SUPERVISOR:

Dr Wan Ahmad Hafiz B. Wan Md Adnan

Nephrology Department

Department of Medicine

University Malaya Medical Centre

Kuala Lumpur

CO-SUPERVISOR:

Dr Ong Chee Seong

Nephrology Department

Department of Medicine

University Malaya Medical Centre

Kuala Lumpur

UNIVERSITY OF MALAYA

ORIGINAL LITERARY WORK DECLARATION

Name of Candidate: Norfariza Bt Abd Rahim ([redacted])

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IMPACT OF TIMELY DIALYSIS ON MORTALITY IN PATIENTS NEEDING EMERGENCY HEMODIALYSIS

ABSTRACT

BACKGROUND: It is intuitive that in patients with clear indication for urgent hemodialysis (HD), earlier dialysis may have better outcomes. Renal Unit University Malaya Medical Centre (UMMC) had developed a quality assurance initiative for urgent HD, whereby initiation of urgent HD is within 120 minutes after decision made. We therefore compared timely and delayed initiation of HD with mortality rate and factors contributing to it.

OBJECTIVES: Our primary aim is to examine mortality rate in patients requiring urgent HD on admission. We also aim to determine factors contributing to mortality among these patients.

METHODS: This is a retrospective cohort study using data obtained from Urgent HD Census from Renal Unit UMMC for 24 months between 1st January 2015 and 31st December 2016. Patients were classified into timely group, if HD initiation was within 120 minutes after decision to dialyze made and into delayed group, if it was more than 120 minutes. The primary end-point was all-cause inpatient mortality comparing the 2 groups. Factors contributing to mortality among patients requiring urgent HD on admission were examined.

RESULTS: Data from 415 patients were analyzed, with mean age of 60±13 years old were included. The average time from decision to dialysis was 75 minutes in patients with timely initiation group and 227 minutes in delayed initiation group. The median time from decision to dialysis was 120 minutes. Overall mortality rate for patients needing urgent dialysis is 12.8%. Cox survival analysis showed no difference in in-patient mortality between timely initiation and delayed initiation (adjusted HR for delayed group, 0.90 [0.51-1.61]). Median hospitalization days for patients in timely initiation was 4 days and in delayed initiation was 5 days (p=0.03). There was significantly higher likelihood of death in patients aged 60 and above (HR 2.14 [1.15-3.99], p-value 0.017).

CONCLUSION: Performing dialysis within 120 minutes after decisions made does not seem to reduce in-patient mortality and does not affect the length of stay in patients requiring urgent HD. Age is the only significant predictor for mortality in this study. In addition, we need to adjust the potential confounders in this study such as to determine medical diagnosis of patients upon admission and to evaluate time of admission to time of HD among these patients to prevent bias that can distort the result in this study.

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LIST OF SYMBOLS AND ABBREVIATIONS

ED: Emergency department

UMMC: University Malaya Medical Centre

HD: Hemodialysis

RRT: Renal replacement therapy

MO: Medical Officer

AKI: Acute Kidney Injury

CKD: Chronic kidney disease

ESRF: End Stage Renal Failure

APO: Acute Pulmonary Edema

CRBSI: Catheter related blood stream infection

RCT: Randomized controlled trials

TOA: Time of arrival

TOD: Time of decision

TOH: Time initiation of hemodialysis

IHD: Ischemic heart disease

ICU: Intensive care unit

ARF: Acute renal failure

HPT: Hypertension

ESRF: End stage renal failure

DM: Diabetes mellitus

IHD: Ischemic heart disease

Hb: Hemoglobin

SPO2: Saturation pulse oximetry

CXR: Chest X-ray

eGFR: Estimated glomerular filtration rate

KDIGO: Kidney Disease Improving Global Outcomes

CRRT: Continuous Renal Replacement Therapy

CHAPTER 1: INTRODUCTION

1.1 Research background

Severe renal failure is a condition that is associated with a high mortality and enormous treatment expenditure (Sven Kresse et al., 1999). Renal replacement therapy (RRT) is one of the important treatment in patients with severe renal failure. According to the guideline by Kidney Disease Improving Global Outcomes (KDIGO) on acute kidney injury (AKI), patients requires urgent initiation of RRT when life-threatening changes in fluid, electrolytes, and acid- base balance exist. Urgent initiation of RRT is in the form of HD. Classic indications for urgent HD are hyperkalemia, severe metabolic acidosis, volume overload, oligoanuria, uremic complications and drug intoxications (Tolwani et al., 2012). Early initiation of HD in AKI has mixed results in previous studies, mainly because there were different target population and different definitions of 'early' and delayed' initiation of dialysis. For example, there were two latest randomized controlled trials (RCT) examining early and delayed initiation of dialysis, namely ELAIN (The Early Versus Late Initiation of RRT in Critically Ill Patients with AKI) and AKIKI (Artificial Kidney Initiation in Kidney Injury), both trials used staging of AKI as criteria to initiate urgent HD. In ELAIN trial, patients who randomized into the early group should initiate HD within 8 hours of diagnosis of KDIGO AKI stage 2, while in the delayed group should initiate HD within 12 hours of diagnosis of AKI stage 3. Meanwhile, in other earlier study, patients in early group initiated HD within 12 hours after fulfilling the inclusion criteria (Bouman C et al, 2002).

Data on mortality of patients requiring urgent HD on general admission regardless underlying kidney function and factors contributing to it is lacking among

Asian patients and worldwide. Most of the studies that we encountered only focusing on AKI and acute renal failure (ARF) in critically ill patients per se and most of them studied the complications upon the patients' admission to Intensive Care Unit (ICU). A previous community-based meta-analysis in timing of HD initiation in ARF was only focus on several databases for studies that compared the effect of "early" and "late" HD initiation on mortality in patients with ARF based on estimated glomerular filtration rate (eGFR). Another study published recently, also focus on influence of the method of different type of continuous RRT (CRRT) use in ICU on the outcome of patients with ARF.

Some studies have suggested that early initiation of urgent HD has been shown to be associated with improved outcomes in patients with severe renal failure (Wald R. et al., 2014), while earlier studies showed no difference (Zarbock et al., 2005). Early initiation of urgent HD may allow for better control of fluid and electrolytes status, removal of uremic toxins, and prevention of complications such as gastric hemorrhage and metabolic encephalopathy (Wald R et al., 2014). Early initiation of urgent HD in AKI patients showed that it largely resolves azotemia/uremia and its harmful sequels, and provides adequate treatment of complicating conditions (Sven Kresse., 1999). It also showed early initiation of urgent HD can prevent fatal uremic complications and improve patient survival (Jeonghwan Lee et al., 2014). Indirect evidence has suggested that early initiation of HD could confer a survival benefit (Vaara ST et al., 2014, Gibney et al., 2008, Bagshaw SM., 2009). On the other hand, there were two observational studies reported high survival rates among patients who did not receive early HD (Scheider et al., 2012, Elseviers MM et al., 2010) and one study reported adverse outcomes in association with very early HD in patients with sepsis (Payen D et al., 2009). Unfortunately, most of the studies mentioned above are not randomized controlled trials (RCT).

Most of the earlier RCTs studied about early versus late initiation of HD in patient with AKI showed no benefit of early initiation group. According to two randomized control trials (RCT), ELAIN trial and AKIKI trial, both trials showed no difference between early and delayed initiation of HD in term of mortality. The ELAIN trial resulted median time for HD initiation in early group was 6 hours as compared 25.5 hours in delayed group when urgent indication is there. Meanwhile, the AKIKI trial resulted median time for HD initiation in early group was 2 hours as compared 57 hours in delayed group, after randomization when urgent indication is there. An updated meta-analysis also showed no added benefit of early initiation of HD for patients with AKI (Girish C.B et al., 2016).

Delaying HD initiation is intuitively unlikely to have any immediate benefit per se. However, a delay may allow time for the stabilization of a patient's condition before HD is initiated and may avoid the need for such support, which is not devoid the risk (Wald R et al., 2014). As for us, in our study, we consider 120 minutes as the time that we need to initiate the urgent HD after decision made, based on quality assurance initiative had been set by Renal Unit UMMC. There is no data about the optimal time to initiate urgent HD as there is no consensus on it (Saber D.B et al., 2014). Therefore, to fill this perceived need, in this study we compared timely initiation with delayed initiation in patients presented to ED whom met the criteria to receive urgent HD, then studied the mortality rate and factors contributing to it. Again, to our knowledge, in previous RCTs, treatment is given in highly outlined settings and may not reflect real life. Therefore, as it seems counterintuitive that delayed initiation of HD which is a marker of potentially poorer care is associated with no significant reduction in mortality.

1.2 Definition of terms

Following are the terms and their definitions used widely in the chapters: -

Time of arrival (TOA): The time when the patients arrived ED

Time of decision (TOD): The time when the decision was made by nephrologist to initiate urgent HD

Time of HD (TOH): The time patient initiate urgent HD

Timely initiation of HD: Within 120 minutes from TOD

1.3 Objectives of the study

-Primary objective: To determine mortality rate of patients whom requiring urgent HD on admission

-Secondary objective: To identify factors that contributing to the mortality among these patients

CHAPTER 2: LITERATURE REVIEW

2.1 Severe renal failure, when to dialyze

The timing of urgent HD initiation in severe renal failure has been discussed since its introduction over 50 years ago. There were 2 randomized controlled trial done recently, which were ELAIN and AKIKI trial. In ELAIN study, patients were randomized into 2 categories: early HD (starting <8 hours of fulfilling Kidney Disease: Improving Global Outcomes (KDIGO) stage 2 AKI) with delayed HD (starting within <12 hours of developing KDIGO stage 3 AKI or upon absolute indication). In ELAIN trial, eligible patients were required to have blood neutrophil gelatinase- associated lipocalin (NGAL) > 150ng/ml and at least one of sepsis, fluid overload, worsening Sequential Organ Failure Assessment (SOFA) score, or receiving vasoactive support. Meanwhile, in AKIKI trial, urgent HD started within 5 hours of validation of KDIGO Stage 3 AKI, defined by at least 1 of the following: Creatinine >34mnmo/L or greater than 3 baseline, anuria (urine output <100ml/day) for 12 hours or oliguria (urine output <0.3 ml/kg/hour or <500ml/day) for 24 hours. ELAIN trial showed significant mortality reduction for early group while AKIKI trial showed no significant difference between the 2 groups. Earlier initiation of HD may produce benefits by avoiding hypervolemia, eliminating of toxins, establishing acid- base homeostasis, eliminating of toxins, establishing acid-base homeostasis, and preventing other complicating other complications attributable to AKI. Survival rate was significantly increased among AKI patients who were started on HD when the urea level less than 60mg/dl; compared to those who starting dialysis when urea more than 60mg/dl (39% vs. 20.3%, p=0.041) (Gettings et al., 1999). In a meta-analysis, early initiation of HD may be associated with improvement in survival among

AKI patients. (Seabra et al., 2008). The above studies were observational studies, except for ELAIN and AKIKI trials which were RCTs.

2.2 Effect of dialysis initiation timing on clinical outcomes

One of the meta- analysis of RCT showed early initiation of HD was associated with a significant 36% mortality risk reduction (RR, 0.64 to 0.82; P<0.001). Meta-regression yielded no significant associations. Several other meta-analysis studies reported that early initiation of HD is associated with certain harmful clinical outcomes. (Crews D.C et al.,2014). To date, there has been only one prospective, randomized, controlled study reported that planned early initiation of HD was not associated with improvements in either survival or clinical outcomes (Cooper BA., 2010).

Conversely, in cohort studies, early initiation of HD was associated with a statistically significant 28% mortality risk reduction (RR, 0.72; 95% confidence interval, 0.64 to 0.82; P<0.001). The overall test for heterogeneity among cohort studies was significant. (P=0.005); however early HD therapy was associated more strongly with lower mortality in smaller studies (n<100) by means of subgroup analysis. Old observational reports suggested that early initiation of HD therapy might improve survival. An observational and retrospective study that have been conducted with patients with AKI, with or without sepsis, suggest that there may be a benefit to early initiation of HD. Timely initiation of HD might improve nutrition with consequent decrease in hospitalization, mortality and cost (Srinivasan et al., 2002). Late HD initiation might be associated with longer length of stay (Bagshaw et al., 2009).

One of the prospective cohort study in Korea showed that before matching, the early-HD start group seemed to have poorer survival than the late start group. However, after matching, these differences in survival disappeared, and there were no significant differences in all-cause mortality or other clinical outcomes. Notably, contrary to general expectations, recent observational studies have shown that early HD initiation was irrelevant to survival benefits or even associated with poor clinical outcomes (Stel V.S. et al., 2009). Starting dialysis early can expose patients to dialysis-associated complications (Wright S., 2009). The decline in residual renal function can progress at a rapid pace, even after dialysis. Dialysis therapy can also result in protein loss and aggravate patient's nutritional status. (Mehrotra R., 2007). Catheter related bloodstream infection (CRBSI) is increase in patients undergoing HD. These factors can thus collectively contribute to the poor survival and negative clinical outcomes of patients with early HD initiation. Early HD initiation did not improve patient survival or other clinical outcomes, including hospitalization, cardiovascular events or vascular access complications. (Mehrotra R., 2007). However, it is important to emphasize here that most of the studies mentioned above were observational studies and not RCT.

2.3 Common indications for urgent HD

The goal of HD initiation is to attain solute clearance and fluid balance while waiting for kidney function to recover. Early institution of HD is fundamental to achieving this goal (Sebra et al., 2008). Current indisputable indications for initiation HD include hyperkalemia, severe acidosis, and hypervolemia that are unresponsive to conservative measures; uremic serositis; bleeding diathesis; and severe encephalopathy. Hyperkalemia and volume overload are widely utilized triggers the initiation of urgent HD (Clark et al., 2012). Even there was consensus around starting urgent HD, there was no uniformity regarding rationale (Fouque D et al., 2008).

2.4 Common outcomes associated with delayed urgent HD

When HD is initiated late, mortality rates were higher (Parseon et al., 1961). Delayed initiation of HD had been supported by the belief that reduced solute clearance and could worsening patient survival and clinical outcomes. Prolonged uremia can decrease appetite and evoke anorexia, poor oral intake and malnutrition. In addition, there has been concern that delaying HD might fail to prevent fatal uremic complications, including severe hyperkalemia, uncontrolled hypertension, pulmonary edema, pericarditis and encephalopathy. CRBSI is increase in patients undergoing delayed HD (Nguyen DB et al., 2015). Most of these studies were not RCT. Again, we need to emphasize that latest RCT so far did not show any difference in outcomes.

2.5 Multiple comorbidities causing the serious complications in associated with severe renal failure in patients requiring urgent HD

Most deaths were attributed to a cardiovascular event or infection and more likely to occur in older patients. A potentially modifiable risk factor, low body mass index (BMI) less than 18.5 which is also a surrogate for malnutrition, was a strong predictor of early mortality in patients with severe renal failure [adjusted hazard ratio (HR) 4.22 (CI: 3.12-5.17)]. Malnutrition may increase susceptibility to infection in patients with severe renal failure (McMurray et al., 1981). Several features of malnutrition such as increased oxidative stress, increased plasma levels of fibrinogen, and inflammation may also increase the risk of cardiovascular disease (Bergstom et al., 1998). Also, central venous catheter use was associated with a 2.4-fold increase risk of death (CI:1.4-3.9). An even more striking increase in the risk of death associated with catheter use with the relative risk being 2.18 for catheter use compared to arteriovenous fistula (AVF) use (D. Schon et al., 2007). Incident catheter use was associated with a 6 times greater risk of death compared with fistula or graft use combined (L.M. Moist., 2008). Central venous catheters associated with higher risks of mortality and hospitalization in severe renal failure patients (Polkinghorne et al., 2004). The native AVF is the preferred vascular access because of its longevity and lower rates of infection and intervention. Furthermore, sustained use of tunneled central venous catheters for vascular access in renal failure patients have been associated with higher risk of all-cause cardiovascular and infection-related mortality. Increasing age was associated with poor survival, with patients over 75 years of age representing 50% of patients whom died early. A worse survival rate in older patients (age> 67 years), DM, low serum albumin, malignancy, chronic obstructive pulmonary disease and history of IHD in patients requiring urgent HD using Kaplan- Meier survival method (M.J Soler et al., 2014). Other main causes of mortality were: infection (24.5%), and stroke 8.6%. No differences in mortality were observed comparing the type of vascular access at dialysis initiation (M.J. Soler et al., 2014).

2.6. Initiation of urgent HD within 120 minutes

It is the policy of the renal unit UMMC to do urgent HD within 120 minutes. This is just an arbitrary value, and not based on any RCT as no RCT has been done to address this question before. The 120-minutes mark is deemed adequate for patients to be wheeled to the HD unit and catheter insertion if needed.

Based on AKIKI trial, early RRT aimed to start within 6 hours of documentation of stage 3 KDIGO acute injury. For those who required urgent HD after randomization is put under delayed group. The median interval between the occurrence of at least one criteria for urgent HD and its initiation was 4.7 hours (IQR 2.7-5.9) post documentation of stage 3 injury and fulfillment of other inclusion criteria

CHAPTER 3: METHODOLOGY

3.1 STUDY DESIGN, SAMPLING AND DATA COLLECTION

The study design was a single center, retrospective, observational study. Data was obtained from Urgent Hemodialysis Census from Renal Unit UMMC collected by a dedicated Renal Unit UMMC Sister. Data on all patients who fulfilled in the inclusion criteria were collected over a period of 24 months from 1 January 2015 to 31 December 2016.

Clinical data obtained include demographic characteristics, comorbidities, clinical characteristics, reason for urgent HD and clinical parameters at the onset of HD such as urea, potassium, creatinine, total carbon dioxide, Hb, calcium and phosphate level using electronic medical records UMMC (EMR). Details of time of admission, time of decision and time of hemodialysis initiation had been recorded. Severe renal failure that requiring HD was defined as severe metabolic acidosis (pH less than 7.25, HCO3<15 mmol/L), clinical evidence of fluid overload (generalized edema, raised jugular venous pressure, SPO2 <95% that requiring oxygen, respiratory rate more than 25 breath per minute, lungs crepitation up to midzone, chest Xray changes), life threatening hyperkalemia (with potassium more than 6 mmol/L which refractory to lytic cocktail or ECG changes-such as tall tented T waves), and uremia/uremic complications. Time of arrival (TOA), time of decision (TOD) and time of HD (TOH) were identified. In this case, a nephrologist consultation was performed before the urgent HD treatment and decision was made by nephrologist whether the patients need to be dialyze urgently or not.

Sample size calculation: In a recent 2016 study, Pannochia N et al. demonstrated that the overall mortality rate for patients with chronic kidney disease (CKD) requiring urgent HD was 31.3%. Previous studies with positive impact of early HD have shown that early HD reduced mortality by 20-40%. If our timely dialysis in patients needing urgent dialysis reduces the mortality rate to 18.8% (40% reduction), we will need to study 187 experimental subjects and 187 control subjects to be able to reject the null hypothesis that the failure rate for experimental and control subjects are equal with probability (power) 0.8.

3.2: INCLUSION CRITERIA

The inclusion criteria were as follows:

a) Clinical diagnosis of severe renal failure that requiring urgent HD

i) Severe metabolic acidosis (pH <7.25, Bicarbonate <20 mmol/L)

ii) Clinical evidence of fluid overload (generalized edema, raised jugular venous pressure, SPO2 <95% that requiring oxygen, respiratory rate> 25 breath per minutes, crepitation up to midzone, CXR changes)

iii) Life threatening hyperkalemia (refractory to lytic cocktail, ECG changes such as tall tented T-waves)

iv) Uremia or uremic complications

b) Adult patient presented to ED > 18 years

3.3: EXCLUSION CRITERIA

The exclusion criteria were as follows:

a) Existing inpatients who later required urgent HD

b) Patient who planned to be admitted to ICU upon admission

3.4. TERM DEFINITIONS

i) Time of arrival (TOA): The time when the patients arrived ED

ii) Time of decision (TOD): The time when the decision was made by nephrologist to initiate urgent HD

iii) Time of hemodialysis (TOH): The time patient initiate urgent HD

iv) Timely initiation: within 120 minutes after decision made

v) Delayed initiation: more than 120 minutes after decision made

3.5 RESEARCH HYPOTHESIS

- Null Hypothesis: Time taken to initiate urgent HD did not affect mortality

- Alternative Hypothesis: Timely initiation of urgent HD is associated with reduced mortality

3.6 DATA PROCESSING AND ANALYSIS

Manual and electronic medical records (EMR) data were entered to a database (Excel) and then analyzed with the Statistical Package of Social Sciences (SPSS) version 23.0 (IBM-SPSS statistics). Data on patient's demographic and baseline characteristic are presented as mean and standard deviation. Categorical data such as gender, race, comorbidities (ESRF, DM, HPT, IHD and stroke), vascular access status and AKI status are presented as number of patients and percentages. Based on Quality Assurance Data for Urgent HD Renal Unit UMMC, the timely initiation of patient for urgent HD is within 120 minutes after decision made by nephrologist. Timing for initiation of urgent HD was calculated and identified whether they fall into timely initiated group or delayed initiated category. Data for each category were compared for differences. The primary end-point was all-cause inpatient mortality. Factors contributing to mortality in these patients were also identified. The association between all variables with mortality were also analyzed. Categorical variables were analyzed with Chi Square test, while continuous variables were analyzed with Student T-test if they were normally distributed (described as mean ± standard deviation) or if they were not normally distributed (described as median). Kaplan-Meier analysis was performed to compare the mortality of the 2 groups and Cox survival analysis was used to determined relevant factors that may contribute to the mortality. Mean of various parameters were compared among the survivors and non-survivors using appropriate statistical tests. Two-sided P value <0.05 was considered statistically significant.

CHAPTER 4: RESULTS

4.1 DEMOGRAPHIC DATA

415 patients from a total 452 patients with severe renal failure requiring urgent HD whom met the inclusion and exclusion criteria between 1st January 2015 until 31st December 2016 were recruited. Baseline characteristics were shown in Table 1.1. The mean age was 59.9± 13.03 years. The majority were male with 60.5% (251 patients) and patients with comorbid of DM were the highest 74.0% (307 patients) reflecting the main cause of severe renal failure. Patient with AKI was 155 patients (37.3%). Of all patients, most of the patients were on AVF (31.8%), very few patients on tunnel cuff catheters (6.3%), while 49.6% need catheter insertion for dialysis. The majority patients have fluid overload (49.6%) as an indication to start urgent HD, followed by hyperkalemia, metabolic acidosis and uremia. In patients with timely initiation of HD, the average time from decision to dialysis was 75±32 minutes and 227±102 minutes for patients in the delayed group. The median time from decision to dialysis was 120 minutes (95% CI 118.84-149.12).

4.2 BIOCHEMICAL AND CLINICAL CHARACTERISTICS

A comparison of the patient's biochemical characteristics according to timely initiation and delayed initiation group were summarized in Table 1.1. Mean urea level for most of the patients was 30.3 mmol/L ± 40.6, mean creatinine level 866 mmol/L ± 439, mean total CO2 level 18.9 mmol/L ± 5.9, mean Hb level 9.4 g/dL ± 2.2 and mean potassium level 5.4 ± 1.3. From these biochemical characteristics, mean bicarbonate level in delayed group was significantly lower

4.3 PRIMARY OUTCOMES

The primary outcome in this study was all-cause in-patient mortality rate which estimated with the use of Kaplan- Meier analysis. There were total 53 deaths in this study. Overall mortality rate for patients needing urgent dialysis is 12.8%, with 31 death (12.8% of total) occurred in early group and 22 deaths (12.7% of total) occurred in delayed group shown in Figure 1.1. The Kaplan-Meier analysis showed no significant difference for all-cause in-patient mortality rate for timely and delayed group, based on time to dialysis (Figure 1.2) with p-value 0.75. Different censoring time points were also used, using 7-days and 30-days cumulative survival. In the analysis using different censoring time-point for mortality, using 7-days and-30 days cumulative survival also did not show any significant difference (Figure 1.3 and 1.4). Using Cox Regression Analysis (Table 1.2), inpatient mortality did not differ significantly between the two-study groups: adjusted hazard ratio (HR) for 7-day mortality and 30-day mortality were 1.2 (95%CI 0.5-2.7) and 0.9 (95%CI 0.5-1.7), respectively shown in Table 1.3. The reason why we censor the mortality at 3 different time-point, is because mortality from urgent HD, may be more pronounced in shorter interval, in this case: in 7-day mortality.

This suggests that in earlier initiation of HD, noted increase trend to increase mortality. Whereas, 30-day mortality may be related to inpatient complications.

4.4 SECONDARY OUTCOMES

We also aim to determine factors contributing to in-patient mortality comparing timely initiation versus delayed initiation group and length of stay of these patients. Hazard Ratio (HR) for in-patient mortality in patients needing urgent HD for gender, ESRF status, DM, HPT, IHD, stroke, urea level, potassium level, bicarbonate level, Hb level, initiation timing, and vascular access availability showed non-significant difference. There was significantly higher likelihood of death in patients age 60 and above (HR 2.12 [1.15-3.94]) with p-value 0.016 shown in Forest Plot (Figure 1.5)

For length of hospitalization, median for timely group was 4 days (range 1-108) and 5 days (range 1-68) for delayed group. There was no significant difference, after adjustment for age, gender, race, comorbidity and vascular access, between timely and delayed initiation group.

CHAPTER 5: DISCUSSION

5.1 INTERPRETATION AND FINDING

This study evaluated the mortality rate and factors associated with mortality in patients requiring urgent HD during acute admission. Our study revealed that around 12.8% (53 patients) who required urgent HD died as inpatient. This is considerably lower when compared to the study by Pannochia N et al., 2016 quoted in power calculation, which showed the mortality rate was 31.3%. Although there are not clear reasons for this finding, we may consider this as a reflection of multiple factors during admission contributing to lower mortality rate including: effective stabilization of patient status in ED prior to initiate urgent HD, younger patients in our study (mean age 59 years) as compared to the quoted study (mean age 69 years) and possible rapid consultations by nephrologist of patients admitted who required urgent HD. One also may question the true urgency of the dialysis, and factors why time to make decision differ between patients. As noted in demographic data result, mean potassium level in this study was 5.4 mmol/L (it was less than 6 mmol/L). We also excluded patients who required intubation or intensive care unit (ICU) admission which may contribute to higher mortality in other study. Both factors resulted lower mortality in our study. However, further evaluations need to be done to establish the association of the mortality with these factors.

By using Cox Regression Analysis, inpatient mortality did not differ significantly between the two-study groups of timely initiations versus delayed initiation of HD in 7 and 30-days mortality. It is interesting to see the trend of mortality from 7days to 30 days, which shows the HR were reducing from 1.6 to 0.8 in a graded manner, although it was not significant. This may suggest that early HD may have more impact when death was censored at 7 days, compared to at 30 days, although none of these are significant. Given that the mortality rate in this study is much lower than expected, more patients are needed in order to have significant result. It is estimated that if early HD may reduce the mortality rate from 12.8% to 10%, 1000-2000 patients are needed for each arm to give similar 80% power to detect the difference.

In the background demographic of this study, there were more patients with vascular access (AVF, internal jugular catheter, or tunnel cuff catheter) in the timely initiation group as compared to the delayed initiation group. This may suggest that patients without vascular access may be sicker that they may need to be stabilized first, or they need more time for the insertion of dialysis catheter. We also examined factors contributing to in-patient mortality, other than the time. This is also consistent with the fact that more patients in timely initiation group has diagnosis of ESRF. This was because in patients with ESRF, most of them already have vascular access available making the initiation of HD became faster. Mean bicarbonate level in the delayed group was significantly lower as they may be more ill and may require stabilization before transferring for urgent HD. This study also suggested that Hb level below 10 g/dL may have better mortality outcome compared to those with Hb level above 10. Although not at the level of 10g/dL, other studies have shown that Hb level above 13 g/dL was associated with higher stroke incident in patients taking erythropoietin. Perhaps there were more patients with ESRF in this group who may have established anemia due to renal failure. However, after adjustment, this difference became non-significant.

We found that all-cause mortality is increased with increasing age. Not surprisingly, increasing age is the strong predictors of poor outcome. Our results suggested that the mortality in patients more than 60 years of age was higher as usually older patient has prevalence of comorbidities including heart failure and myocardial infarction, and as a result, may be associated with poor clinical outcomes and have a higher mortality rate (Kim H.Y. et al., 2013). Older age more than 60 years old is the predictor for mortality in patients with AKI irrespective of their stages of CKD (AOR=1.06, 95% CI=1.02-1.12, p=0.009) (Ng Y.M et al., 2016). Other reasons for this, in elderly HD patients, the overall clinical status is poor and RRT may further compromise their condition. In other study, age factor was found to be associated with mortality as mortality rate was extremely high in patients aged 81-90 years, 71-80 years and 61-70 years, while it dropped significantly in patients less than 60 years (Panocchia et al., 2016). Urea and creatinine levels at the onset of HD did not showed significant predictors of mortality among patients with severe renal failure, which is consistent with the other study (De Corte et al., 2009). The mixture of patients with AKI and ESRF may be too heterogeneous to show a significant result.

Early nephrologist consulting resulted in lower mortality (Meier P.et al., 2011) and reduction of kidney dysfunction progression (Balaubramiam G et al., 2011). One of the factors contributing to mortality is the late referral to nephrologist upon patient arrival to ED which delay the HD initiation. There are several possible explanations for those late referrals to nephrologist in this study, such as to stabilize the patients who came with severe renal failure to ED first. For example; these patients receiving fluid resuscitation in hoping renal function will be improving, sodium bicarbonate and lytic cocktail administration in patients with metabolic acidosis and hyperkalemic and awaiting blood pack transfusion in patients with severe anemia. These factors associated in delaying the initiation of urgent HD and may indirectly contributing to the in-patient mortality.

For length of hospitalization in this study, there was no significant difference between timely and delayed initiation group with median stay of 4 days. Possible explanations for this that we did not evaluate the diagnosis of patients upon arrival.

Patients might come with different admission diagnosis for example sepsis secondary to various causes, cardiovascular disease, hepatic disease or others. As the admission diagnosis was not evaluated, the length of hospitalization might not due to renal causes per se, but the overall patient condition might be contributing to the length of stay. Therefore, this study did not show any significant difference in between timely and delayed HD initiation in terms of length of hospitalization.

The question of the right time to initiate urgent HD remains unanswered and controversial, and poses a real problem in the management of patients requiring urgent HD (Saber et al., 2014). Although numerous studies over more than a half century have attempted to resolve the issue of optimal timing, the level of evidence guiding current practice remains weak, derived primarily from retrospective and observational cohort studies and small, underpowered prospective trials. We acknowledge, however, that if our sample size was larger, we might have observed statistically significant differences in mortality. In addition, we need to adjust the potential confounders in this study such as to determine medical diagnosis of patients upon admission and to evaluate time of admission to time of HD among these patients to prevent bias that can distort the result.

5.2 STRENGTH AND LIMITATIONS

Strength: Since there is no other study comparing the time to initiate emergency HD at admission in ED, this study provides one of the studies that evaluate the mortality rate and factors contributing to it, comparing timely initiation versus delayed initiation of patients requiring urgent HD, regardless their underlying kidney function. Our study differs from other studies as we look at the 120-minutes mark for HD initiation based on the Renal Unit UMMC standard timing for urgent HD, whereas other early HD studies conducted before, focus on staging of AKI, urea level, using critically ill patients in intensive care unit (ICU) as the sample with different mode of continuous RRT and more emphasize on early HD initiation based on eGFR.

Limitation: This study was a retrospective study. A randomized controlled trial is considered the gold standard for comparing of different interventions, as effective randomization coupled with sufficient sample size would result in equal distribution of baseline factors across treatment groups. Several limitations merit consideration. First, as this was an observational study, our findings are subject to lead time bias, and indication bias. Survival time defined as the time from dialysis initiation till death would falsely amplify actual survival time for the timely initiation group because of lead time bias, resulting in an underestimation of survival advantage for late initiation group. On the other hand, some patients who came for urgent HD also had more than one indications for urgent HD, possibly leading to their worse survival experience, namely indication bias. Residual confounding remains through unmeasured variables potentially influencing mortality such as acute illness, comorbidities, type of vascular access for dialysis, presence of uremic symptoms and related complications. Comorbidities are also potentially associated with mortality in these group of patients.

Low muscle mass (malnutrition) with albumin level upon presentation also not included as it is possible a better survival experience may be seen in patients with good nutritional status. Anemia parameters, eGFR and markers of bone and mineral metabolism did not seem to explain the observed associations.

Unfortunately, in this study we were not able to objectively evaluate for malnutrition. Persons with poor nutritional status will have a higher mortality (Paganini et al., 1996). Other than that, progression of patients should be observed periodically on the long-term follow up even though the patients survived during the admission. Factors affecting the survival included biochemical parameters for example peak creatinine and other status of recovery of kidney function at discharge should be evaluated, but in this study, we did not compare those biochemical parameters periodically.

The limited samples could affect our ability to explore other variables potentially associated with mortality: etiology, diagnosis of admission, other associated factors ex: malnutrition. Initial power calculation seems to be suggest that 400 patients were adequate to show a difference in mortality. After we have the result, it seems like the event rate is too low to give similar statistical power. Our study only has a total of 12.8% mortality rate. If we want to show that timely initiation of urgent HD may reduce the rate to 9% (4% absolute reduction), we need a total of 2000 subjects.

On the other hand, we do not have data on the completion of dialysis, although all patients underwent HD. Some may not complete the 4-hours dialysis, and some may have complications afterward that may be important and have significant impact on mortality. There was also a short follow-up period and we did not evaluate other factors that may have influenced the relationship between time to dialysis with mortality and length of hospitalization. This study was conducted in a single hospital; however, being a national reference hospital with one of the largest nephrology unit in Malaysia, this hospital could serve as a reliable sample of the rest of the public hospitals in Malaysia. In the absence of the established protocol to admit patients for dialysis in case of severe renal failure in our hospital, the time of admission for HD much depends on the criteria of the in-service nephrologist, which prevents the standardization of the sample. Perhaps, all of the above were possible the confounders in this study that might contributed to the reasons of why timely initiation of HD did not reduce in-patient mortality, although the number of the samples were large enough.

5.3 SUMMARY

Although the use of urgent HD to support patients with severe renal failure has become routine, many of the fundamental questions regarding optimal timing of urgent HD remain. The optimal timing of urgent HD in patients without clear indication continues to be the subjects of debate. Mortality rate and factors contributing to mortality in patients requiring urgent HD need to be evaluated. In previous RCT, early initiation of HD did not confer much mortality benefit. Similarly, in this study, performing dialysis in timely initiation, did not seem to reduce in-patient mortality in patients requiring urgent HD, but we need to see this statement in different perspective and need to exclude all the potential confounders carefully. Age was the only significant predictor for mortality in this study.

CHAPTER 6: CONCLUSION

In this retrospective observational study, noted that there was no significant different either in inpatient mortality or length of stay between timely initiation group and delayed initiation group. 53 patients (12.8%) out of 415 patients with severe renal failure requiring urgent HD died. A lower mortality reported in those patients less than 60 years old. The overall results of these studies would seem to indicate that there is no benefit in term of inpatient mortality and of length of stay from early initiation of RRT between timely initiation and delayed initiation group, but the exact definition of early remains to be determined, as does the definition of the criteria for necessitating RRT. The question of the right time to initiate RRT remains unanswered and controversial, and poses a real problem in the management of patients with severe renal failure. Thus, a large randomized controlled study with a robust and relevant clinical end-point is warranted to resolve this issue. In this context, we propose a randomized, multicenter, controlled trial on the mortality in patients needing emergency HD during acute admission and its associated factors.

CHAPTER 7: TABLES

Table 1.1: Baseline Demographic of patients admitted for urgent HD

Parameters		Total (N=415)	Dialysis <120 minutes (N= 242)	Dialysis > 120 minutes (N= 173)
Age, N (%)		60 ± 13.0	59.3 ± 12.4	61.0 ± 13.8
Gender, N (%)	Male	251 (60.5)	145 (59.9)	106 (61.3)
	Female	164 (39.5)	97 (40.1)	67 (38.7)
Race, N (%)	Malay	187 (45.1)	112 (27.0)	75 (18.1)
	Chinese	101 (24.3)	55 (13.3)	46 (11.1)
	Indian	122 (29.4)	75 (18.1)	47 (1.2)
	Others	5 (1.2)	0 (0)	5 (2.9)
Co-morbidity,N (%)	HPT	313 (75.4)	176 (72.7)	137 (79.2)
	DM	307 (74.0)	185 (76.4)	122 (70.5)
	IHD	124 (29.9)	75 (31.0)	49 (28.3)
	Stroke	88 (21.2)	48 (19.8)	40 (23.1)
	Known ESRF	261 (62.9)	169 (69.8)	92 (53.2)
Indications, N (%)	Fluid overload	206 (49.6)	129 (31.1)	77 (18.6)

	Hyperkalemia	103 (24.8)	58 (14.0)	45 (10.8)
	Metabolic acidosis	89 (21.4)	48 (11.6)	41 (9.9)
	Uremia	17 (4.1)	7 (1.7)	10 (2.4)

Table 1.1: Baseline Demographic of patients admitted for urgent HD… continued

Parameters		Total (N=415)	Dialysis <120 minutes (N= 242)	Dialysis > 120 minutes (N= 173)
Time from admission to dialysis, min			320 ± 206	465 ± 211
Time-from decision-to-dialysis, min			75 ± 32	227 ± 102
Vascular access availability, N (%)	AVF	132 (31.8)	89 (36.8)	43 (24.9)
	Catheter	77 (18.6)	52 (12.5)	25 (6.0)
	No access	206 (49.6)	101 (41.7)	105 (60.7)

Table 1.1: Baseline Demographic of patients admitted for urgent HD… continued

Parameters	Dialysis <120 minutes (N= 242)	Dialysis > 120 minutes (N= 173)
Urea, mmol/L	30.3 ± 40.6	31.3 ± 16.5
Creatinine, micromol/L	866 ± 439	844 ± 639
Potassium, mmol/L	5.4 ± 1.3	5.4 ± 1.2
Bicarbonate, mmol/L	18.9 ± 5.9	16.9 ± 5.9
Hemoglobin, g/dL	9.4 ± 2.2	9.0 ± 2.2

Table 1.2: Adjusted Hazard Ratio for patients delayed initiation compared to timely initiation of HD

Mortality	Death			Adjusted HR	p-value
	Total	Timely HD	Delayed HD		
7-day mortality, N (%)	26 (6.3)	13 (5.4)	13 (7.5)	1.2 (0.5-2.7)	NS
30-day mortality, N (%)	43 (10.4)	24 (9.9)	19 (11.0)	0.9 (0.5-1.7)	NS
In-patient mortality, N (%)	53 (12.8)	31 (12.8)	22 (12.7)	0.8 (0.4-1.4)	NS

Table 1.3 Adjusted Hazard Ratio for patients delayed compared to timely dialysis

Length of hospitalisation	Death			Adjusted HR	p-value
	Total	Timely HD	Delayed HD		
Length of hospitalisation, days (mean)	8.59 ± 11.9	8.1 ± 12.2	9.2 ± 11.2	n/a	NS
Length of hospitalisation, days (median)	4.0 (1-108)	4.0 (1-108)	5.0 (1-68)	n/a	NS

Table 1.4 Adjusted Hazard Ratio for relevant factors that may influence in-patient mortality in patients needing urgent HD

Variables		Total, N (%)	Death, N (%)	Adjusted HR	p-value
Delayed dialysis	Ref: timely dialysis	173 (41.7)	22 (12.7)	0.90 (0.51-1.61)	NS
Female	Ref: male	164 (39.5)	20 (12.2)	0.82 (0.46-1.47)	NS
Age >60	Ref: aged <60	217 (52.3)	38 (17.5)	2.14 (1.15-3.99)	0.017
DM	Ref: non-DM	307 (74.0)	43 (14.0)	1.54 (0.75-3.18)	NS
ESRF	Ref: non-ESRF	261 (62.9)	22 (8.4)	0.88 (0.40-1.93)	NS
Without access	Ref:With access	206 (49.6)	36 (17.5)	1.32 (0.55-3.15)	NS

Table 1.4 Adjusted Hazard Ratio for relevant factors that may influence in-patient mortality in patients needing urgent HD....continued

Variables		Total, N (%)	Death, N (%)	Adjusted HR	p-value
Urea > 30	**Ref: urea<30**	177 (42.7)	28 (15.8)	1.14 (0.61-2.12)	NS
K >6.0	**Ref: K<6.0**	126 (30.4)	19 (15.1)	1.18 (0.65-2.15)	NS
CO2 < 18	**Ref: CO2>18**	233 (56.1)	34 (12.8)	0.92 (0.48-1.79)	NS
Hb < 10	**Ref: Hb>10**	281 (67.7)	30 (10.6)	0.62 (0.34-1.11)	NS

CHAPTER 8: FIGURES

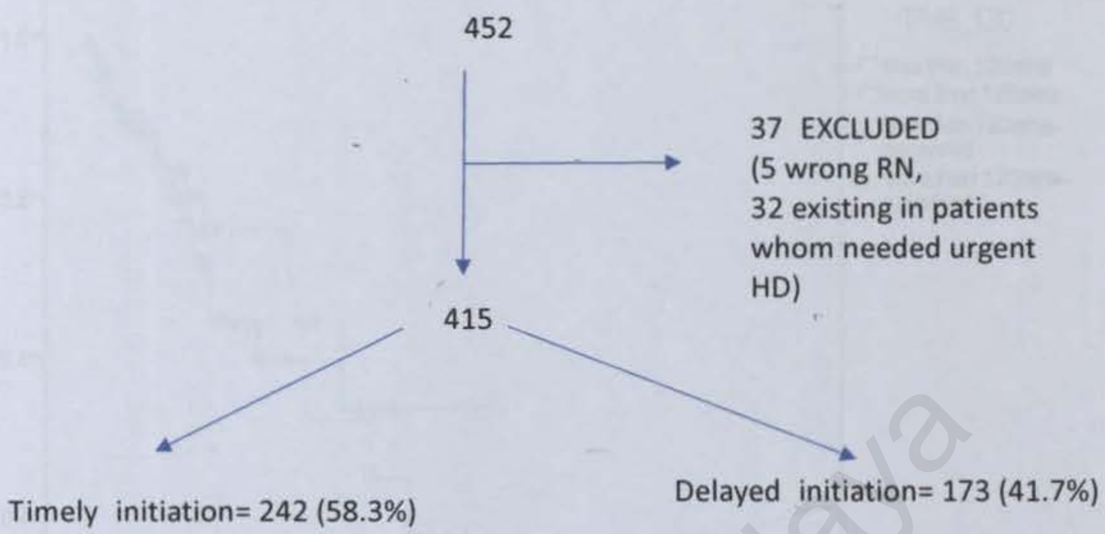

Figure 1.1 Flow chart for timely versus delayed HD

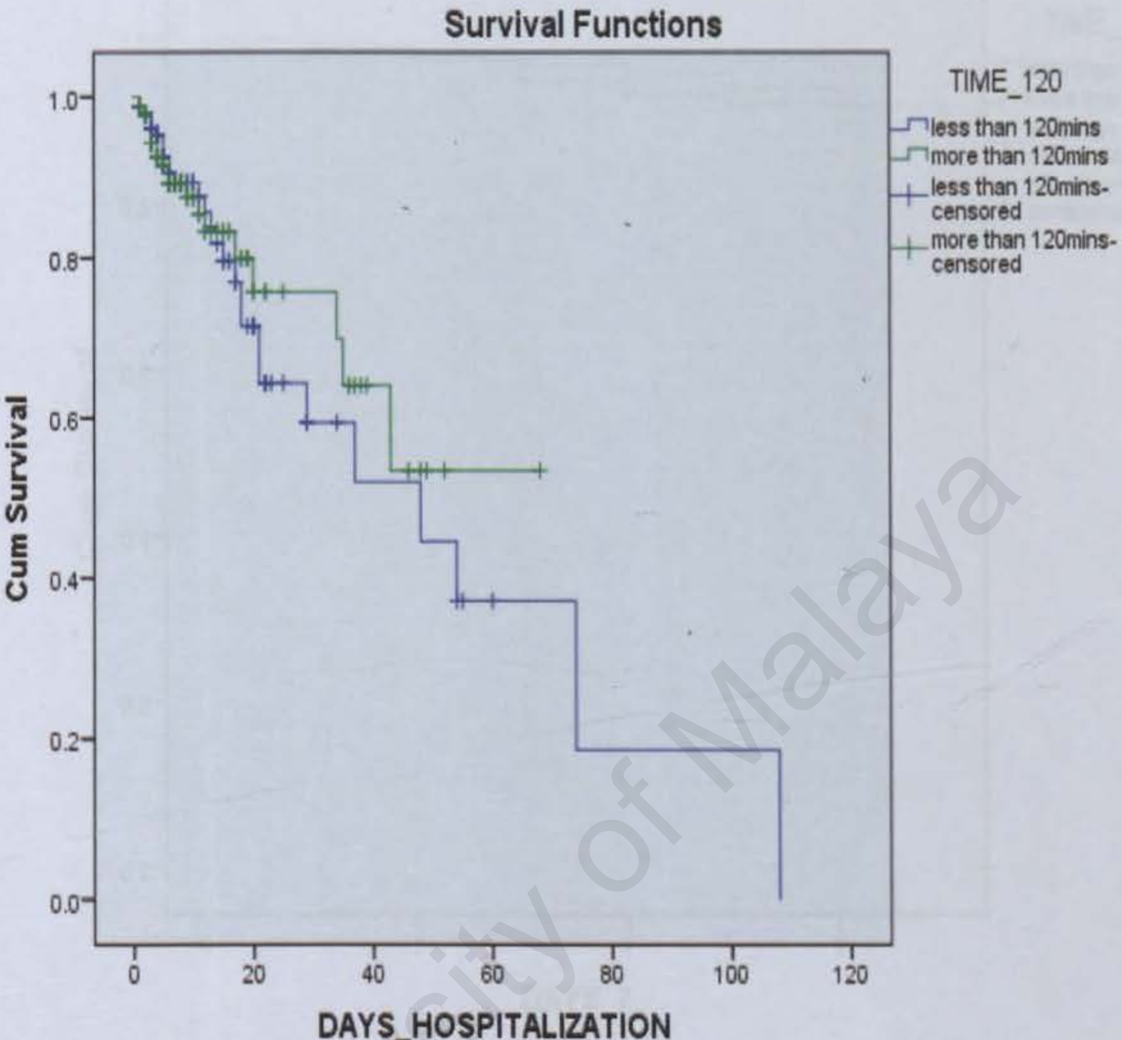

Figure 1.2: Kaplan-Meier Curve shows inpatient cumulative survival for 2 groups (timely dialysis (<120 minutes) & delayed dialysis (>120 minutes), p-value 0.75

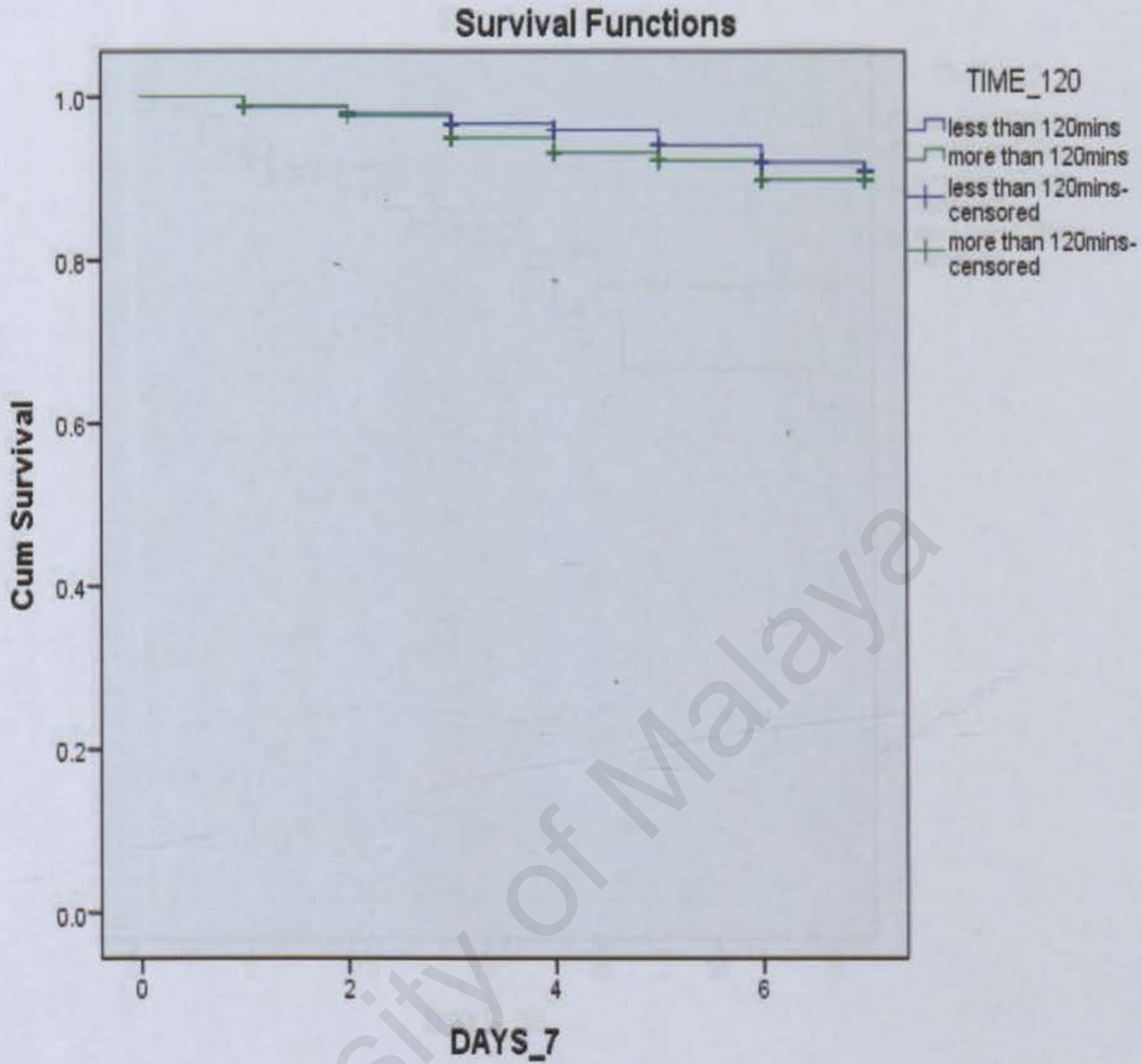

Figure 1.3: Kaplan-Meier Curve shows 7-day cumulative survival for 2 groups (timely dialysis (<120 minutes) & delayed dialysis (>120 minutes), p-value=0.61

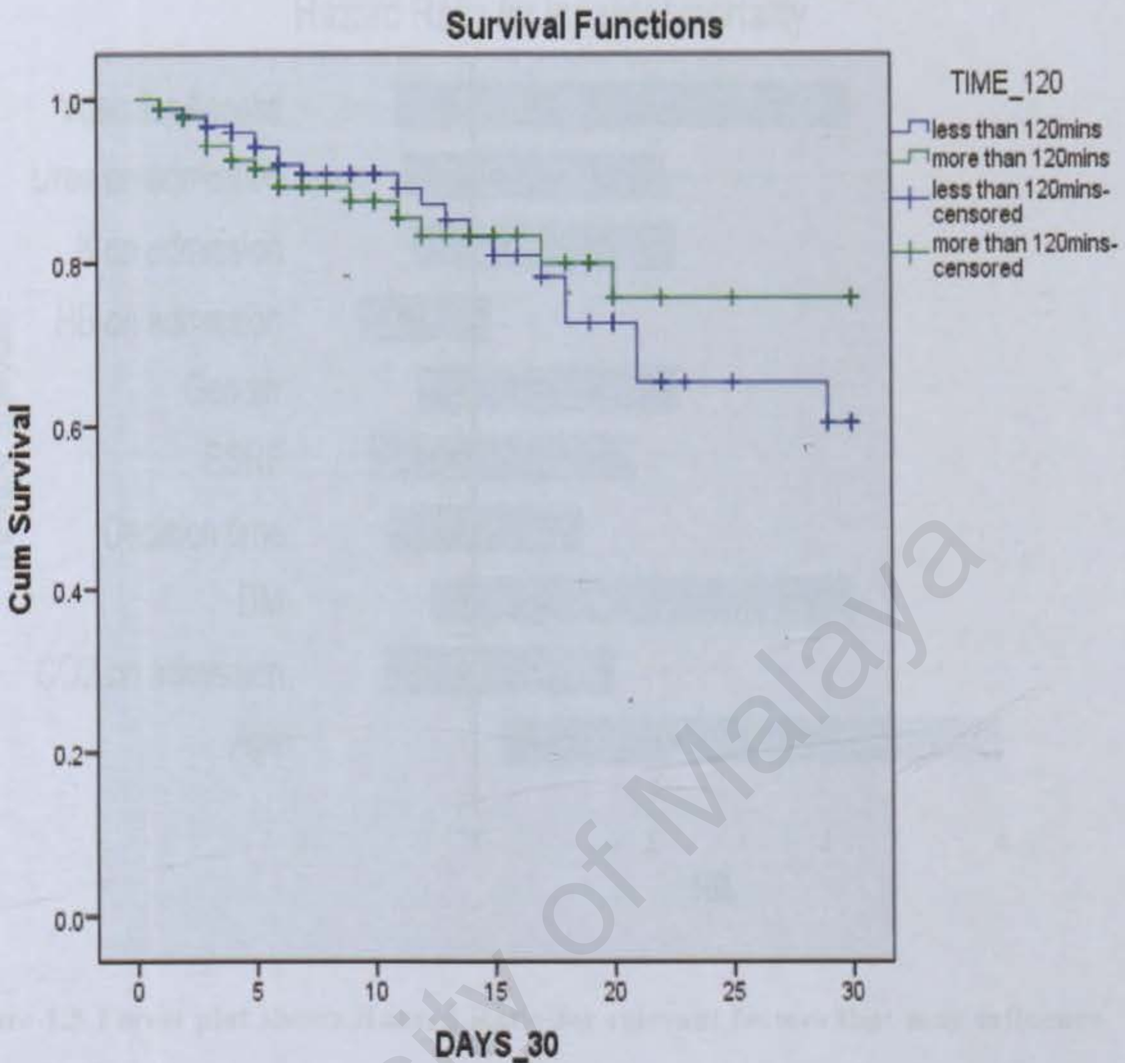

Figure 1.4: Kaplan- Meier Curve shows cumulative survival for 2 groups (timely dialysis (<120 minutes) & delayed dialysis (>120 minutes), p-value =0.88

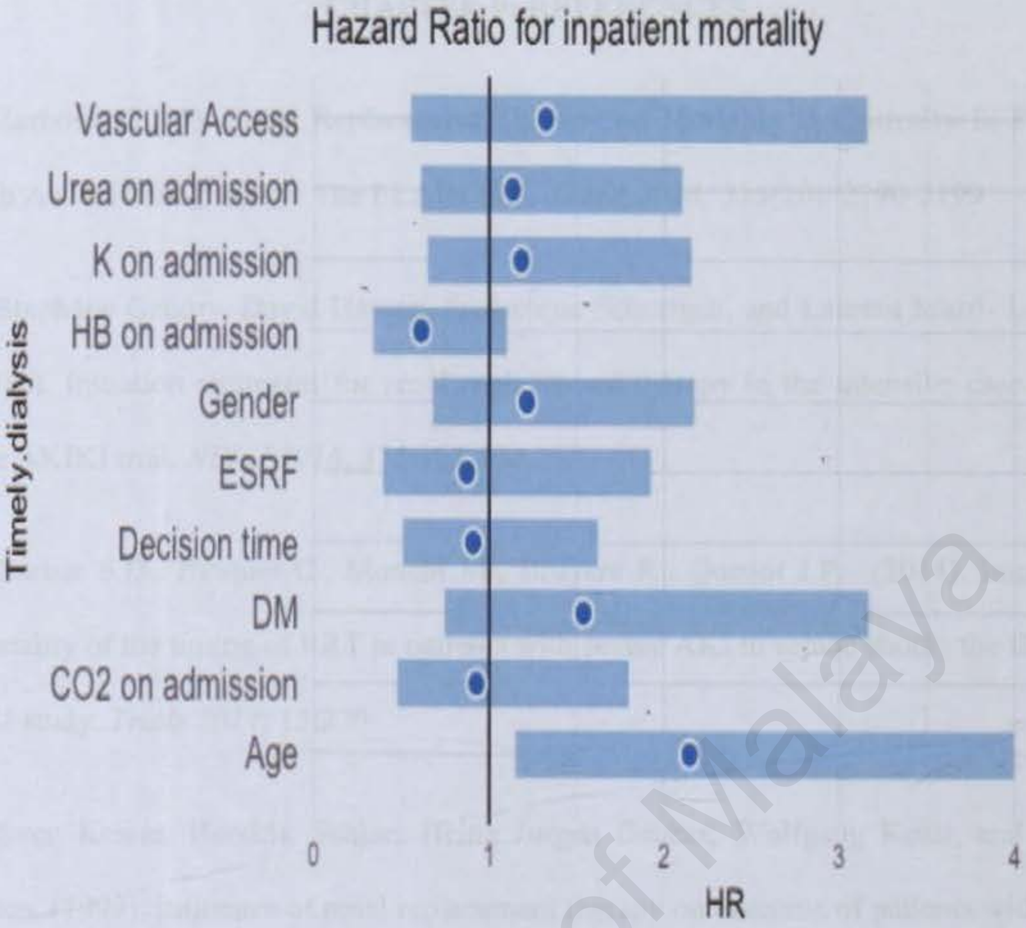

Figure 1.5 Forest plot shows Hazard Ratio for relevant factors that may influence in-patient mortality

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