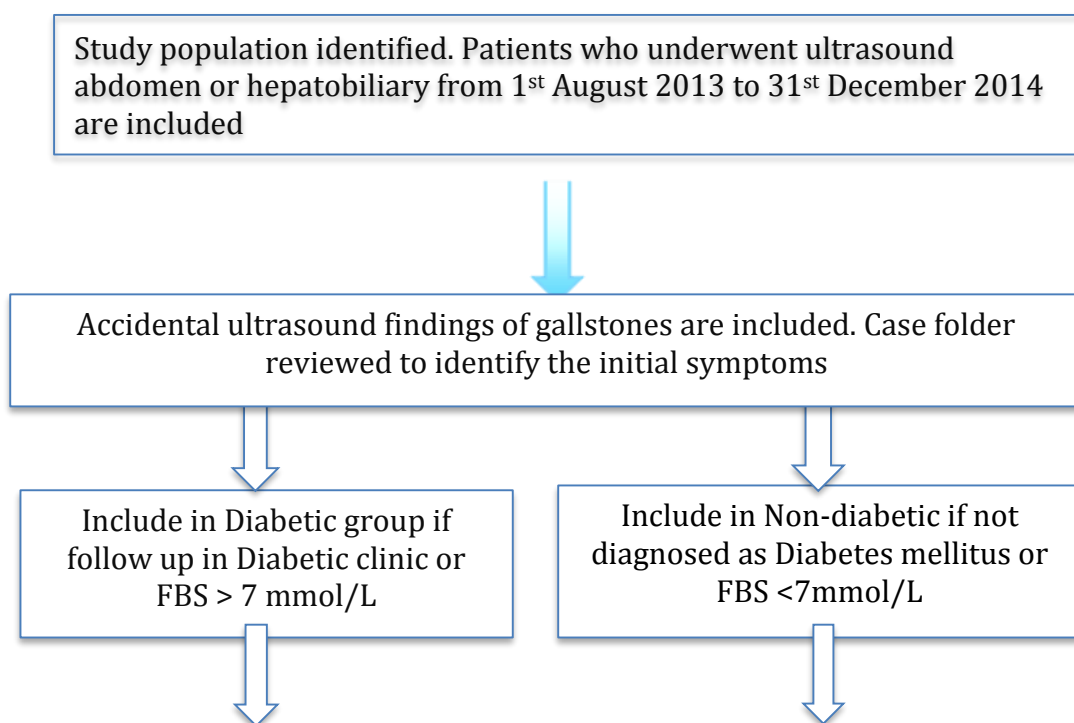
- Data collection is collected by a single researcher.
- Study subjects will be identified from the ultrasound finding of gallstones from the abdomen or hepatobiliary examinations. The information will be retrieved from ViaRad software.

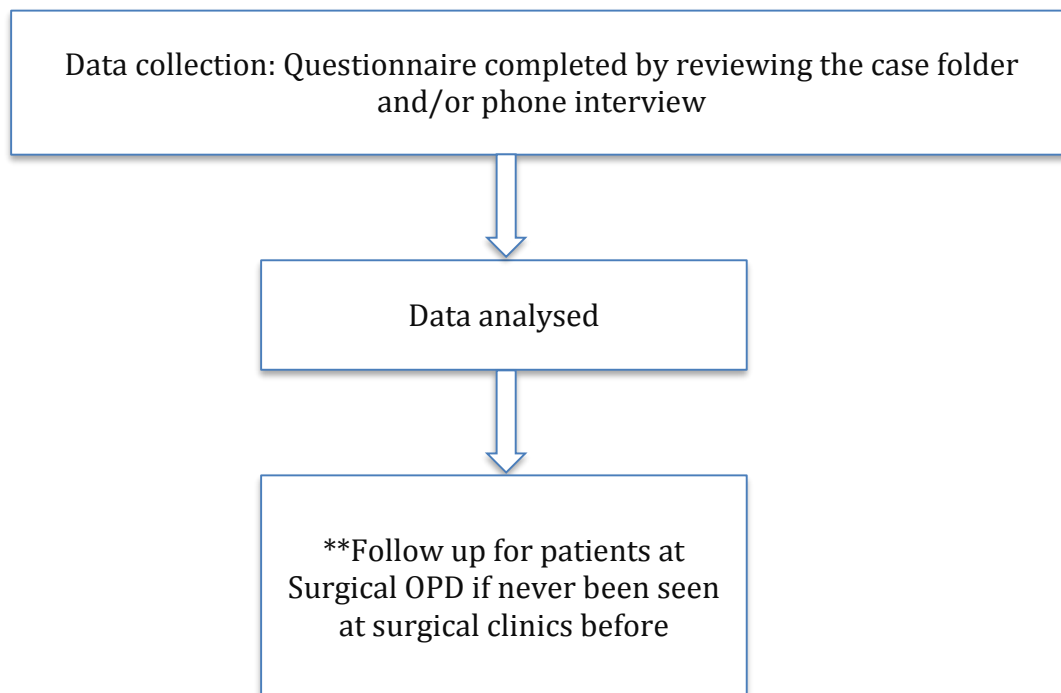
- The case folder will be reviewed to identify the initial symptoms that indicate the patients for the ultrasound examination.
- Proforma will be completed according to the information from the case folder and/or phone interview if necessary.
- Collected data will be analyzed using SPSS version 20.0. Patients are analyzed in term of development of gallstones in relation with identified risk factors. Statistical test used will be independent t-test, Chi-Square and Fischer Exact test. Significant finding in this study will be assessed with Chi-Square test. The parameter assesses is significant if p value is less or equal to 0.05
- Records were also analyzed concerning age, gender and ethnicity to give an overall picture of epidemiology trend and outcome of this study
- Research tools are ViaRAD software from the Radiology Department HUSM which is available widely in the HUSM wards and clinics.

#### **SAMPLE SIZE CALCULATION:**

From the literature review, the prevalence for diabetic group developed gallstones is 15 to 40% while the control group prevalence is range from 7 to 17% (Chapman *et al.*, 1996; Raman *et al.*, 2002; BB, 2007; Elmehdawi *et al.*, 2009; Al-Bayati and Kodayer, 2012; Liu *et al.*, 2012). From Elmehdawi et al, the prevalence for the test group (gallstone with diabetes mellitus) is estimated at 40% ( $p_1$ ) and control group (gallstones without diabetes mellitus) is 15% ( $p_0$ ), the power of study is set at 0.8 and  $\alpha$  is set at 0.05, by using Power and sample size program (PS version 3.0.43) it would be 49 patients for each group. To anticipate 20% non-responder, the calculated sample size was 117.

## FLOWCHART





Dummy tables

Variables	Diabetes melitus group	Non-diabetic group
	Asymptomatic Frequency (%)	Asymptomatic Frequency (%)
Age: 30-39 40-49 50-59 >60		
Gender : Male Female		
Ethnicity: Malay Chinese Indian Thai		

Orang Asli Others		
Fasting blood sugar		
HbA1c	*	*
Body mass index (kg/m <sup>2</sup> ) <19 20-24.9 >25		
Family history		

\*Mean (SD)

Table 1: Prevalence of diabetes in asymptomatic and symptomatic group

Group	Subjects	p-value
	Asymptomatic n (%)	
Diabetes mellitus		
Control		

Table 2: Association between age, body mass index, family history in Asymptomatic and symptomatic group.

Group	Asymptomatic gallstones		
	Diabetic n(%)	Control n(%)	p value
Age groups (years) 30-39 40-49 50-59 >60			
Body mass index (kg/m <sup>2</sup> ) <19 20-24.9 >25			
Family history: Positive Negative			

Table 3: Association between gender and parity and status of symptoms in gallstones disease.

Group	Asymptomatic gallstones		
	Diabetic n(%)	Control n(%)	p value
Gender: Female Male			
Parity <3 >3			

Table 4: Association between the duration of type 2 diabetes mellitus and state of control in diabetic group

Duration of diabetes (years)	Asymptomatic gallstones with diabetes (n)		p-value
	Hemoglobin A1c		
	<6.5	>6.5	
<5			
5-10			
>10			

**GANTT CHART**

	2014	2015
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