SURVIVAL AND PROGNOSTIC FACTORS OF MORTALITY IN PATIENTS WITH PERITONEAL DIALYSIS - RELATED PERITONITIS

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LIST OF ABBREVIATIONS

ACEI	-	Angiotensin-converting enzyme inhibitor
ALP	-	Alkaline phosphatase
APD	-	Ambulatory peritoneal dialysis
ARB	-	Angiotensin receptor blocker
BMI	-	Body mass index
CAPD	-	Continuous ambulatory peritoneal dialysis
CKD	-	Chronic kidney disease
eGFR	-	Estimated glomerular filtration rate
EPS	-	Encapsulating peritoneal sclerosis
ESRD	-	End-stage renal disease
ESA	-	Erythropoietin stimulating agent
GFR	-	Glomerular filtration rate
HD	-	Haemodialysis
HR	-	Hazard ratio
iPTH	-	Intact parathyroid hormone
ISPD	-	International Society of Peritoneal Dialysis
JEPeM	-	Jawatankuasa Etika Penyelidikan Manusia
KDOQI	-	National Kidney Foundation Kidney Disease Outcomes Initiatives
LML	-	Log minus log
MDTR	-	Malaysian Dialysis and Transplant Registry
MOH	-	Ministry of health
MREC	-	Medical Research Ethics Committee
MRRB	-	Malaysian Registry of Renal Biopsy
NKF	-	National Kidney Foundation
NRR	-	National Renal Registry
NSAID	-	Non-steroidal anti-inflammatory drug
PD	-	Peritoneal dialysis
PPI	-	Proton pump inhibitor
QOL	-	Quality of life

RRT	-	Renal replacement therapy
SHR	-	Sub distribution hazard ratio
WHO	-	World Health Organization
TIBC	-	Total iron-binding capacity
TVC	-	Time-varying covariate
USRDS	-	United States Renal Data System

LIST OF SYMBOLS

B	Beta coefficient
n	Number of sample
μ	Micro
±	Plus minus
α	Type 1 error
β	Type 2 error

KEMANDIRIAN DAN FAKTOR PROGNOSTIK UNTUK KEMATIAN DALAM KALANGAN PESAKIT *PERITONITIS* BERKAITAN DIALISIS PERITONEAL

ABSTRAK

Pengenalan: *Peritonitis* adalah satu daripada komplikasi utama dialisis *peritoneal* (DP). Median masa dan kadar kemandirian dalam kalangan pesakit DP telah banyak dikaji dengan mendalam di seluruh dunia dan berbeza-beza mengikut negara. Walaubagaimanapun, kajian mengenai median masa dan kadar kemandirian dalam kalangan pesakit *peritonitis* berkaitan DP tidak banyak dilakukan di peringkat dunia dan juga tempatan. **Objektif:** Kajian ini bertujuan untuk menentukan masa kemandirian dan faktor prognostik untuk penyakit *peritonitis* berkaitan DP. **Metodologi:** Kajian kohot retrospektif ini menggunakan data sekunder daripada Registri Renal Kebangsaan dari 2010 sehingga 2015 bertempat di Hospital Kuala Lumpur. Lima kumpulan pemboleh ubah utama telah dikaji, terdiri daripada sosio-demografi, parameter klinikal, parameter biokimia, rejim DP dan ubat-ubatan. Hasil kajian adalah kematian semua sebab dan tempoh kemandirian dikira dari episod pertama *peritonitis* hingga ke kematian. Hasil *censored* meliputi pesakit yang masih hidup pada akhir kajian, pesakit pindah rawatan ke haemodialisis dan kehilangan temujanji susulan. Analisis yang digunakan adalah Kaplan Meier dan jadual hayat untuk analisis mudah dan Cox Regression untuk analisis berganda. **Keputusan:** Keseluruhannya kajian ini melibatkan seramai 2,002 pesakit. Kajian ini mendapati 40% pesakit mati pada akhir kajian. Secara keseluruhannya, purata umur pesakit *peritonitis* berkaitan DP adalah 59 tahun dengan sisihan piawai 17.4, dan 50.2% adalah wanita. Median masa kemandirian untuk *peritonitis* berkaitan DP adalah 46.3 bulan (95% selang keyakinan (SK): 42.2, 56.7). Kadar kemandirian untuk satu, dua dan tiga tahun untuk *peritonitis* berkaitan DP adalah masing-masing 75.6% (95% SK: 73.7,77.5),

64.6% (95% SK: 62.5, 66.7) dan 55.6% (95% SK: 53.3,57.8). Lima faktor prognostik dikenal pasti yang mempengaruhi kematian pesakit *peritonitis* berkaitan DP iaitu umur (Nisbah bahaya terselaras (NBT): 1.04; SK: 1.03,1.04), serum albumin (NBT: 1.37; SK: 1.20, 1.57), permulaan *peritonitis* (NBT: 1.24; SK: 1.08,1.43), penghalang reseptor angiotensin (NBT: 1.37; SK: 1.11, 1.60) dan episod *peritonitis* (NBT: 0.36; SK: 0.27,0.46). **Kesimpulan:** Kajian mendapati umur lebih tua, hipoalbuminemia, tidak mengambil ubat penghalang reseptor angiotensin, tambahan episod *peritonitis* dan *peritonitis* bermula lewat merupakan faktor prognostik yang bererti. Penemuan ini menyumbang maklumat kepada pakar perubatan dan pengurusan klinikal hospital berdasarkan bukti saintifik bagi tujuan rawatan dan intervensi lebih efektif.

Kata kunci: *peritonitis*, dialysis peritoneal, peringkat akhir buah pinggang, analisis kemandirian, kematian.

SURVIVAL AND PROGNOSTIC FACTORS OF MORTALITY IN PATIENTS WITH PERITONEAL DIALYSIS-RELATED PERITONITIS

ABSTRACT

Introduction: Peritonitis is one of the major complications of peritoneal dialysis (PD). The median survival time and survival rate in PD patient has been studied extensively globally and varies from one country to another. However, the median survival time and survival rate of PD related peritonitis data is scarcely studied both locally and globally. **Objective:** This study aimed to to determine the survival time and prognostic factors of PD related peritonitis. **Method:** This study was a retrospective cohort study that used secondary data from the National Renal Registry from 2010 until 2015 located in Hospital Kuala Lumpur. Five main group variables were studied comprising of socio-demographic, clinical parameters, biochemical parameters, PD regime and medications. The outcome studied was the survival time which was calculated from the first peritonitis episode until the outcome of death. The primary event was all-cause mortality and censored outcome included patient still alive at end of study, changed to heamodialysis and loss to follow-up. Kaplan Meier estimate and lifetable analysis were used for univariable and Cox Proportional Hazard Regression was used for multivariable analysis. **Results:** Overall the study included a total of 2,002 patients. This study observed 40% of the patient had death as outcome. Overall, the mean age of the patients were 59 (standard deviation) 17.4 and 50.2% of the patients were woman. The median survival time for PD related peritontis was 46.3 months (95% confidence interval (CI): 42.2, 56.7). The one-, two- and three year survival rates of PD related peritonitis were 75.6 (95% CI: 73.7,77.5), 64.6% (95% CI: 62.5, 66.7) and 55.6% (95% CI: 53.3,57.8) respectively. Five prognostic factors were identified in this study affecting survival of PD related peritonitis patients which were age

(Adjusted hazard ratio (AHR): 1.04; 95% CI: 1.03,104), serum albumin (AHR: 1.37; 95% CI: 1.20, 1.57), onset of peritonitis (AHR: 1.24; 95% CI: 1.08,1.43), angiotensin receptor blocker medication (AHR: 1.37: 95% CI: 1.11, 1.60) and peritonitis episode (AHR: 0.36; 95% CI: 0.27, 0.46). **Conclusions:** Multiple Cox Proportional Hazard Regression revealed older age, hypoalbuminemia, not on angiotensin receptor blocker, increase peritonitis episode and late onset peritonitis were significant prognostic factors of mortality. These findings provide evidence based information for clinicians and policy makers in planning preventive measures and interventional programs for peritonitis in PD patients.

Key words: peritonitis, peritoneal dialysis, end stage renal disease, survival analysis, mortality, peritoneal dialysis-related peritonitis

CHAPTER ONE
INTRODUCTION

1.1 Peritoneal dialysis-related peritonitis

Renal failure is a condition resulting from progressive failure of kidney or chronic kidney disease (CKD) in which the kidney is no longer able to sustain life (MOH, 2018). Chronic kidney disease consists of a spectrum of five stages with increasing severity (from stage 1 to stage 5) based on the level of renal function as assessed by the rate of glomerular filtration. A patient with a glomerular filtration rate (GFR) of less than 15ml/min/1.73m^2 is categorized as having CKD stage 5. Once CKD has progressed to stage 5, an individual will often develop sign and symptoms associated with renal function disorder such as pruritis, acid-base or electrolytes abnormalities, uncontrolled blood pressure or cognitive impairment. By this stage, the kidney is no longer adequate to sustain life and renal replacement therapy is indicated, and it is most often recommended to start dialysis (National Kidney Foundation [NKF], 2006).

Throughout the follow-up treatment of chronic kidney disease, practitioners are recommended in educating the patient on the various treatment of renal replacement therapy (RRT) which comprises of haemodialysis, peritoneal dialysis and renal transplant. The kidney has numerous functions in the human body which encompasses regulating water, acid-base balance, electrolytes and blood pressure. It also filters waste such as urea, uric acid and toxins from the body. RRT functions as a replacement for kidney function and filters out excess waste, toxins and water from a patient's body. Compared to haemodialysis, Lu *et al.* (2017a) reported that patients on peritoneal dialysis (PD) had better blood pressure, acid-base balance and phosphate control. It is also noted that PD patient can live more fully and is more cost-effective (Morton *et al.*, 2011).

Peritoneal dialysis uses the peritoneum as a natural permeable membrane. It involves diffusion of uremic solutes and electrolytes from the peritoneal membrane capillaries into the externally infused dialysate. The continuous nature of PD is suitable for heart failure patient or volume-dependent hypertension. However, contraindications in performing PD includes extreme obesity, multiple recurrent abdominal surgeries and recurrent peritonitis. Complications of PD catheter consist of peritonitis, catheter malfunction and failure of PD due to membrane loss or fibrosis (Ford, 2011).

There are two major types of peritoneal dialysis and they include continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD). A patient using CAPD does the exchanges of solute four times a day while for APD, the exchange is done at night when the patient is asleep with the help of a machine called a cycler. APD can be further classified into continuous cycling peritoneal dialysis (CCPD), nocturnal intermittent peritoneal dialysis (NIPD) and tidal peritoneal dialysis (TPD). Some patients require both CAPD and APD to achieve adequate clearance of waste from their body. In this study, both methods of PD are used and will be observed their effect on mortality in PD related peritonitis patients (NKF, 2006).

Peritoneal dialysis has its advantage, but there are a handful of infectious and non-infectious complications that can arise. One of the non-infectious complication is mechanical catheter-related, for example obstruction to flow, leakage or pain on infusion or drainage; and metabolic complications such as hyperglycaemia, hypertriglyceridemia and hyperinsulinemia. Other than the above, peritoneal dialysis use may also lead to hemoperitoneum and encapsulating peritoneal sclerosis (McCormick and Bargman, 2007). The infectious complication of peritoneal dialysis includes peritoneal dialysis-related peritonitis.

Peritoneal dialysis related peritonitis is still one of the major complications of PD and has been reported to cause death in 1 to 6% of PD patients (Fried *et al.*, 1996). Risk factor for peritonitis among patients on PD has been extensively studied, and they include low albumin level (Huang *et al.*, 2014), diabetes (Chen *et al.*, 2019), older age, lower-income and assisted PD (Mushahar *et al.*, 2016). Santhakumaran *et al.* (2016) found that there was an association with overhydration and increase risk of peritonitis whilst Abe *et al.* (2016) also stated that low haemoglobin level before the start of PD was a risk factor.

The source of infection for PD related peritonitis is mainly the catheter where it provides entry into the sterile peritoneum (Salzer, 2018). Common pathogens include coagulase-negative staphylococcal species and *staphylococcus aureus*. After the inflammation is set, it is manifested as abdominal pain, fever and cloudy dialysate due to an increase in the number of cells in the peritoneal fluid (Salzer, 2018). Exit site and tunnel infection may lead to peritonitis. Other causes for peritonitis may include diverticulitis, appendicitis, cholecystitis, or a perforated viscus along with intra-abdominal surgery, colonoscopy, hysteroscopy, and transmigration of bowel flora from constipation.

Peritonitis rate has been decreasing over the years but great care must be placed to ensure it sustain. Prevention of peritonitis consists of a multifaceted process involving extensive patient training and focusing on proper technique. The International Society of Peritoneal Dialysis (ISPD) guideline also recommends for prophylactic antibiotics with vancomycin or first or second-generation cephalosporin such as cefazolin reducing post-operative catheter infections.

1.2 The burden of peritoneal dialysis and PD related peritonitis

In 2010, the cost of renal failure in the USA alone was 28 billion USD and was projected to be 54 billion USD 10 years later (Ford, 2011). In Malaysia, the total annual expenditure for renal failure by the public sector has increased by 94% from RM572 million in 2010 to RM1.12 billion in 2016. Out of this, 94% of the expenditure was spent on dialysis (Ismail *et al.*, 2019). Peritoneal dialysis expenditure increased two-fold from RM46,000 to RM 102,977 from 2010 to 2016. The MOH (2018) forecast the total cost estimates of dialysis services to increase toward RM1.5 billion in 2040.

Quality of life is one of the major challenges in healthcare. Amongst haemodialysis and peritoneal dialysis, it has been reported before that quality of life was similar and there was no statistically significant difference (Ramos *et al.*, 2015; Tannor *et al.*, 2017). However, Ramos *et al.* (2015) observed that patients on peritoneal dialysis reported less severity in terms of pain whilst Tannor *et al.* (2017) stated peritoneal dialysis affected patients sleep and body image among females. In Malaysia, the 24th Malaysian Dialysis and Transplant Registry 2016 reported that peritoneal dialysis patients reported a median quality of life (QOL) score of 10 and there was a decline in the proportion of employment from 2010 until 2016.

Among the infectious complication of peritoneal dialysis includes peritoneal dialysis-related peritonitis. Peritonitis can lead to treatment failure such as ultrafiltration failures and inadequacy, catheter loss and subsequent change to haemodialysis, increase health care cost, significant morbidity and even mortality. In 2016, peritonitis contributed to 18% of the main cause of drop out from peritoneal dialysis in Malaysia (Mushahar *et al.*, 2016). It was also noted in the report that peritonitis was a significant factor for change of peritoneal dialysis modality to haemodialysis (HR = 7.4, $p < 0.001$). Another long term complications of peritonitis itself are encapsulating peritoneal sclerosis (EPS) (Ito *et al.*, 2019). Apart

from these complications, peritonitis also increases the rate of hospitalization as reported by a study done in China by Hu *et al.* (2018).

1.3 Prevalence of peritoneal dialysis and PD related peritonitis

Latest studies confirmed that the global burden of chronic kidney disease is high and recently two landmark studies estimated the prevalence of CKD. A meta-analysis of 44 countries prevalence by Hill *et al.* (2016) reported that the prevalence of CKD was at 13.4% whilst Mills *et al.* (2015) segregated the meta-analysis of 33 studies based on gender, with men having CKD prevalence of 10.4% and women 11.8%. In Asia, the prevalence of CKD ranges from as low as 5.5% in Jordan to 18% in both Mongolia and Thailand (Tang *et al.*, 2019). Malaysia last published prevalence rate for CKD was at 9.07% in 2013 and this figure has since increased to 15.5% in 2018 as reported in MOH (2018).

Although haemodialysis remains the most common form of dialysis, peritoneal dialysis has a high prevalence rate in Oceania - Asia particularly in the developing countries. Hong Kong and Thailand for example, has 44.2% and 28.2% of its renal patients on peritoneal dialysis whereas Mainland China, Singapore, New Zealand and Australia each has 14.1%, 10.1%, 31% and 19.5% (Kwong and Li, 2015; Tang *et al.*, 2019). In 2016, the prevalence rate of PD patient in Malaysia was 155 per million population (pmp), although this is still low compared globally. In Malaysia, the number of new dialysis patients continues to increase linearly over a period of ten years from 4014 in 2007 to at least 7663 in 2016. Data in 2016, the top three states in Malaysia with the highest prevalence of dialysis patients were Pulau Pinang, Negeri Sembilan and Johor with 1694, 1772 and 1729 patients per million population respectively (Ahmad *et al.*, 2016). Over the years the number of PD patient has been increasing both globally and in Malaysia (Ahmad *et al.*, 2016).

The question of how frequent and how soon patients with PD developed peritonitis in Malaysia has been previously explored. In Malaysia, the median peritonitis rate was 1 in 42.3 patients month in 2016, an increase from 1 in 39.9 patients month the previous year and was varied from one hospital to another (Mushahar *et al.*, 2016). A retrospective study done recently in Miri from 2013 to 2017, reported a four year peritonitis rate of 0.184 episodes per patient-year (Andy Tang *et al.*, 2019). Contrasting globally, the incidence rate of peritonitis ranges from 0.16 to 1.66 episodes per patient-year (Kerschbaum *et al.*, 2013; Tian *et al.*, 2016).

1.4 Survival time of PD related peritonitis

In many areas of healthcare, the primary target parameter is the time to an event occurring. This event may include but not restricted to cure, relapse, death or even failure. Initially, the value at the beginning of a period and the time of an event is defined. The value of time obtained by calculating the number of days, months or years between these two calendar date is known as survival time. The survival time for PD related peritonitis in this study is the total months from the first episode of peritonitis to the primary event (death) of the patient.

The mean survival time is hugely affected by censoring, and due to this reason, median survival time is often used. The median survival time is the time at which half the patient has experienced the event. The median survival time in PD patient has been studied extensively globally and varies from one country to another and ranges from 20 – 48 months. In a cohort of 322 patient in Thailand studied from 1995 to 2005, the reported median survival time was 46.4 months (Pongskul *et al.*, 2006). A study done in the French region using data from 2003 to 2008 of 7,003 renal failure patients reported that the median survival time of patients undergoing PD was 20.4 months which was lower than those in haemodialysis group of 36.7 months (Sens *et al.*, 2011). Meanwhile, the national

24th Malaysian Dialysis and Transplant Registry 2016 reported that the median survival time for PD patients a cohort of 1996 to 2016 was 48 months (Seng *et al.*, 2016). However, there is a lack of studies reporting on median survival time in PD related peritonitis cohort only. A study of 208 participants done in Kuwait by El-Reshaid *et al.* (2016) reported that the median survival time in peritonitis patients undergoing CAPD was 13.1 months while those undergoing APD had 14 months.

Studies on PD patients survival rate at one, two and three years have been done throughout the globe but much lesser in comparison with median survival. In a study done in Japan consisting of 1,601 of PD patients, the one and two-year survival rate was reported as 88.3% and 84% (Abe *et al.*, 2018). No study that has been found reporting on the survival rate in a population of PD patients with peritonitis. There is however, a study done in Taiwan studying peritonitis survival in haemodialysis patients with a survival rate of 38.8% and 10.1% at 1 and 5 years respectively (Lu *et al.*, 2017b).

1.5 Problem statement

In recent years, there has been an increase in dialysis number both locally as well as globally. According to the 2018 United States Renal Data System (USRDS) data report, Malaysia is among the top ten countries having the highest percentage rise in dialysis prevalence which includes peritoneal dialysis. Peritonitis is still a major complication of peritoneal dialysis. Even with improved PD techniques, the mortality from peritonitis is high. Another study in China reported that peritonitis was independently associated with a higher risk of all-cause mortality, infection-related mortality and cardiovascular mortality (Ye *et al.*, 2017). Few studies have been done to assess prognostic markers or factors that can affect the survival of PD patients with PD related peritonitis and no known studies in Malaysia have observed the median survival and survival rate of patients with PD related peritonitis.

1.6 Justification of the study

Many studies have been done in other countries including Malaysia, to determine the prognostic factors of peritonitis and survival of patients on peritoneal dialysis. Nevertheless, there is a paucity of such studies that look at the median survival time as well as overall survival rate in PD patient with peritonitis. Amongst the focus of research has been revolving around risk factors of peritonitis, incidence rate, prognostic factors such as albumin, potassium and BMI on mortality, risk factors for peritonitis rate and also factors affecting the severity of peritonitis. However, some factors have not been reported previously such as the effect of Asian race, smoking status, medications such as erythropoietin and iron, biochemical parameters for instance calcium, phosphate and intact parathyroid hormone (iPTH) on mortality. Thus this study provides added information regarding the survival time in PD patients with peritonitis specifically and factors that may affect the survival time. This study allows physicians to have the opportunity to identify factors that affect the survival and identify patients that are at risk of death and intervene to help reduce mortality due to peritonitis.

1.7 Research questions

1. What is the median survival time for PD related peritonitis in PD patients from 2010 to 2015?
2. What are the one-, two- and three - year survival rates for PD related peritonitis in PD patients from 2010 to 2015?
3. What are the prognostic factors of mortality for PD related peritonitis in PD patients registered in the National Renal Registry (NRR)?

1.8 Objective

1.8.1 General objective

To determine the survival time and prognostic factors of PD related peritonitis patients in Malaysia.

1.8.2 Specific objectives

1. To estimate the median survival time of PD related peritonitis in PD patients registered in NRR.
2. To estimate the one-, two- and three-year survival rates of PD related peritonitis in PD patients registered in NRR.
3. To identify the prognostic factors of mortality of PD related peritonitis in PD patients registered in NRR.

1.9 Hypothesis

The research hypothesis is factors sociodemographic, clinical, biochemical and PD regime are significant prognostic factors influencing the mortality of PD related peritonitis patients.

CHAPTER TWO

LITERATURE REVIEW

2.1 Methods and result of the literature search

The literature search was done by using phrase searching such as citation search and Boolean operators. Keywords used were grouped into two, and the first group included "survival AND (median OR proportion) AND peritoneal dialysis AND peritonitis. Among the keywords used in the second group includes "peritonitis AND risk AND peritoneal dialysis", "peritonitis AND (mortality OR survival) AND age", "peritonitis AND (mortality OR survival) AND (gender OR sex)", "peritonitis AND (mortality OR survival) AND race". "peritonitis AND (mortality OR survival) AND BMI", "peritonitis AND (mortality OR survival) AND smoking", "peritonitis AND (mortality OR survival) AND (rate OR episode)", "peritonitis AND (mortality OR survival) AND albumin" . Search engines used were Scopus, Pubmed, Sciencedirect and articles were imported to Endnote and Zotero.

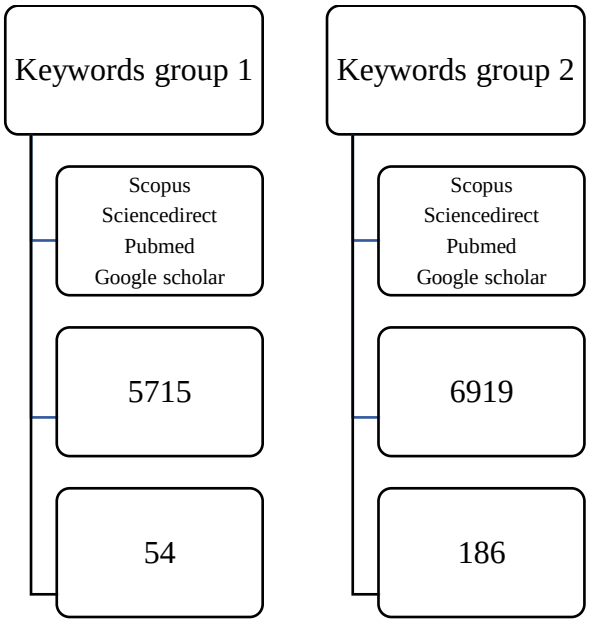

Figure 2 1: Flowchart of literature search in databases showing result obtained from search

2.2 Definition and diagnosing PD related peritonitis

Peritonitis is used to describe the inflammation of the peritoneum from any cause. It is classified broadly with two categories; PD related peritonitis and secondary caused by underlying pathology of the gastrointestinal tract (Burkart, 2018). PD related peritonitis typically has infectious aetiology that is primarily caused by bacteria. These bacterial infections mainly come from contamination during the peritoneal dialysis process. The ISPD has outlined an algorithm for diagnosing peritonitis. Peritonitis is diagnosed when a patient has any two out of three criteria present; (1) clinical features consistent with peritonitis; abdominal pain and/or cloudy dialysate effluent; (2) dialysis effluent cell count >100u/L with 50% polymorphonuclear; and (3) positive dialysis effluent culture (ISPD, 2016).

PD related peritonitis has been studied numerously and among the focus of research has been revolving around risk factors of peritonitis (Hsieh *et al.*, 2014a; Hu *et al.*, 2018; Karagulle *et al.*, 2013), incidence rate, prognostic factors such as albumin (Lee *et al.*, 2016), potassium (Lee *et al.*, 2017) and BMI (Liu *et al.*, 2017) on mortality, risk factors for peritonitis rate (Kerschbaum *et al.*, 2013) and also factors affecting the severity of peritonitis (Kofteridis *et al.*, 2010). Nevertheless, some factors that have not been reported previously such as the effect of Asian race, smoking status, medications such as erythropoietin and iron, biochemical parameters for instance calcium, phosphate and intact parathyroid hormone (iPTH) on mortality.

2.3 Median survival time and survival rate

The median survival of the overall cohort of peritoneal dialysis patients ranges from 20 – 48 month (Pongskul *et al.*, 2006; Seng *et al.*, 2016). Only one study was found reporting median survival in PD related peritonitis cohort done in Kuwait by El-Reshaid *et al.* (2016), that compared between two groups of patients with peritonitis and those without and further sub-group into modality. This retrospective study involved 416 participants where patients with peritonitis undergoing CAPD showed median of 13.1 months while those undergoing APD had 14 months.(El-Reshaid *et al.*, 2016)

No previous study has ever reported survival rates specifically among patients with PD related peritonitis. The survival rate of HD patients with peritonitis was previously reported by Yueh-An *et al.* (2017). The study was conducted over 13 years in Taiwan population. The cumulative survival rates at the end of one and five year were 38.8% and 10.1% respectively. Another study conducted in Thailand with 320 participants reported that the one- and three-year survival rates were 84% and 61% respectively (Pongskul *et al.*, 2006)

2.4 Prognostic factors for mortality in PD related peritonitis.

Several studies have been published concerning the factors that can predict peritonitis, but predictors on the survival of PD related peritonitis in PD patients are relatively few. Among the prognostic factors that have been studied includes sociodemographic (age, gender, race, body mass index, education level, and smoking status), clinical characteristics (cell counts in PD fluid, antibiotic usage, the onset of peritonitis and peritonitis rate), co-morbidities, medications and biochemical parameters.

2.4.1 Sociodemographic of PD related peritonitis patients

Age is one of the prognostic factors that has been widely studied in PD patients overall. Fried *et al.* (1996) reported that survival was lower for older people, specifically those over the age of 60 (RR:1.57; P<0.001). Other studies are also in agreement with age as a significant predictor of death in PD patient overall with age increased by one year, the risk of death among CAPD patients increased by 3% (95% CI: 1.01-1.05) (Pongskul *et al.*, 2006). In PD patients with peritonitis, Tsai *et al.* (2013) report that old age was a predictor of death (OR: 1.93; p=0.026). A retrospective study done in the USA by Guo and Mujais (2003) studying 11,373 participants on PD showed that the first-year survival for patients more than 55 years old was 78.9% (95% CI: 77.92 – 79.97) whilst those less than 55 years had first-year survival of 85.8% (95% CI: 85.36 – 86.33). They, however, did not study the survival rate in PD related peritonitis patients specifically.

Another important demographic factor for mortality is gender, and its effect on survival on mortality among PD patient has also been extensively studied. A prospective study in Britain involving 221 participants reported that there was no significant association between gender and mortality (Lamping *et al.*, 2000). Contrarily, Perez Fontan *et al.* (2005) observed in their retrospective study done in Spain on 41 PD related peritonitis patients which stated that female had a 13% higher risk of mortality compared to male (RR: 2.13; 95% CI: 1.24 – 4.09).

The effect of race on survival in PD patients has been undertaken in many part of the world studying difference race. In a study done in the USA by Fried *et al.* (1996), the authors compared between whites and blacks. The result showed that whites had better survival but were not significant (RR = 0.58, p =0.066).

The International Society for Peritoneal Dialysis (ISPD) specified that smoking is a modifiable risk factor for peritonitis. In a study done in Australia by Kotsana *et al.* (2007) stated that smoker at entry into dialysis had 1.71 higher risk of peritonitis than a non-smoker (OR: 1.71; 95% CI: 1.04 – 2.82). In a recent study done, the authors reported that smoking might render the patient more prone to peritonitis and suggested that smoking history should be considered when selecting dialysis modality (Karagulle *et al.*, 2013).

Distance to PD centre may influence the outcome of a PD patient with peritonitis. The cause of this happens due to delay in healthcare access, delayed diagnosis and delayed sampling of the dialysate. In a study done in Australia by Cho *et al.* (2012), they reported that the distance of PD centre influences peritonitis rate and also survival. They observed that those that lived distantly more than 100km had higher rate of peritonitis (0.77 episodes per patient-year) and a shorter time to first peritonitis.

Only a small number of studies have been conducted to examine the influence of Body mass index (BMI) on the mortality of PD patients, and none studies have ever been conducted in PD patients with peritonitis. A systematic review and meta-analysis of the Asian population by Liu *et al.* (2017) reported that there was a V-shaped curve association between BMI and mortality in PD patients, with the highest risk in the lowest and highest BMI group. The obese group was reported to have a 46% higher risk of all-cause mortality compared to the normal BMI group (HR = 1.46, 95% CI: 1.07–1.98).

As a summary, for sociodemographic factors associated with mortality, there is still no study reporting the effect of race, gender, smoking and distance to PD centre on mortality in PD related peritonitis in PD patients.

2.4.2 Clinical characteristics associated with mortality among patients with PD related peritonitis

There are numerous studies done on the impact of peritonitis on survival. However, not much has been studied on the effect of number of peritonitis episode on survival in PD related peritonitis. A study done in Mexico has found that a higher peritonitis rate increased mortality risk ($p = 0.002$) (Leanos-Miranda, 1997). Additionally, this study was supported by Sipahioglu *et al.* (2008) where their study showed that peritonitis rate predicted mortality (RR: 1.87, $p < 0.001$) . Though a recent studies in China showed that there was no difference in mortality between high peritonitis and low peritonitis episode (HR: 1.16; 95% CI: 0.493 – 2.754) (Tian *et al.*, 2016) as well as Hu *et al.* (2018) that showed higher peritonitis rate had no difference on mortality with low peritonitis rate (log-rank 0.357; $p =0.550$).

Exit site infection involves either erythema or purulent around the PD catheter. A study done retrospectively in Greece on PD related peritonitis patients reported that when an episode of peritonitis concurrently had exit site infection, it was significantly associated with complicated course (OR =11.3, $P <0.001$) (Kofteridis *et al.*, 2010). The complicated course was define as a composite of relapse peritonitis, transfer to HD and death. No published study has been done on the effect of this factor on mortality.

In the early phase after starting PD, peritonitis may occur easily attributable to poor technique. In studies done in China by Feng *et al.* (2016) and Tian *et al.* (2017), it was found that PD patients having early peritonitis define as less than six month were an independent predictor for mortality and associated with higher peritonitis rate with poorer clinical outcomes (HR: 1.98, 95% CI: 0.87-4.46) . This was supported by a Hsieh *et al.* (2014b) that reported a 3% decrease of mortality rate with a one-month increase in time to

peritonitis (HR per 1-month increase in the time to first peritonitis, 0.96; 95% CI, 0.93 – 0.98).

Peritonitis is often treated with antibiotics based on site antibiogram. Kofteridis *et al.* (2010) showed in their study that a previous usage of antibiotic in the preceding three months was a significant predictor of complicated course with an odds ratio of 3.22, p <0.007. No study has been done on the effect of antibiotic usage on mortality in PD related peritonitis.

Effluent cell count is one of the clinical parameters used in diagnosing peritonitis. Chow *et al.* (2006) reported in their study that there was a significant association between PD effluent cell count on day three with peritonitis outcome. Concurrent with this study is by Kofteridis *et al.* (2010) where they stated that the PD effluent cell count remaining at more than 100 x 10^6/l for more than five days was a significant predictor for a complicated course.

2.4.3 Co-morbidities

Diabetes is one of the co-morbidities in renal failure patients. Tsai *et al.* (2013) reported that diabetes was a significant predictor for death in PD patients with peritonitis. In contradiction a study done previously showed that people with non-diabetes had lower survival than those with diabetes with 4% increase risk with every 0.5/year increase in peritonitis rate (Fried *et al.*, 1996). Concurrently, Lamping *et al.* (2000) reported that diabetes was not significantly associated with mortality.

Pecoits-Filho *et al.* (2018) have shown that there is a 22% increase in hazard ratio in cardiovascular disease (CVD) mortality in patient experiencing one episode of peritonitis compared to no peritonitis. This study also stated that there was a stepwise increase in the risk of CVD as the episode of peritonitis increased. No published study has been reported on the effect of co-morbid CVD on survival in PD related peritonitis.

Ye *et al.* (2017) conducted a study comparing between patients with peritonitis and without peritonitis and has shown that the PD related peritonitis is associated with a 95% increase in all – cause mortality (HR:1.95; 95% CI: 1.46–2.60) . The hazard ratio for all-cause mortality among PD patients with peritonitis was 0.80 within two years of follow up and increased to 3.98 after two years of PD initiation. The study also reported that PD related peritonitis was associated with an increase of infection-related mortality (HR: 4.94, 95% CI: 2.47-9.86) and cardiovascular mortality (HR = 1.90, 95% CI: 1.28-2.81).

2.4.4 Medications taken by PD patients

Limited studies have been done that looks into the effect of medications in PD related peritonitis in PD patients. Antihypertensives such as Angiotensin Ⅱ receptor blocker (ARB) and Angiotensin-converting enzyme inhibitors (ACEi) have been shown to preserve residual renal function in many studies (Zhang *et al.,* 2014). However, their effect on patients with peritonitis has not been studied. A systematic review done by Zhang *et al.* (2014) reported that there were three studies done that considered the effect of ARB and ACEi on peritonitis. Zhang *et al.* (2014) reviewed the study done by Suzuki *et al.* (2004) and noted there was no difference in numbers of patients experiencing peritonitis in those taking ARB and other antihypertensives drugs (RR 0.67, 95% CI 0.18 to 2.54) . Another two studies reviewed, Reyes-Marin *et al.* (2012) compared the effect of ARB with ACE inhibitors (RR:1.17, 95% CI: 0.44-3.06) while Li *et al.* (2003) compared groups between ACE inhibitors with the control group (RR: 1.13, 95% CI: 0.50-2.52) . A study done in Austria reported that the use of oral vitamin D reduces the risk of peritonitis and all-cause mortality in PD patients (Kerschbaum *et al.,* 2013). Wang *et al.* (2018) also reported that the use of oral calcitriol was associated with peritonitis but did not mention its impact on survival.

2.4.5 Biochemical parameters

Albumin levels have been studied extensively as a predictor for mortality in PD patients generally. One of the studies, which was done by (Mittman *et al.,* 2001) found that serum albumin was a significant predictor for mortality in PD patients (RR: 0.51, P =0.01). In addition, this study was later concurred by Huang *et al.* (2014) (HR 0.55, 95% CI: 0.37-0.81), Lee *et al.* (2016) and Pongskul *et al.* (2006). However, no studies have been reported on the effect of albumin levels on mortality in PD related peritonitis.

In PD patient, hypokalaemia is a common condition as a result of diffusion of potassium out of the peritoneal. A study done by Silvia Carreira *et al.* (2015) reported that hypokalaemia was highly associated with mortality. Additionally, this study was later supported by Lee *et al.* (2017) that showed in PD patient, hypokalaemia that they set at 4.5mmol/L in the study is a significant predictor of mortality (unadjusted SHR: 1.71, 95% CI: 1.48–1.97) . No study has been done as of this time looking at the effect of potassium level on mortality in PD related peritonitis.

Low haemoglobin is common in dialysis patients and causes some of the symptoms such as dyspnea, fatigue and depression. One study has identified low haemoglobin level as a predictor for peritonitis (Abe *et al.,* 2016). In their article, they stated that haemoglobin level correlates with PD related peritonitis (OR = 2.018, CI = 1.048 – 3.088, p = 0.035). No study has been done on the impact of the level of haemoglobin on mortality in PD related peritonitis.

2.4.6 Peritoneal dialysis regime

Modality is the mode of PD used by patients. There is two well-used PD modality which is automated peritoneal dialysis (APD) and continuous ambulatory peritoneal dialysis (CAPD). CAPD requires patients to undergo peritoneal dialysis four times throughout the day. APD, on the other hand requires patients to undergo peritoneal dialysis at night time during sleep. A study done by Cnossen *et al.* (2011) showed that there was no statistically significant difference in patient survival between CAPD and APD modality (AHR: 1.31, 95% CI: 0.76 – 2.25). In a more recent study done by El-Reshaid *et al.* (2016), it was reported that median survival was better in APD patients without peritonitis (23.1 ± 3.1 months, p =0.025) but was similar when compared in CAPD patients having peritonitis (13.1 ± 1.0 months vs 14.1 ± 1.4 months).

2.5 Conceptual framework

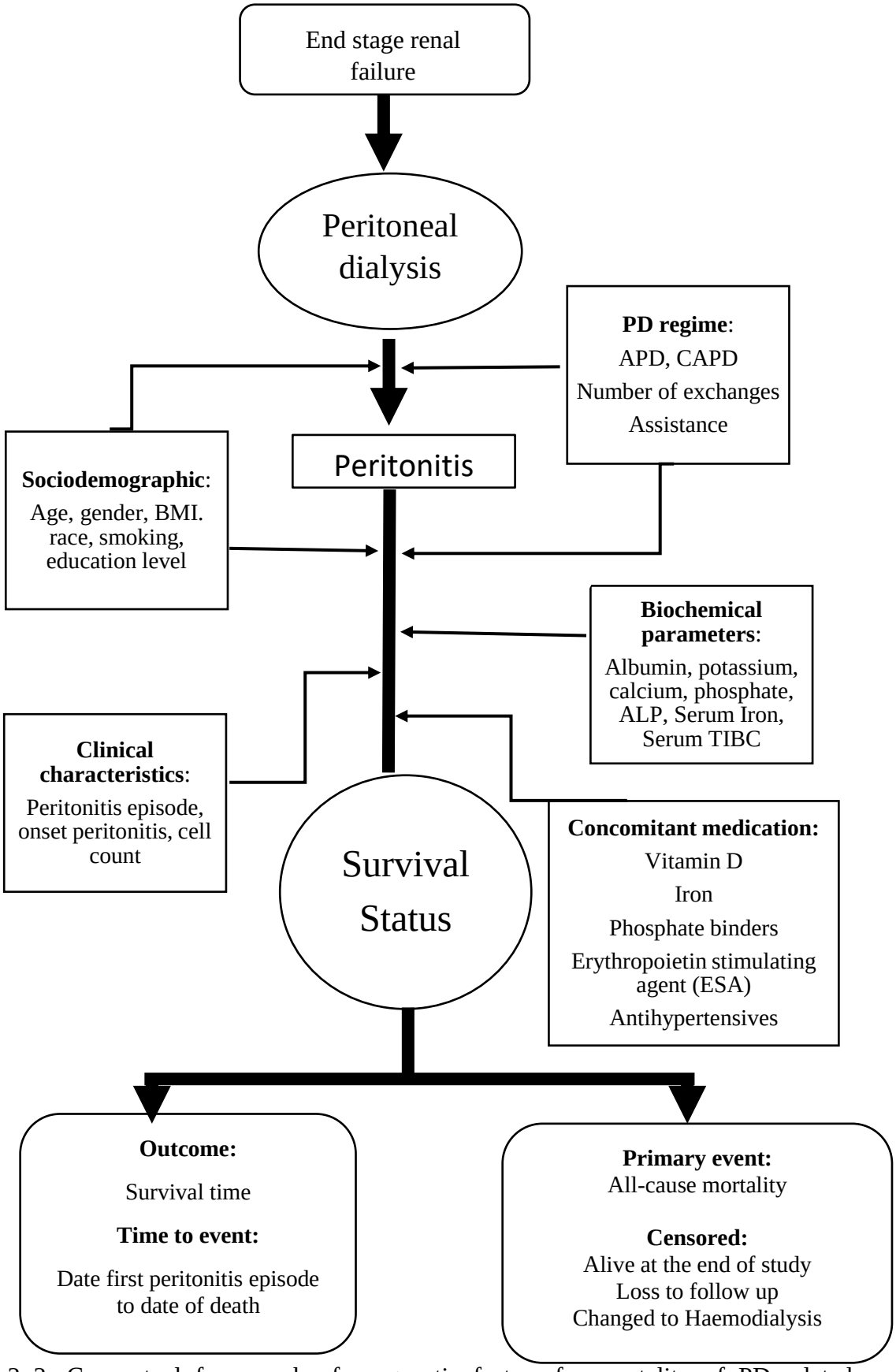

Figure 2 2: Conceptual framework of prognostic factors for mortality of PD related peritonitis in PD patients

CHAPTER THREE
METHODOLOGY

3.1 Study design

The study design applied in this study was a retrospective cohort study. Patients' data from the year 2010 until 2015 were extracted from the National Renal Registry (NRR). The starting of peritoneal dialysis was the initial starting point for entry into this study, and all patients were retrospectively followed-up until 31st December 2018.

3.2 Study location

This study was conducted at the National Renal Registry (NRR) Secretariat Office, Hospital Kuala Lumpur

3.3 Study period

The period of the study was from September 2019 until April 2020. The data extraction and analysing was conducted from 1st October 2019 until 31st December 2019.

3.4 Study population

3.4.1 Reference population

The reference population was all peritoneal dialysis patients with peritonitis in Malaysia.

3.4.2 Source population

The source population was peritoneal dialysis patients with peritonitis registered in the NRR from 1st January 2010 until 31st December 2015.

3.4.3 Sampling frame

The sampling frame was all listed peritoneal dialysis patient with peritonitis registered in the NRR during 1st January 2010 until 31st December 2015 that fulfil inclusion and exclusion criteria as below.

3.4.3.1 Inclusion criteria

- Chronic kidney disease patients on PD
- Age 18 years old and above on the start of PD
- At least one episode of peritonitis after the start of PD

3.4.3.2 Exclusion criteria

- Non-Malaysian patients
- Acute kidney injury receiving PD registered in NRR, for example hemodynamically unstable patients requiring dialysis for uraemia

3.5 Sample size calculation

The calculation for sample size was based on the objective 3 of this study (To identify the prognostic factors of mortality of PD related peritonitis) as calculations based on objectives 1 & 2 are not readily available (estimation of median survival time and survival rate). Based on the results of sample size as in Table 3.1, the minimum required sample size for the first objective is 1627. However, more sample size is needed to be enrolled to compensate for dropout or missing data. If $n_{calculated}$ is the sample size required as per formula and *dropout* is the dropout rate then $n_{corrected}$ is obtained as $n_{corrected} = \frac{n_{calculated}}{1-dropout}$ (Sakpal, 2010). *Dropout* is set at 20% for this study following the rule of thumb of 20% as it is a non-interventional study, and intervention characteristics play an important role in the dropout rate. Furthermore, in a meta-analysis study reported that the average dropout rate in 168 randomized controlled trial was 11% (Cramer *et al.*, 2016). The minimum sample size required after adjusting for dropout rate calculated is 2033.

The sample size was calculated using only variable PD regime, albumin level and gender as other variables had no studies reporting on their median survival times. The sample size was calculated using Power and Sample Size Calculation (PS) Software version 3.1.6 (Schoenfeld and Richter, 1982). The researcher selects the option to detect the number of experimental patients *n* that must be recruited to detect a true hazard ratio with a specified *power*, given *m* controls per experimental subject, Type I error probability α, and median survival time m_1 on the control treatment. The researcher specifies the ratio of the number of patients in the cohorts being compared and the input as in Table 3.2.

Table 3. 1: Explanation of symbols in sample size calculation

Symbol	**Description**
M1	Median survival time for the group without prognostic factors
HR	Patients with prognostic factor compared to those without prognostic factor
A	Accrual time during which patient is recruited = 72 months
F	Additional follow up after recruitment = 36 months
M	The ratio between group without prognostic factor to the group with prognostic factor
α	Type 1 error in this study = 0.05
β	Type 2 error in this study = 0.2
n	Calculated sample size

Table 3 2: Sample size calculation

Variables	Reference	M1	HR	M	n	n+n(M)	$n_{corrected}$
PD Regime CAPD(control) vs. APD	(El-Reshaid *et al.*, 2016)	48	1.2	1.4	678	1627	2033
Albumin level Low albumin (control) vs. High albumin	(Lee *et al.*, 2016)	60	1.3	2.1	334	701	1293
Gender Male (control) vs Female	(Fried *et al.*, 1996)	36	1.4	1.05	315	416	520

For all calculation, Type I error is set at 5%, Type II error is set at 20%, Accrual time is 72 months and Additional follow-up time is 36 months.

3.6 Sampling method

There were 58,059 peritoneal dialysis patients registered from the year 2010 to 2015 and aged 18 years and above in the National Renal Registry 2018 database. Of these, 2,002 had at least one episode of peritonitis. For this study, we did not do any sampling where all patients having at least one peritonitis episode were included in the study. This method was used as the number of peritonitis cases were smaller compared to the PD population.

3.7 National Renal Registry (NRR)

The NRR was established in 1992 by the Department of Nephrology Hospital Kuala Lumpur and subsequently transferred to the Malaysian Society of Nephrology in 1995. It consists of the NRR advisory board, Steering committee and expert panels. The advisory board oversees the operations of the NRR database and registry with the coordinating officers which consist of a Clinical Registry Manager and two Clinical Registry Assistants.