HYPERAMYLASAEMIA AND 6 HOURS POST ERCP PANCREATITIS AMONG PATIENTS ATTENDING HOSPITAL RAJA PEREMPUAN ZAINAB II (HRPZ II) KELANTAN

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

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May this piece of work blessed. Insyaallah.

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LIST OF ABBREVIATIONS

ERCP	Endoscopic Retrograde Cholangiopancreatogram
SOD	Sphinctor of Oddi Dysfunction
PEP	Post ERCP pancreatitis
ULN	Upper Limit Normal
HRPZ II	Hospital Raja Perempuan Zainab II
SD	Standard Deviation
OR	Odds Ratio
USM	Universiti Sains Malaysia

ABSTRAK

Latar belakang: Radang pankreas adalah kesan sampingan paling utama selepas prosedur endoscopic retrograde cholangiopancreatogram(ERCP) dijalankan dengan prevalens sebanyak 2% -9%. Faktor umur yang muda, wanita, kesukaran untuk 'cannulate' salur hempedu, spinkterotomi salur pankreas, dan sphincter of Oddi dysfunction (SOD) adalah didapati antara faktor risiko yang boleh menyebabkan radang pankreas selepas ERCP. Tahap amilase dan lipase di dalam darah dianggap sebagai penanda aras untuk mengesan radang pankreas lebih awal. Walau bagaimanapun, waktu tahap amilase di dalam darah yang diambil selepas ERCP dalam kajian-kajian sebelum ini adalah tidak seragam. Kajian ini adalah untuk menyiasat perkaitan antara radang pankreas selepas ERCP dengan tahap amilase dalam darah 6 jam selepas ERCP.

Cara kajian: Ini adalah tinjauan retrospektif pesakit yang menjalani ERCP di Hospital Raja Perempuan Zainab II dari 1 Januari 2015 hingga 31 Disember 2018. Tahap amilase dalam darah pada 6 jam selepas ERCP dan komplikasi selepas ERCP dikaji. Hubungan tahap amilase 6 jam selepas ERCP dan radang pankreas ditentukan.

Keputusan: Sebanyak 308 pesakit terlibat di dalam kajian ini di mana 41 pesakit (13.3%) mengalami radang pancreas selepas ERCP. Tahap amilase dalam darah melebihi 300IU pada 6 jam selepas ERCP ($p < 0.001$) dan sphincterotomy ($p = 0.028$) adalah faktor-faktor yang berkait rapat dengan radang pankreas selepas ERCP.

Kesimpulan: Radang pankreas selepas ERCP dikaitkan dengan peningkatan tahap amilase di dalam darah melebihi 300IU pada 6 jam selepas ERCP.

Keywords: ERCP, amylase, pancreatitis, hyperamylasaemia, ERCP complications.

ABSTRACT

Background: Pancreatitis remains a major complication of endoscopic retrograde cholangiopancreatography (ERCP) with a prevalence of 2%-9%.Young age, female gender, difficulty in bile duct cannulation, pancreatic sphincterotomy, and sphincter of Oddi dysfunction have been found to be risk factors. Serum amylase and lipase levels are regarded as useful markers for early diagnosis of pancreatitis. However timing of amylase level taken after ERCP is not standardised among different centres. This study is to determine association of post ERCP pancreatitis with 6-hour amylase level after ERCP.

Methods: This is a retrospective review of patients undergoing ERCP in Hospital Raja Perempuan Zainab II from 1st January 2015 to 31st December 2018. Serum amylase level at 6-hour after ERCP and complications after ERCP were reviewed. The association of amylase level 6-hour after ERCP and pancreatitis was determined.

Results: A total of 308 patients were included in this study of which 41 (13.3%) had post ERCP pancreatitis. Amylase level of more than 300IU at 6-hour after ERCP ($p < 0.001$) and sphincterotomy ($p=0.028$) associated with post ERCP pancreatitis.

Conclusion: Post ERCP pancreatitis is associated with an increase in serum amylase level greater than 300IU at 6-hour after ERCP.

Keywords: ERCP, amylase, pancreatitis, hyperamylasaemia, ERCP complications.

CHAPTER 1: INTRODUCTION

1.1 LITERATURE REVIEW

Endoscopic Retrograde Cholangiopancreatogram (ERCP) is an important endoscopic procedure in managing biliary system diseases and used as a diagnostic or therapeutic tool or both. It was first performed successfully by an obstetrician, Dr William McCure in 1968. Subsequently, the first biliary sphincterotomy was done in 1973 by Dr Meinhard Classen from Germany and Keichi Kawai from Japan. Since then, ERCP has been evolved from diagnostic to therapeutic tool (1).

According to Malaysia Gastrointestinal Registry report in 2009, total of 1160 ERCP performed in 6 centres in Malaysia, which is contributing about 7.1% of all endoscopic procedure performed in those centres (MGIR, 2009). The common indications for performing ERCP were bile duct stones (24.3%), obstructive jaundice (19.5%) and dilated biliary system noted on imaging (7.3%). Overall complication rate was 3.6 % and the most common immediate complication was bleeding following sphincterotomy. However, delayed complications that occurred in ward were most likely under reported, for example pancreatitis.

ERCP is an endoscopic procedure that carries highest risk of morbidity and mortality. It is related to many complications and the most common complication after ERCP is pancreatitis. (3)(4). Generally, the incidence of post ERCP pancreatitis (PEP) is between 1-10% and most commonly are mild to moderate in severity (4). The incidence increased up to 30% in high-risk patients. Severity of acute pancreatitis post ERCP are depending on the patient's clinical findings and intervention needed.

Diagnosis of post ERCP pancreatitis is made based on the persistent abdominal pain more than 24 hours with an increase of serum amylase level greater than 3x upper normal limit after the procedure (Testoni, 2002). Transient increase of serum amylase level after ERCP above normal upper limit without abdominal pain is also common, with minimal clinical significance (5).

Kei Ito et al run a prospective study in 2007 to look for relationship of amylase level with frequency of post ERCP pancreatitis. Numbers of 1291 patients were included in the study. Serum amylase level were taken before ERCP and at 3 hours, 6 hours and 24 hours after ERCP. The study found that post ERCP pancreatitis associated with serum amylase level greater than 2 times the normal limit at 3 hours after ERCP, with elevation at 6 hours. Besides that, reduction of amylase level at 6 hours after ERCP suggest unlikelihood of development of post ERCP pancreatitis. (Ito *et al.*, 2007). From this study, biliary stent placement without sphincterotomy was recognized as a risk factor for post-ERCP pancreatitis by univariate analysis.

Thomas et al runs a prospective study in 2001 predicting post-ERCP pancreatitis in 2001. Numbers of 263 patients were involved. Thomas evaluated the 4-hour serum amylase level as predictor of pancreatitis. They found out that 4-h post-ERCP amylase level is a useful test to predict PEP, but it needs to be interpreted together with clinical assessment (7). A similar study by Sutton et al in 2011 involving 886 patients who had ERCP performed in a single centre in Australia retrospectively. Four-hour amylase level was recorded after ERCP together with patient demographics, procedure details, presence of pancreatogram and morbidity and mortality. The study concluded that 4-hour amylase level is a useful measure

in the prediction of post ERCP pancreatitis (8). They also found out that having a pancreatogram increases the risk of pancreatitis.

A recent prospective study by Jin Hong et al evaluate the usefulness of 4-hour and 6-hour serum amylase level predicting post ERCP pancreatitis and to predict the cut off value for PEP. 583 ERCP was done from October 2015 till June 2016, and 3.6% had PEP. From this study, the 6-h post ERCP amylase level of 2.5 x UL perceived as the best cut off value for prediction of PEP (9).

Severe pancreatitis occur in about 0.3-0.6% and contributes to high risk of mortality. Other complications associated with ERCP includes infection (1.33%), bleeding (1.34%) and perforations (0.6%) (10). Many measures are taken to reduce the incidence of PEP either endoscopically or pharmacologically.

1.2 RATIONALE OF STUDY

Since pancreatitis is the most common complications of ERCP, predicting the likelihood of patients to develop such complication is important. Patient is assessed clinically together with serum amylase level for early diagnosis of pancreatitis. Early diagnosis will allow prompt initiation of appropriate supportive therapies for the patient at risk, and safe discharge of others.

Early recognition of PEP is important to make sure respective management for acute pancreatitis is carried out to prevent its complications. In Hospital Raja Perempuan Zainab II (HRPZ II), Kota Bharu, it is practised to monitor serum amylase level after ERCP at 1 hour and 6 hours in patient who had ERCP done. This is because it is generally accepted that serum amylase level is useful to predict the incidence of PEP. Early detection of patients who will develop PEP can guide decisions regarding aggressive management and hospital discharge.

This study is to investigate the association between the serum amylase level at 6-hours after ERCP with post ERCP pancreatitis in HRPZII. Early detection of PEP is crucial and the main benefit is to provide early prompt treatment for pancreatitis and enable safe discharge after ERCP. This study will also help to identify possible risk factors that predispose patients for developing PEP.

CHAPTER 2: STUDY PROTOCOL

2.1 DOCUMENTS SUBMITTED FOR ETHICAL APPROVAL

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Diagnosis of post ERCP pancreatitis is made based on the persistent abdominal pain more than 24 hours with an increase of serum amylase level greater than 3x upper normal limit after the procedure [2]. Transient increase of serum amylase level after ERCP above normal upper limit without abdominal pain is also common, with minimal clinical significance [3].

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PROBLEM STATEMENT

ERCP is an endoscopic procedure that carries highest risk of morbidity and mortality. It is related to many complications and the most common complication is post ERCP pancreatitis [8] [9]. Generally the incidence of PEP is between 1-10% and most commonly are mild to moderate in severity [10] . The incidence increased up to 30% in high-risk patients. Severity of acute pancreatitis post ERCP are depending on the patients' clinical findings and intervention needed.

Severe pancreatitis occur in about 0.3-0.6% and contributes to high risk of mortality. Other complications associated with ERCP includes infections (1.44%), bleeding (1.34%) and perforations (0.6%) [11] . Many measures are taken to reduce the incidence of PEP either endoscopically or pharmacologically.

Since pancreatitis is the most common complications of ERCP, predicting the likelihood of patients to develop such complication is important. Patient is assessed clinically together with serum amylase level for early diagnosis of pancreatitis. Early determination would allow prompt initiation of appropriate supportive therapies for the patients at risk, and safe discharge of others.

RATIONALE OF STUDY

Early recognition of post-ERCP pancreatitis is important to make sure respective management for acute pancreatitis is carried out to prevent its complications. In Hospital Raja Perempuan Zainab II, Kota Bharu, it is practised to monitor serum amylase level after ERCP at 1 hour and 6 hours in patients who had ERCP done. This is because it is generally accepted that serum amylase level is useful to predict the incidence of post ERCP pancreatitis. Early detection of patients who will develop PEP can guide decisions regarding aggressive management and hospital discharge.

This study is to investigate the association between the serum amylase level at 6-hours after ERCP with post ERCP pancreatitis in HRPZ II. Early detection of post-ERCP pancreatitis is crucial and the main benefit is to provide early prompt treatment for pancreatitis and enable a safe discharge after ERCP. This study will also help to identify possible risk factors that predispose patients for developing post-ERCP pancreatitis.

OBJECTIVE AND HYPOTHESIS

General objective

To determine the prevalence of post ERCP pancreatitis and its association with hyperamylasaemia at 6 hours post ERCP in HRPZ II.

Specific objectives

1 - To determine the prevalence of post ERCP pancreatitis at 6 hours post ERCP.
2 - To determine the association between hyperamylasaemia at 6 hours post ERCP and pancreatitis

Research questions

There is association between hyperamylasaemia at 6 hours post ERCP with pancreatitis among patients in HRPZ II.

Operational Definitions

Post-ERCP pancreatitis (PEP) refers to a presence of pancreatic-type abdominal pain (epigastric pain radiating to the back), and tenderness requiring analgesia and persisting for at least 24 h after the procedure with a raised of serum amylase level higher than 3 times the upper limit of normal (ULN) [2].

Hyperamylaseamia refers to the increase of serum amylase level higher than the ULN without abdominal pain after ERCP. The normal range of serum amylase level in Hospital Raja Perempuan Zainab II is 28 - 100 U/L.

Major bleed refers to bleeding during or after ERCP that requires interventions or blood transfusion

Minor bleed refers to bleeding during or after ERCP that resolved spontaneously

Cholangitis defined as fever (>38°C) with new or worsened abdominal pain and new or worsened LFTs and requiring treatment with prolonged hospitalization (13).

METHODOLOGY

Study design

Retrospective review of medical records in Hospital Raja Perempuan Zainab II (HRPZ II), Kota Bharu, Kelantan from January 2015 until December 2018.

Reference population

Patients who underwent ERCP in HRPZ II, Kota Bharu, Kelantan.

Source population

Patients who underwent ERCP in HRPZ II, Kota Bharu, Kelantan from year 2015 to 2018

Study population

Patients who underwent ERCP in HRPZ II, Kota Bharu, Kelantan from year 2015 to 2018 with the following exclusion criteria.

1- Unavailability of serum amylase level result

2- Diagnosed as acute pancreatitis 2 weeks before ERCP

Sampling method

Universal sampling of medical records of patients who underwent ERCP in HRPZ II, Kota Bharu, Kelantan from year 2015 - 2018.

SAMPLE SIZE CALCULATION

Objective 1 is to determine the prevalence of post ERCP pancreatitis at 6 hours post ERCP. Single proportion formula was applied [12].

$$n = \left[\frac{Z_{\alpha/2}}{\Delta} \right]^2 P(1-P)$$

N = Minimum required sample size
$Z_{\alpha/2}$ = Value of standard normal distribution was 1.96
Δ = Precision of 0.05
P = prevalence of post ERCP pancreatitis was 9.8% [13]

The prevalence of post ERCP pancreatitis was 9.8% [13] and taking the precision of 0.05 with 95% confidence, the minimum required sample size was 136. After considering a non-response rate of 10%, the calculated sample size was 152 patients.

Objective 2 is to determine the association between hyperamylasaemia at 6 hours post ERCP and pancreatitis. Sample size calculating for comparing 2 proportion was applied using PS software.

P_0 = Proportion of hyperamylasaemia at 6 hours post ERCP without pancreatitis was 16.6 % [14]

P_1 = Proportion of hyperamylasaemia at 6 hours among post ERCP pancreatitis was 6 % [14]

The minimum sample size was 278 and after considering a non-response rate of 10%, the calculated sample size was 308 patients.

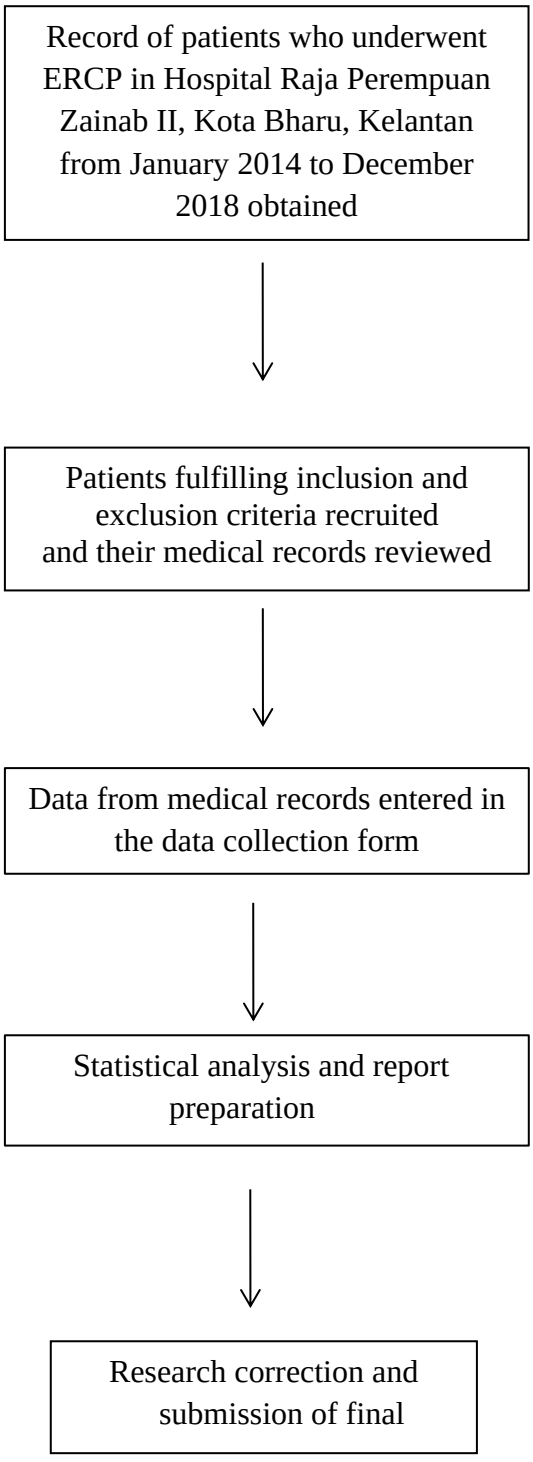
By calculating sample size based on objective 1 and objective 2, my sample size for this study is 308 patients.

RESEARCH TOOLS

Medical records of patients who underwent ERCP in HRPZ II from January 2014 until December 2018 will be obtained from the record office. Information such as demographic data, indications of ERCP, procedure done during ERCP, serum amylase level at 6-hours after ERCP and complications after ERCP will be retrieved.

In HRPZ II, all ERCP procedures are performed by surgeons and gastroenterologist in Endoscopy unit. All patients were given sedation before the procedure. The serum amylase levels are measured at 1-hour and 6-hour after the procedure, and post ERCP pancreatitis diagnosed based on the presence of pancreatic type of pain and serum amylase level more than 3 times ULN. The attending surgeons or gastroenterologist will assess the severity of pancreatitis based on Marshal's score.

In this study, medical records of patients who underwent ERCP from January 2015 til December 2018 will be obtained from endoscopy record and Unit Rekod Hospital Raja Perempuan Zainab II, Kota Bharu. Medical records will be reviewed, and information will be transferred to case report form.


Record of patients who underwent ERCP in Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan from January 2014 to December 2018 obtained
Patients fulfilling inclusion and exclusion criteria recruited and their medical records reviewed
Data from medical records entered in the data collection form
Statistical analysis and report preparation
Research correction and submission of final

DATA ENTRY AND ANALYSIS

Data entry is by using the SPSS version 23.0.

Objective 1 - To determine the prevalence of post ERCP pancreatitis at 6 hours post ERCP. This objective will use descriptive analysis.

Objective 2 - To determine the association between hyperamylasaemia at 6 hours post ERCP and pancreatitis. Simple and multiple logistic regression confirmatory analysis will be performed. The dependant variable is post ERCP hyperamylasaemia (0 = NO , 1 = YES). The independant variable is hyperamylasaemia. The controlled variables are bile duct cannulation, pancreatogram, pancreatic duct cannulation, sphincterotomy, basket retrieval, balloon dilatation, biliary stenting, pancreatic stenting and mechanical lithotriptor.

EXPECTED RESULTS

Table 1 - Characteristic of patients

	POST ERCP PANCREATITIS		HYPERAMYLASAEMIA	
	Mean (SD)	n (%)	Mean (SD)	n (%)
Age ≥ 55y < 55y				
SEX Male Female				
INDICATIONS FOR ERCP Obstructive jaundice Stone disease Cholangitis Pancreatitis Post cholecystectomy leak				
History of post ERCP pancreatitis YES NO				
PROCEDURES Bile duct cannulation Pancreatogram Pancreatic duct cannulation Sphincterotomy Basket retrieval Balloon dilatation Biliary stenting Pancreatic stenting Mechanical lithotriptor	YES	NO		

Table 2 - Association between serum amylase level at 6 hours after ERCP and post ERCP pancreatitis

	SIMPLE LOGISTIC REGRESSION (SLR)			MULTIPLE LOGISTIC REGRESSION [a]		
	Crude OR (95%)	Wald (df)	P value	Crude OR (95%)	Wald (df)	P value
AMYLASE LEVEL						
< 3 X UL						
≥ 3 X UL						

[a] adjusted for techniques

YEAR	2019				2020											
MONTHS	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
PROPOSAL PRESENTATION																
ETHICS APPROVAL																
DATA COLLECTION																
DATA ANALYSIS AND REPORT PRESENTATION																
SUBMISSION OF DRAFT AND REVISION																
SUBMISSION OF FINAL RESEARCH																

ETHICAL CONSIDERATION

Approval will be obtained from the Research and Ethics committee of Universiti Sains Malaysia (USM) and Ministry of Health before starting the study.

DECLARATION

There is no conflict of interest.

PRIVACY AND CONFIDENTIALITY

All forms are anonymous and will be entered into SPSS software. Only research team members can access the data, confidentially of the data will be maintained strictly. Data will be presented as grouped data and the participant individually or the involved patient will not be identified.

COMMUNITY SENSITIVITIES AND BENEFITS

This study may benefit surgeons as well as patients. Surgeons will be more aware and make a justified patient selection for ERCP and will be able to predict those who are more likely to develop post ERCP pancreatitis and provide early management for pancreatitis.

Blood taking is definitely cause anxiety to patients. Result of this study may reassure patients the need of serum amylase level monitoring after ERCP.

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2.2 ETHICAL APPROVAL LETTERS

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(*Medical Research & Ethics Committee*)
KEMENTERIAN KESIHATAN MALAYSIA
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Tarikh : 05-Dec-2019

Dr ANN DASIMAKAMALIA BT MAT
UNIVERSITI SAINS MALAYSIA HOSPITAL

Dato'/ Tuan/ Puan,

SURAT KELULUSAN ETIKA: NMRR-19-3122-51478 (IIR)
HYPERAMYLASAEMIA AND 6 HOURS POST ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAM PANCREATITIS AMONG PATIENTS ATTENDING HOSPITAL RAJA PEREMPUAN ZAINAB II, KOTA BHARU, KELANTAN

Dengan hormatnya perkara di atas adalah dirujuk.

2. Bersama dengan surat ini dilampirkan surat kelulusan saintifik dan etika bagi projek ini. Segala rekod dan data subjek adalah SULIT dan hanya digunakan untuk tujuan kajian dan semua isu serta prosedur mengenai *data confidentiality* mesti dipatuhi. Kebenaran daripada Pengarah Hospital / Institusi di mana kajian akan dijalankan mesti diperolehi terlebih dahulu sebelum kajian dijalankan. Dato' / Tuan / Puan perlu akur dan mematuhi keputusan tersebut dan undang-undang lain yang berkaitan, termasuklah Akta Akses Kepada Sumber Biologi dan Perkongsian Faedah 2017.

3. Penyelidik- penyelidik dan lokasi kajian yang terlibat ialah:

   HOSPITAL RAJA PEREMPUAN ZAINAB II
   Dr Ann Dasimakamalia Bt Mat (Penyelidik Utama)

4. Adalah dimaklumkan bahawa kelulusan ini adalah sah sehingga **04-Dec-2020.** Tuan/Puan perlu menghantar dokumen-dokumen seperti berikut selepas mendapat kelulusan etika. Borang-borang berkaitan boleh dimuat turun daripada laman web Jawatakuasa Etika & Penyelidikan Perubatan (JEPP) (http://www.nih.gov.my/mrec).

   i. ***Continuing Review Form*** selewat-lewatnya dalam tempoh 2 bulan (60 hari) sebelum tamat tempoh kelulusan ini bagi memperbaharui kelulusan etika.
   ii. ***Study Final Report*** pada penghujung kajian.
   iii. Mendapat kelulusan etika sekiranya terdapat pindaan ke atas sebarang dokumen kajian / lokasi kajian / penyelidik. Pihak JEPP mempunyai hak untuk menarik balik kelulusan etika sekiranya terdapat perubahan dokumen kajian yang tidak diisytiharkan.

5. Kajian tersebut hanya melibatkan pengumpulan data melalui:

   i. Retrospektif
   ii. Rekod perubatan

6. Sila ambil maklum bahawa sebarang urusan surat-menyurat berkaitan dengan penyelidikan ini haruslah dinyatakan **nombor rujukan surat** ini untuk melicinkan urusan yang berkaitan.

Sekian terima kasih.

Komen (Jika ada) : NIL

Lokasi Kajian:
Hospital Raja Perempuan Zainab II

Ruj.Kami: KKM/NIHSEC/ P19-2587 (6)

Keputusan Jawatankuasa Etika dan Penyelidikan Perubatan:
(√) Lulus
( ) Tidak Lulus

Tarikh kelulusan etika : 05-Dec -2019

"BERKHIDMAT UNTUK NEGARA"

MD/Approval2019/Mrecshare

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(*Medical Research & Ethics Committee*)
KEMENTERIAN KESIHATAN MALAYSIA
d/a Kompleks Institut Kesihatan Negara
Blok A, No 1, Jalan Setia Murni U13/52,
Seksyen U13, Bandar Setia Alam,
40170 Shah Alam, Selangor.
Tel: 03-3362 8888/8205

Ref : KKM/NIHSEC/ P19-2587 (7)
Date: 05- Dec -2019

Dr ANN DASIMAKAMALIA BT MAT
UNIVERSITI SAINS MALAYSIA HOSPITAL

Dear Sir / Mdm,

ETHICS INITIAL APPROVAL: NMRR-19-3122-51478 (IIR)
HYPERAMYLASAEMIA AND 6 HOURS POST ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAM PANCREATITIS AMONG PATIENTS ATTENDING HOSPITAL RAJA PEREMPUAN ZAINAB II, KOTA BHARU, KELANTAN

This letter is made in reference to the above matter.

2. The Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH) has provided ethical approval for this study. Please take note that all records and data are to be kept strictly **CONFIDENTIAL** and can only be used for the purpose of this study. All precautions are to be taken to maintain data confidentiality. Permission from the District Health Officer / Hospital Administrator / Hospital Director and all relevant heads of departments / units where the study will be carried out must be obtained prior to the study. You are required to follow and comply with their decision and all other relevant regulations, including the Access to Biological and Benefit Sharing Act 2017.

3. The investigators and study sites involved in this study are:

   HOSPITAL RAJA PEREMPUAN ZAINAB II
   Dr Ann Dasimakamalia Bt Mat (Penyelidik Utama)

4. The following study documents have been received and reviewed with reference to the above study:

Documents received and reviewed with reference to the above study:
1. Study Protocol_Version 2.1, dated 15-Nov-2019
2. Data Collection Form_Version 2, dated 02-Nov-2019
3. Investigator's documents : Declaration of Conflict of Interest (COI), IA-HOD-IA, and CV:
a) Dr Ann Dasimakamalia Bt Mat (Penyelidik Utama)

5. Please note that ethical approval is valid until **04-Dec-2020**. The following are to be reported upon receiving ethical approval. Required forms can be obtained from the Medical Research Ethics Committee (MREC) website (**http://www.nih.gov.my/mrec**).

i. **Continuing Review Form** has to be submitted to MREC within 2 month (60 days) prior to the expiry of ethical approval.
ii. **Study Final Report** upon study completion to the MREC.
iii. Ethical approval is required in the case of **amendments / changes** to the **study documents/ study sites/ study team**. MREC reserves the right to withdraw ethical approval if changes to study documents are not completely declared.

6. This study involves the following methods:

   i. Retrospective