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Five-year survival analysis and predictors of mortality of adult hemodialysis patients in Indonesia: a nationwide database analysis

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Abstract

Background Hemodialysis (HD) is the modality of renal replacement therapy (RRT) with the highest mortality rate. The identification of prognostic factors will help achieve better outcomes among HD patients. In this study, we sought to conduct a survival analysis and determine the predictors of mortality among adult Indonesian HD patients using data obtained from Indonesian Renal Registry (IRR).

Methods This is a retrospective cohort study which reviewed all adult hemodialysis patients in Indonesia based on the records of IRR during 2007–2022. Variables analyzed in this study include age, sex, etiology of CKD, cause of death, HD frequency, and initial vascular access. A 5-year follow-up was performed until the outcome of death or drop out was found.

Results Among 99,552 eligible patients, the mean survival length was 1536.21 ± 2.50 days. The 5-year survival rate was 77%. Cox proportional hazard regression model revealed demographic and clinical characteristics that are significantly associated with mortality: male sex (HR: 1.038, 95% CI 1.002–1.075), age of 60 years or older (HR: 1.329, 95% CI 1.281–1.379), diabetic nephropathy (HR: 1.347, 95% CI 1.249–1.452), twice-weekly hemodialysis frequency (HR: 1.080, 95% CI 1.011–1.155), initial vascular accesses with femoral vein puncture (HR: 2.710, 95% CI 2.568–2.860), and CVC (HR: 2.992, 95% CI 2.848–3.144).

Conclusions The 5-year survival rate of Indonesian HD patients is 77. Male sex, age of HD onset at 60 years or older, diabetic nephropathy, twice-weekly HD frequency, and the initial vascular accesses with femoral vein puncture and CVC are associated with increased risk of mortality.

Keywords Survival · Mortality · Hemodialysis

Introduction

End-stage renal disease (ESRD) has become a major public health problem and one of the leading causes of mortality worldwide due to its life-threatening complications. Over the last 2 decades, advances in the treatment of ESRD, especially renal replacement therapy (RRT), have helped increase the survival and quality of life of patients. In 2017, estimates indicated that 3.9 million persons with ESRD were treated with RRT globally [1]. Hemodialysis (HD) is the most common form of RRT, accounting for around 69% of all RRT [2]. In 2018, Indonesian Renal Registry (IRR), a nationwide web-based database for chronic kidney disease patients and RRT, reported a consistent rise in new and active HD patients in Indonesia, i.e., a two times increase compared to 2017 [3].

Despite being the major form of RRT across the globe, HD is also the modality with the highest mortality rate, followed by renal transplantation and peritoneal dialysis [4]. In 2018, IRR reported a mortality rate of 78% among patients who stopped HD, with the most common cause being cardiovascular complications (42%) followed by sepsis (10%) [3]. The identification of prognostic factors associated with ESRD, including demographics, comorbid conditions, and

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initial vascular access, will help reduce morbidity and mortality and achieve better outcomes among this population. In this study, we sought to conduct a survival analysis and determine the factors associated with mortality among adult hemodialysis patients in Indonesia using data obtained from IRR.

Methods

Study design, subjects, and data collection

This is a retrospective cohort study which reviewed all hemodialysis patients in Indonesia based on the records of IRR database during 2007–2022. IRR is a database program developed by the Indonesian Society of Nephrology to record and monitor the quality of dialysis in Indonesia. IRR database contains patients' data since the onset of dialysis and includes: name, gender, birthdate, address, level of education, dialysis unit, city/town, state, date of first dialysis session, initial vascular access, etiology of kidney disease, comorbidities, dialysis frequency and duration, last date of dialysis (if applicable), and cause of dialysis termination. Variables analyzed in this study include: age, sex, etiology of CKD, cause of death, HD frequency, and initial vascular access.

Patients were included if they started a routine hemodialysis of twice-weekly frequency and 3–5 h duration between 1 January 2007 and 31 December 2022. A 5-year follow-up was performed until the outcome of death or drop out was found. Patients were excluded if: they are less than 18 years old or have any missing data.

Statistical analysis

Numerical data are presented as mean ± standard deviation or median (interquartile range) as appropriate. Categorical data are presented as frequency and percentage. Survival analysis was performed with Kaplan–Meier survival analysis and predictors of mortality were analyzed with Cox proportional hazard regression model. Hazard ratio (HR) was determined to compare each category of risk factor. All analyses were performed with SPSS version 26.0 (IBM, USA).

Ethical considerations

This study was conducted in line with the Declaration of Helsinki and has been approved by the Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (No. KE/FK/0886/EC). Subjects had been informed and had given consent for the data to be analyzed in this study.

Results

A total of 152,520 data were obtained from IRR, among which only 99,552 were eligible for analysis (Fig. 1). Among the patients included in the analyses, 54.2% are male and the mean age is 52.66 ± 12.75 years. The age of the patients ranges from 18 to 96 years old. Thirty percent of the patients are 60 years or older. The most common etiology of ESRD was hypertension (48.9%) followed by diabetes mellitus (24.8%) and primary glomerulopathy (7.2%). The majority of HD patients (89.7%) were prescribed twice-weekly hemodialysis. The most prevalent initial vascular access was central venous catheter (CVC) (43.8%). Meanwhile, AV fistula, the first-choice vascular access, was utilized at the initiation of HD only in 30.1% of the patients. Mortality rate among patients was 11.1% (11,070/99552), with the most common cause of death being cardiovascular complications (34.4%). Characteristics of the subjects are presented in Table 1. The mean survival among the patients was 1536.21 ± 2.50 days (Fig. 2).

Based on Kaplan–Meier survival analysis, there was no significant difference of mean survival time among different genders ($p = 0.259$) (Fig. 3a). Meanwhile, the mean survival times were significantly different among different age categories, etiologies of kidney disease, HD frequencies, and initial vascular accesses ($p < 0.0001$) (Fig. 3b–e).

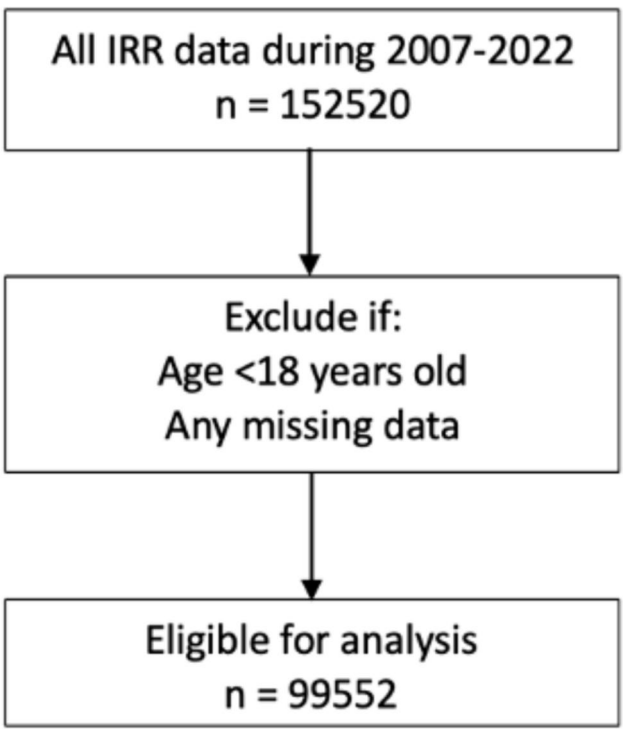

Fig. 1 Flowchart of patients' recruitment

Table 1 Characteristics of subjects

Characteristics	*n* (%) or mean ± SD (min–max) (total = 99,552)
Sex	
Female	45,580 (45.8%)
Male	53,972 (54.2%)
Age (years)	52.66 ± 12.75 (18–96)
< 60 years	69,650 (70.0%)
≥ 60 years	29,903 (30.0%)
Etiology of ESRD	
E1 (primary glomerulopathy)	7128 (7.2%)
E2 (diabetic nephropathy)	24,708 (24.8%)
E3 (lupus nephropathy)	490 (0.5%)
E4 (hypertensive kidney disease)	47,326 (48.9%)
E5 (polycystic kidney disease)	754 (0.8%)
E6 (uric acid nephropathy)	1074 (1.1%)
E7 (obstructive nephropathy)	3467 (3.5%)
E8 (chronic pyelonephritis)	2840 (2.9%)
E9 (others)	6501 (6.5%)
E10 (unknown)	5264 (5.3%)
Hemodialysis frequency	
1 time/week	7428 (7.5%)
2 times/week	89,281 (89.7%)
3 times/week	2670 (2.7%)
> 3 times/week	119 (0.1%)
Initial vascular access	
AV fistula	29,943 (30.1%)
Femoral vein puncture	25,993 (26.1%)
CVC	43,616 (43.8%)
Outcome	
Death	11,070 (11.1%)
Loss to follow-up	1622 (1.6%)
Cause of death	*n* = 11,070
K1 (cardiovascular)	3806 (34.4%)
K2 (cerebrovascular)	678 (6.1%)
K3 (gastrointestinal bleeding)	228 (2.1%)
K4 (sepsis)	1089 (9.8%)
K5 (others)	1263 (11.4%)
K6 (unknown)	4006 (36.2%)

We also summarized the 1–5-year survival rate of the patients based on each variable in Table 2.

Furthermore, Cox proportional hazard regression model revealed demographic and clinical characteristics that are significantly associated with mortality (Table 3): male sex (HR: 1.038, 95% CI 1.002–1.075), age of 60 years or older (HR: 1.329, 95% CI 1.281–1.379), diabetic nephropathy (HR: 1.347, 95% CI 1.249–1.452), twice-weekly hemodialysis frequency (HR: 1.080, 95% CI 1.011–1.155), initial vascular access with femoral vein puncture (HR: 2.710, 95% CI 2.568–2.860), and CVC (HR: 2.992, 95% CI 2.848–3.144).

Discussion

Variability of mortality among hemodialysis patients has been widely reported across different countries in the world. Indonesian Renal Registry (IRR) was established in 2007 and has been consistent in collecting dialysis patients' data all over the country. However, to date, there have been no reports on survival rates or predictors of mortality that include the whole cohort of patients registered on IRR. To our knowledge, this is the first survival analysis study to include all nationwide IRR data from the year it was first established (2007) up till the present time. In Indonesia, the standard prescription of hemodialysis frequency is reduced to twice weekly, instead of the recommended thrice-weekly regimen, due to limited resources relative to the demand. Hence, this study provides findings that represent such population, which is prevalent in developing countries. In this study, we evaluated for the first time the 5-year survival rate and demographic and clinical factors associated with mortality in adult hemodialysis patients using data obtained from IRR. Our study provided a set of parameters that was found to be associated with mortality, including sex, age, etiology of CKD, HD frequency, and initial vascular access.

The mean survival time of all subjects was 1536.21 ± 2.50 days or approximately 4.21 years, and the mortality rate was 11,070 out of the 99,552 patients (11.1%). The survival rate of our cohort is 87% at 1 year, 84% at 2 years, 81% at 3 years, 78% at 4 years, and 77% at 5 years. A study by Ferreira et al. followed up a cohort of HD patients in Viçosa, Brazil for 20 years and demonstrated a survival time of 6.79 ± 0.37 years and a mortality rate of 60.2% [5]. In another study by Nguyen et al. in 2017 involving chronic HD patients at a hospital in Vietnam, the average survival time is 5.27 ± 0.31 years with survival rates of 85% at 1 year, 58% at 5 years, and 20% at 10 years [6]. A retrospective cohort study in Tuyserkan, Iran followed up the cohort for 20 years and revealed a survival rate of 65% at 1 year, 16% at 5 years, and 5% at 10 years [7]. Ebrahimi et al. followed up the data of 1014 HD patients in Shiraz University of Medical Sciences, Iran for 4 years. The study showed a median survival time (95% CI) of 624 days (550–716). The overall 1-, 2-, 3-, and 4-year survival rates for the patients undergoing HD were, respectively, 74, 42, 25, and 17% [4]. Another single-center study conducted at Dubai Hospital demonstrated a 5-year mortality rate of 27.3% among 511 adult patients with ESRD on HD [8]. The findings in our cohort in comparison with other studies once again demonstrated a wide variability in survival time and mortality rates among hemodialysis patients from different centers and

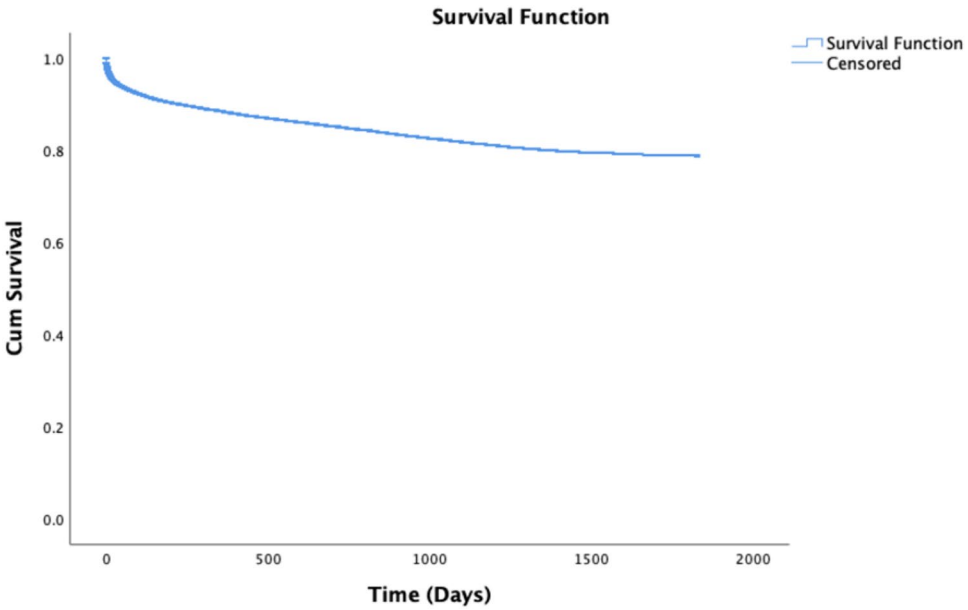

Fig. 2 Kaplan–Meier survival curve of all HD patients

countries. When compared with other developing countries, the mean survival time in Indonesia (4.21 years) is shorter than in Brazil (6.79 years) and Vietnam (5.27 years), but much longer than Iran (624 days or 1.71 years).

Two interesting features in our cohort are that the majority of HD patients (89.7%) were on twice-weekly hemodialysis, with the most prevalent initial vascular access being central venous catheters instead of the first-choice access, i.e., AV fistula. These circumstances are due to the limited resources compared to the load of patients requiring dialysis. In addition, most patients presented to healthcare facilities with conditions that require emergency HD and therefore had no time for AVF preparation. Twice-weekly hemodialysis might not be an accepted form of RRT, since there have not been enough studies to prove its efficacy and sustainability. However, this concept is common and has become an accepted norm in underdeveloped nations. A study by Mendonca et al. in India followed up the outcomes of twice-weekly HD patients for 3 years. The study concluded that initiation at twice-weekly schedules is a viable option with increments when required, and more so in patients with good urine output and residual renal function [9]. Therefore, our cohort can fairly represent hemodialysis patients in limited-resources settings.

The Kaplan–Meier survival curves of the entire cohort (Fig. 1) exhibited a steeper decline in survival during the early period after the initiation of HD. This is consistent with the findings in numerous studies in the past. DOPPS study revealed an increased risk of mortality during the first 120 days compared with 121–365 days after the initiation of HD. In addition, this study identified factors that are associated with elevated mortality early after the initiation of HD, which include older age, catheter vascular access, low serum albumin levels (< 3.5 g/dL) and phosphorus levels (< 3.5 mg/dL), and inadequate predialysis nephrology care [10] Thus, to enhance the outcomes of HD patients, the emphasis should be on improving patients health status during predialysis time and the initial months of the dialysis treatment.

Based on Kaplan–Meier survival analyses, we observed significant difference in mean survival times between different age categories, etiologies of CKD, HD frequencies, and initial vascular accesses, but not with different sexes. Meanwhile, analysis with Cox proportional hazard regression model revealed that all demographic and clinical characteristics considered in this study are significantly associated with mortality, including male sex, age of 60 years or older, diabetic nephropathy, twice-weekly HD frequency, and the initial vascular accesses with femoral vein puncture and CVC.

In this study, we found that males have a 3.8% (HR 1.038) higher risk of mortality compared to females. This finding is consistent with a previous study involving 12 countries, The Dialysis Outcome and Practice Patterns Study (DOPPS). This study found men have higher risk of mortality compared to women (HR: 1.03, 95% CI 0.99–1.08, unadjusted baseline model) [10]. Another multi-center study in Egypt also showed a similar finding, i.e., the overall mortality rate among HD patients was significantly higher in male (7.9%) compared to female (5.6%) ($p = 0.03$) [11]. A study involving 944,650 adult patients using the United States Renal Data System (USRDS) revealed that women have a 2% lower risk of death at 1 year after dialysis initiation compared to men [12]. On the other hand, some studies reported almost equal mortality ratios among both sexes [13, 14]. These heterogeneous findings might be caused by difference in cohort

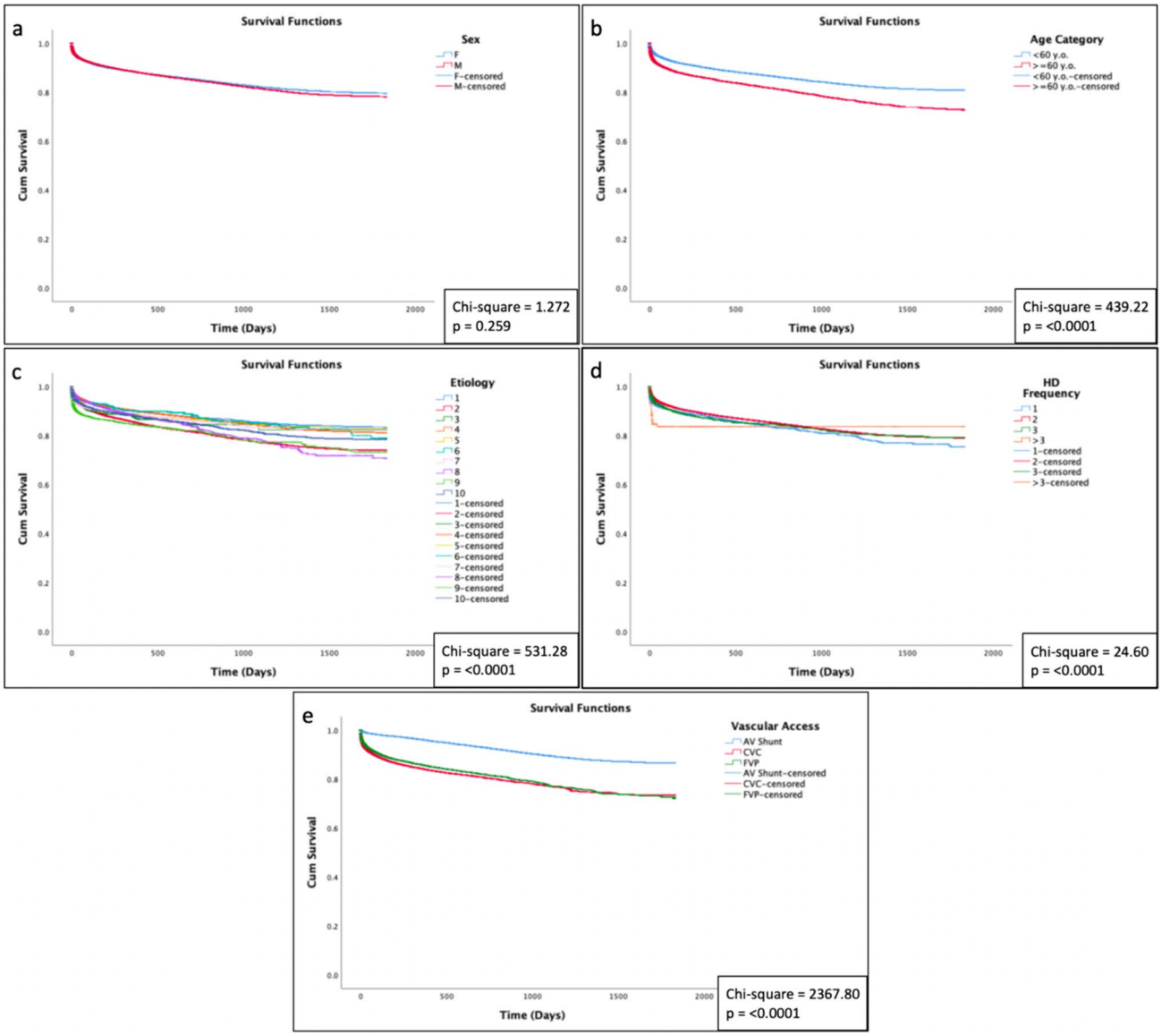

Fig. 3 Kaplan–Meier survival curves based on **a** sex, **b** age category, **c** etiology, **d** HD frequency, and **e** initial vascular access

and criteria of eligibility. It would be also interesting to further explore sex-related differences of clinical and laboratory parameters that might influence mortality. This finding also suggests the possible need for sex-specific treatment strategies in the care of hemodialysis patients.

Our study also demonstrated a poorer survival and an increased risk of mortality in HD patients who started HD at 60 years or older (HR 1.329, 95% CI 1.281–1.379). This is consistent with the findings in several previous studies. Msaad et al. showed that among hemodialysis patients, the surviving ones were significantly younger (43.07 ± 13.52 years) than the deceased patients (53.09 ± 13.56 years) ($p = 0.001$) [15]. Likewise, a study by Zhao et al. revealed the increase in mortality rates with age ($p < 0.001$) [16]. Coric et al. investigated the mortality rate among hemodialysis patients by age groups and found that the case-fatality rate was significantly higher among patients aged ≥ 65 years compared to younger patients [17]. In a study by Ferreira et al., a significantly poorer survival was observed among patients aged 60 years or older [5]. Given the higher risk of mortality of elderly patients, geriatric evaluation and care should be taken into consideration in among this population.

Risk of mortality was also shown to be higher among individuals with CKD caused by diabetes mellitus (DM)—diabetic nephropathy (HR 1.347). Several previous studies have demonstrated similar results. In a study by Soleymanian et al. comparing HD diabetic patients with non-diabetics,

Table 2 1–5-year survival rate

Survival rate (%)					
Year	1	2	3	4	5
Total (95% CI)	87 (86.6–87.4)	84 (83.5–84.5)	81 (80.4–81.6)	78 (77.4–78.6)	77 (76.5–77.5)
Covariates					
Sex					
Female	87	84	81	79	78
Male	87	83	80	78	76
Age category					
< 60 years	89	85	82	80	79
≥ 60 years	83	79	76	72	70
Etiology of ESRD					
E1 (primary glomerulopathy)	89	87	85	83	82
E2 (diabetic nephropathy)	84	80	76	74	72
E3 (lupus nephropathy)	86	83	81	81	81
E4 (hypertensive kidney disease)	89	86	83	81	79
E5 (polycystic kidney disease)	87	85	83	82	81
E6 (uric acid nephropathy)	89	87	84	82	76
E7 (obstructive nephropathy)	86	84	82	81	81
E8 (chronic pyelonephritis)	87	83	77	71	70
E9 (others)	82	79	75	73	69
E10 (unknown)	88	84	81	78	78
Haemodialysis frequency					
1 time/week	85	81	78	75	73
2 times/week	87	84	81	79	77
3 times/week	85	83	80	79	77
> 3 times/week	77	77	77	77	77
Initial vascular access					
AV fistula	96	93	89	87	86
Femoral vein puncture	84	80	76	73	70
CVC	82	78	75	72	71

mortality rate was found to be two times higher among diabetics (24 vs 12 per 100 patient years) with a HR of 1.9 in Cox regression proportional hazard model. Soleymanian et al. also revealed a higher proportion of overweight and obese individuals and inferior profiles of serum creatinine and albumin among the diabetics [18]. The poor survival among diabetics is also associated with greater cardiovascular disease in these patients [19]. This indicates that diabetic nephropathy conveys poorer outcomes among HD patients. Therefore, prompt diagnosis and management of the complications of DM are strongly recommended.

In this study, we also observed that HD patients receiving a twice-weekly HD frequency had higher mortality rate (HR 1.080) compared to reference (once weekly). Meanwhile, statistical significance was not observed in those with the frequency of 3 times per week and > 3 times per week. We speculate that the reason behind this is that patients who require twice-weekly hemodialysis are inherently worse in the course of the CKD, i.e., more severe decline in kidney function. Meanwhile, data from retrospective registry and smaller pilot studies have been supportive and shown the feasibility of incremental hemodialysis. However, larger randomized-controlled trials are required to completely examine the efficacy and safety to allow for more widespread acceptance [20]. Mathew et al. also reported that among incident HD patients with low or moderate comorbid diseases, survival was similar for patients initiated on an incremental or conventional HD regimen [21]. On the contrary, a survival analysis study in Lithuania in 2010 revealed that patients dialyzed < 3 times per week survived shorter than those receiving a higher dose. Duration of HD session of ≤ 8 h per week was also an independent risk factor for mortality [22]. The heterogeneous results suggest that more robust evidence from RCTs are required to elucidate the outcomes of different frequencies of hemodialysis.

Regarding the initial vascular access, we observed that HD patients initially having femoral vein punctures and central venous catheters as the vascular access have

Table 3 Predictors of mortality using Cox proportional hazard regression model

Variables	HR	95% CI	*p* value
Sex			
Female	Ref		
Male	1.038	1.002–1.075	**0.036**
Age category			
< 60 years	Ref		
≥ 60 years	1.329	1.281–1.379	**< 0.0001**
Etiology of ESRD			
E1 (primary glomerulopathy)	Ref		
E2 (diabetic nephropathy)	1.347	1.249–1.452	**< 0.0001**
E3 (lupus nephropathy)	1.157	0.894–1.498	0.267
E4 (hypertensive kidney disease)	0.972	0.903–1.046	0.454
E5 (polycystic kidney disease)	1.023	0.826–1.267	0.837
E6 (uric acid nephropathy)	0.949	0.783–1.149	0.591
E7 (obstructive nephropathy)	1.028	0.912–1.158	0.655
E8 (chronic pyelonephritis)	1.060	0.936–1.200	0.359
E9 (others)	1.362	1.242–1.494	**< 0.0001**
E10 (unknown)	1.298	1.178–1.430	**< 0.0001**
Haemodialysis frequency			
1 time/week	Ref		
2 times/week	1.080	1.011–1.155	**0.023**
3 times/week	1.092	0.968–1.231	0.154
> 3 times/week	1.296	0.823–2.043	0.263
Initial vascular access			
AV fistula	Ref		
Femoral vein puncture	2.710	2.568–2.860	**< 0.0001**
Central venous catheter	2.992	2.848–3.144	**< 0.0001**

Statistically significant if $p < 0.05$ (in bold)

significantly poorer survival and higher risk of mortality (HR 2.710 and 2.992, respectively) compared to those already with AV fistula at the initiation of HD. Patients who had CVC and femoral vein puncture as the vascular access at the initiation of HD started HD emergently or urgently under unstable conditions or acute exacerbations of the disease, and thus did not have enough time and preparation to construct an AV fistula. High prevalence of CVC and femoral vein puncture as the initial vascular access reflect low awareness of deterioration among CKD patients or delayed detection of CKD. Our findings are in line with numerous reports in the past. Yeh et al. demonstrated an adjusted hazard ratio of 1.55 (95% CI 1.09–2.21) among patients using CVC compared to AVF [23]. Similarly, in Kim et al., patients with AVF showed significantly better survival compared with patients with other vascular accesses ($p < 0.001$) [24]. Meanwhile, tunneled femoral vein catheters have been associated with lower catheter survival and significant complications, including deep vein thrombosis and malfunction/occlusion [25].

The strength of our study is that we adopted total sampling of the entire cohort in Indonesia from a nationwide database and thus the large number of subjects. In addition, our study provides results that represent ESRD patients receiving only twice-weekly hemodialysis instead of the recommended thrice-weekly regimen. It is worthwhile and important to explore the survival probability and factors in this population, since it represents the majority of ESRD patients in developing countries throughout the world. Meanwhile, the limitations of this study include: (1) retrospective data—a lot of missing data for some variables due to different reporting practice and routine from different dialysis units, (2) short follow-up period (5 years)—the national registry was founded in 2007 and has only been widely used for the past few years, and (3) no data of laboratory parameters—as they are not routinely checked among Indonesian HD patients due to limited resources and funding. In the future, improvement and standardization in routine reporting to IRR should be conducted to be able to provide better and more accurate data.

Conclusions

In summary, the 5-year survival rate of Indonesian HD patients is 77%, with cardiovascular complications being the most common cause of mortality. There was a significant difference in mean survival times between different age categories, etiologies of CKD, HD frequencies, and initial vascular accesses. Male sex, age of HD onset at 60 years or older, diabetic nephropathy, twice-weekly HD frequency, and the initial vascular accesses with femoral vein puncture and CVC are associated with higher risk of mortality.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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