### 🍃 Original Article 【

# Survival and Prognostic Predictors of Primary Arteriovenous Fistula for Hemodialysis

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**Objectives**: This study aims to evaluate the survival and prognostic predictors of arteriovenous fistulas (AVFs) among patients undergoing AVF creation. The significant predictors were incorporated into a prognostic model to determine its prognostic performance for five-year AVF survival.

**Materials and Methods**: Data on 290 patients who underwent first-time AVF creation and who had been followed up for at least 5 years or until AVF failure were reviewed. The Kaplan–Meier survival curves and Cox proportional hazards model were generated to determine the AVF survival and associated prognostic predictors. Significant predictors were used to derive a prognostic model.

**Results**: The mean age of the patients was  $59.7\pm14.6$  years, and the 5-year AVF survival rate was 34.5%. Three features were found to be independent prognostic factors for the five-year AVF survival: old age, diabetes mellitus, and prior central venous catheter placement. These three significant factors were integrated into a prognostic scoring model that ranged from zero to five points. According to this model, the patients whose scores were 0, 1, 2, 3 and 4 or more had five-year AVF survival rates of 60.0%, 45.3%, 36.6%, 15.0%, and 2.9%, respectively.

**Conclusion**: The five-year survival rate of AVFs was modest, and a prognostic model could excellently estimate the five-year AVF survival.

*Keywords:* arteriovenous fistula, hemodialysis, prognostic predictors, survival

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### Introduction

An increase in the global incidence of end-stage renal disease (ESRD) has led to the increasing demand for hemodialysis.<sup>1,2)</sup> The success of dialysis depends on the creation and maintenance of adequate vascular access for chronic use. Although a native arteriovenous fistula (AVF) is recommended by guidelines as the primary choice for long-term hemodialysis access with a steady increase of its use in many countries,<sup>3–5)</sup> the ongoing challenge facing vascular surgeons is the difficulty in forecasting the types of AVFs that will successfully mature and have long-term survival.

Previous studies reported a wide range of AVF survival rates: 68% to 92% for one-year survival, 57% to 85% for two-year survival, and 4% to 71% for five-year survival.<sup>6–10</sup> Many clinical features were reported as prognostic indicators for long-term AVF patency, such as medical diseases, medications used, prior central venous catheter (CVC) placement, and interventions used to achieve AVF maturation.<sup>7–11</sup> However, the findings were inconsistent among trials because of the dissimilarities in the populations studied. Some authors found old age as a poor prognostic factor for AVF survival,<sup>12,13</sup> whereas other researchers did not confirm such a finding.<sup>7,14,15</sup>

In surgical practice, the ability to predict the long-term survival of an AVF would better assist the surgeon, the patient, and his or her family in making decisions regarding the optimal hemodialysis access for an individual. Prior studies that investigated the predictors of long-term AVF survival were mostly conducted in Western countries.<sup>7,8,10,11</sup> In addition to this, a few studies integrated clinical data into prediction models and assessed their roles as prognostic indicators for AVF patency. However, the survival time evaluated by these models was not longer than two years.<sup>16–18</sup> Given that the median survival of AVFs was approximately 3.2 years,<sup>7</sup> a prediction model that can forecast AVF survival for a longer duration would be beneficial.

This study aims to evaluate the survival and prognostic predictors of AVFs among Thai ESRD patients who underwent primary fistula formation. This study also aims to incorporate significant prognostic factors into a prognostic model and evaluate its prognostic performance for five-year AVF survival.

# **Materials and Methods**

# Patients

A retrospective study that includes all consecutive patients with ESRD who underwent first-time autogenous AVF creation at the author's institution between January 2006 and December 2013 was conducted. The created AVF had to be a radiocephalic or brachiocephalic type. Each patient must be followed up at the vascular surgery and/or nephrology clinics for at least five years or until AVF failure. Patients with incomplete data were excluded from the study. This study was approved by the Vajira Institutional Review Board (Approval No. 065/2562) and was undertaken in accordance with the Declaration of Helsinki.

#### Fistula creation and follow-up care

In the author's institution, the primary AVF performed could be radiocephalic or brachiocephalic anastomosis depending on the vascular surgeon's discretion and the feasibility of vessels. Postoperative surveillance was scheduled at two weeks and then every month for an additional three to six months to monitor the AVF outcomes and possible complications. The implementation of longer follow-up visits for AVF function is at the discretion of the attending surgeon. Patients were also followed up with nephrologists at regular intervals to assess their general health status and any consequences of ESRD.

The first cannulation of the AVF was usually performed after six weeks of operation. AVF maturation was defined as the ability of the fistula to be cannulated and to provide ongoing hemodialysis for at least six sessions.<sup>19</sup> If an AVF failed to generate adequate blood flow for a successful dialysis, an additional surgical or endovascular intervention would be performed to promote fistula maturation or patency.

An AVF that functioned well was defined as AVF survival, whereas an AVF that failed to function despite further intervention was defined as access failure.

# Survival and prognostic predictors of AVF for hemodialysis

Data on the survival and prognostic predictors of AVF were extracted from the hospital electronic database. Survival time was defined as the duration from the date of AVF creation until access failure or until the last follow-up visit in those whose AVF remained patent. The prognostic predictors examined in this study included age, gender, body mass index, comorbid conditions, current medications, history of prior CVC placement, and presence or absence of additional intervention performed to promote AVF maturation. Comorbid conditions included diabetes mellitus (DM), hypertension, ischemic heart disease (IHD), cerebrovascular disease, and cancer. Diabetic patients were classified as patients requiring or not requiring insulin therapy. A diagnosis of IHD was made when the patient had a history of stable angina, unstable angina, or myocardial infarction. Cerebrovascular disease included ischemic stroke and intracerebral hemorrhage. Current medications consisted of antithrombotic agents, statins, calcium channel blockers, angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers, and beta blockers. The intervention performed to promote AVF maturation included surgical and endovascular procedures, which comprised accessory vein ligation, proximal arteriovenous neoanastomosis, and percutaneous transluminal angioplasty.

Information on the survival time of patients, which was defined as the duration from the date of AVF creation until the date of death or the date of last appointment in the hospital, was also collected.

#### Prognostic model development

The significant prognostic predictors of AVF survival were integrated into a prognostic model for five-year AVF survival. Each predictor was assigned a score point proportional to its hazard ratio (HR) from the Cox proportional hazards model (rounded to the nearest integer). All score points were summed to construct the total score point of the prognostic model. The survival curves and five-year survival rates based on the total score were analyzed.

#### Statistical analysis

Statistical analysis was performed with SPSS Statistics version 22.0 (IBM corporation, Armonk, NY, USA). The Kaplan–Meier method was used to estimate the overall survival. The difference between the survival curves of subgroups was assessed using the log-rank test for univariate analysis. The multivariate analysis of prognostic predictors was calculated using the Cox proportional hazards model. Statistical significance was defined as P < 0.05.

# Results

Complete data were collected on 290 ESRD patients who underwent first-time radiocephalic or brachiocephalic AVF creation during January 2006 to December 2013 and who had been followed up for at least 5 years or until AVF failure. The mean age was  $59.7 \pm 14.6$  years (median 60 years, range 19–94 years). A total of 148 patients (51.0%) were female. **Table 1** summarizes the baseline characteristics of the study population.

The overall median survival of AVFs was 3.1 years (range 0.1-12.3 years), whereas the 3-year and 5-year survival rates were 51.0% (95% confidence interval

Table 1 AVF survival rates according to clinical characteristics

Characteristic	Patients (n)	Three years n (%)	Five years n (%)	Median survival (range) (years)	P value
Overall	290	148 (51.0)	100 (34.5)	3.1 (0.1–12.3)	
Age (years)					0.001
<65	178	99 (55.6)	77 (43.3)	3.3 (0.1–12.3)	
65–79	85	41 (48.2)	20 (23.5)	2.5 (0.1–7.8)	
≥80	27	8 (29.6)	3 (11.1)	1.6 (0.3–7.8)	
Gender, n (%)					0.317
Male	142	75 (52.8)	54 (38.0)	3.1 (0.1–10.7)	
Female	148	73 (49.3)	46 (31.1)	2.6 (0.1–12.3)	
Body mass index (kg/m <sup>2</sup> )				(	0.971
<20	28	14 (50.0)	8 (28.6)	2.9 (0.1–7.4)	0.071
20.0–24.9	156	82 (52.6)	54 (34.6)	3.1 (0.1–12.3)	
25.0–29.9	82	42 (51.2)	29 (35.4)	3.3 (0.3–10.7)	
≥30.0	24	10 (41.7)	9 (37.5)	1.5 (0.3–6.3)	
	24	10 (41.7)	3 (37.3)	1.5 (0.5–0.5)	0.003
DM, n (%) No	146	97 (EC O)	60 (44 4)	21/01 10 21	0.003
		87 (56.9)	60 (41.1) 40 (27.8)	3.4 (0.1–12.3)	
Yes	144	61 (42.4)	40 (27.8)	1.8 (0.1–10.7)	
Not requiring insulin	73	32 (43.8)	24 (32.9)	2.0 (0.3–7.6)	
Requiring insulin	71	29 (40.8)	16 (22.5)	1.8 (0.1–10.7)	
Hypertension, n (%)					0.918
No	52	28 (53.8)	18 (34.6)	3.1 (0.1–12.3)	
Yes	238	120 (50.4)	82 (34.5)	3.0 (0.1–10.7)	
IHD, n (%)					0.007
No	240	130 (54.2)	91 (37.9)	3.2 (0.1–12.3)	
Yes	50	18 (36.0)	9 (18.0)	1.6 (0.3–7.2)	
Cerebrovascular disease, n (%)					0.073
No	271	143 (52.8)	97 (35.8)	3.2 (0.1–12.3)	
Yes	19	5 (26.3)	3 (15.8)	1.8 (0.4–5.0)	
Cancer, n (%)					0.283
No	274	142 (51.8)	97 (35.4)	3.1 (0.1–12.3)	
Yes	16	6 (37.5)	3 (18.8)	2.3 (0.3–5.5)	
Antithrombotic agents, n (%)					0.115
No	181	94 (51.9)	69 (38.1)	3.1 (0.1–12.3)	
Yes	109	54 (49.5)	31 (28.4)	2.6 (0.3–7.2)	
Statins			- ( - )		0.237
No	164	81 (49.4)	51 (31.1)	2.5 (0.1–11.1)	
Yes	126	67 (53.2)	49 (38.9)	3.1 (0.3–12.3)	
Calcium channel blockers, n (%)	120	07 (00.2)	40 (00.0)	0.1 (0.0 12.0)	0.962
No	107	56 (52.3)	35 (32.7)	3.2 (0.1–12.3)	0.002
Yes	183	92 (50.3)	65 (35.5)	3.0 (0.1–12.3)	
	103	92 (30.3)	00 (30.0)	5.0 (0.1-10.7)	0 4 2 9
ACE inhibitors or ARBs, n (%)	000	114 (40.0)	76 (22 0)	20/04 40 0	0.428
No	230	114 (49.6)	76 (33.0)	2.8 (0.1–12.3)	
Yes	60	34 (56.7)	24 (40.0)	3.3 (0.1–10.7)	0.000
Beta blockers, n (%)	450	04 (== 0)			0.099
No	152	84 (55.3)	59 (38.8)	3.3 (0.1–12.3)	
Yes	138	64 (46.4)	41 (29.7)	2.2 (0.1–7.8)	
Prior CVC placement, n (%)					<0.001
No	158	94 (59.5)	75 (47.5)	3.8 (0.1–10.7)	
Yes	132	54 (40.9)	25 (18.9)	2.0 (0.1–12.3)	
Intervention before AVF maturation, n (%)					0.939
No	248	124 (50.0)	88 (35.5)	2.9 (0.1–12.3)	
Yes	42	24 (57.1)	12 (28.6)	3.3 (0.5–9.0)	

ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; AVF: arteriovenous fistula; CVC: central venous catheter; DM: diabetes mellitus; IHD: ischemic heart disease; n: number

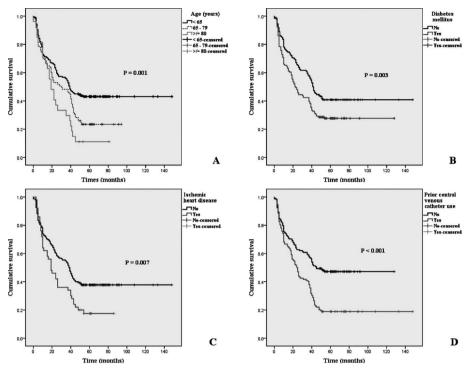


Fig. 1 Kaplan–Meier survival curves of the five-year arteriovenous fistula survival according to (A) patient age, (B) diabetes mellitus status, (C) history of ischemic heart disease, and (D) prior central venous catheter placement.

Variable	HRª	95%CI	P value	Point <sup>b</sup>		
Age (years)						
<65	1.00	_	_	0		
65–79	1.47	1.07-2.03	0.019	1		
≥80	1.70	1.07-2.71	0.026	2		
DM						
No	1.00	_	_	0		
Yes	1.36	1.01-1.82	0.041	1		
IHD						
No	1.00	_	_	_		
Yes	1.19	0.83-1.72	0.350	_		
Prior CVC placement						
No	1.00	_	_	0		
Yes	1.91	1.42-2.56	<0.001	2		

<sup>a</sup>Adjusted for the other variables in the table. <sup>b</sup>Point was assigned to each variable according to its HR value and rounded to the nearest integer. AVF: arteriovenous fistula; CI: confidence interval; CVC: central venous catheter; DM: diabetes mellitus; HR: hazard ratio; IHD: ischemic heart disease

45.3%–56.8%) and 34.5% (95% confidence interval 29.0%–40.0%), respectively. Univariate analysis showed that old age (P=0.001), DM (P=0.003), history of IHD (P=0.007), and prior CVC placement (P<0.001) were significant predictors of AVF survival (**Table 1**). In a group of diabetic patients, those requiring insulin therapy had lower rates of AVF survival at three and five years than individuals not requiring insulin. However, the differences were not statistically significant (P=0.717 and P=0.166,

respectively).

Figure 1 shows the survival curves of the AVFs according to the four significant factors. The multivariate analysis of AVF survival using the four significant factors (old age, DM, IHD, and prior CVC use) from univariate analysis showed that the independent prognostic predictors were old age, DM, and prior CVC placement (Table 2).

The HRs of the independent prognostic predictors were used to derive a prognostic model. These values were 1.48

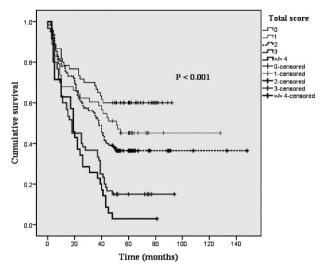


Fig. 2 Kaplan–Meier survival curves of the five-year arteriovenous fistula survival according to total score point.

for ages 65–79 years, 1.79 for ages  $\geq$ 80 years, 1.36 for DM, and 1.93 for prior CVC placement. Each value was rounded to the nearest integer to derive its own score point. Table 2 shows the results. The total score ranged from zero to five points. The total scores of all patients were further categorized into five subgroups: score 0, score 1, score 2, score 3, and score 4 or more. When the Kaplan-Meier survival curves were generated according to the total score subgroup (Fig. 2), the median survival of AVFs were 4.3 years (range 0.1-7.7 years) for score 0, 4.0 years (range 0.1-10.7 years) for score 1, 3.2 years (range 0.3-12.3 years) for score 2, 1.5 years (range 0.1-7.8 years) for score 3, and 1.6 years (range 0.3–6.8 years) for score 4 or more (P<0.001). The five-year AVF survival rates of score 0, score 1, score 2, score 3, and score 4 or more subgroups were 60.0%, 45.3%, 36.6%, 15.0% and 2.9%, respectively.

Further analyses demonstrated that the five-year mortality rate of patients were 25.5%. The total score from a prognostic model was significantly related to the mortality rate of patients at five years. Patients whose scores were zero, one, two, three, and four or more had five-year mortality rates of 5.0%, 24.5%, 23.2%, 38.3%, and 45.7%, respectively.

#### Discussion

When deciding the optimal hemodialysis access for an ESRD patient, clinicians expect to provide an access device with long-lasting functions. Several authors have suggested that AVFs have greater longevity than other vascular access modalities. This suggestion appears to be true only when patients with mature AVFs are included for outcome determination. However, the calculated survival of AVFs would be attenuated when patients with AVF nonmaturation are also involved. This evidence was confirmed by the present

study, which included both mature and nonmature AVFs for data analysis and found that the overall median survival of fistulas was only 3.1 years. The finding of this study was consistent with the reported median survival of 3.2 years by Puskar et al.,<sup>7</sup> who conducted a study in a combined group of patients with or without mature AVFs.

This study identified a 34.5% survival rate of the fistula after five years of creation. A few other studies also reported the five-year survival of primary AVFs. Their observed rates were in a broad range: 4%–12% in Turkey,<sup>8)</sup> 36.0% in Croatia,<sup>7)</sup> and 71% in Morocco.<sup>9)</sup> Nevertheless, when a comparison was made between the present study and the study from Croatia, which had similar median ages of patients (60 years vs. 58 years of age, respectively), the 5-year AVF survival rates were not different: 34.5% in the present study and 36.0% in the study from Croatia.

Regarding the prognostic predictors of AVFs, previous studies examined the effect of old age on AVF loss and found inconsistent results. Some studies identified old age as a poor prognostic indicator,<sup>12,13</sup>) whereas others did not.7,14,15) Of note, the populations included in previous studies were predominantly white people who might have different AVF survival from Asian origin groups.<sup>20)</sup> The present study, which was conducted on ESRD patients of Thai ethnicity, found that old age is a prognostic predictor of AVF survival. Furthermore, the findings of the median AVF survival of 3.3 years, 2.5 years, and 1.6 years in patients aged below 65 years, 65-79 years, and 80 years or older, respectively, reflected a direct relationship between age and risk of AVF loss. According to these results, clinicians should be aware of the likelihood of the short functional survival of AVFs among elderly patients, particularly individuals of Asian ethnicity whose ages are 80 years or older. The results of this study also showed an inverse relationship between age and 5-year mortality rate: 16.9%, 36.5%, and 48.1% in patients aged below 65 years, 65-79 years, and 80 years or older, respectively. These data supported the results of a recent study that assessed the suitability of an AVF or an arteriovenous graft (AVG) as the primary vascular access in many scenarios and suggested that an AVG may be more appropriate than an AVF in some clinical situations, e.g., in patients at risk for AVF nonmaturation or in those with short life expectancies.<sup>21)</sup> Considering that trends in population aging have increased substantially in recent years in most countries across the globe,<sup>22)</sup> vascular surgeons and nephrologists should pay attention to the elderly group and take into account the balance of access failure that leads to additional interventions against life expectancy when determining the optimal vascular access for each patient.

By focusing on the effect of medical diseases on AVF outcomes, several studies found that DM was an independent, poor prognostic factor of AVF survival.<sup>7,8,15,16</sup> In line with previous publications, the current study showed that the median AVF survival of patients with DM was significantly shorter than that of patients without DM (1.8 years vs. 3.4 years, respectively; P = 0.003). One possible reason was that DM-induced vascular calcification,<sup>23)</sup> which can cause vessel wall stiffness and impairment of blood flow, leads to AVF failure.<sup>24)</sup> Furthermore, DM can promote platelet aggregation.<sup>25)</sup> This abnormal platelet function can cause endothelial damage and subsequent thrombus formation, thus consequently resulting in AVF dysfunction.<sup>26</sup> Data from this study showed that the severity of DM at the time of AVF creation, as assessed by the requirement of insulin therapy, was not correlated with long-term AVF survival. Nevertheless, it is not known whether changes in diabetic severity over time would affect late AVF functionality. This issue is needed to be explored further in future research.

With respect to other medical diseases, Twine et al.<sup>16</sup>) identified IHD as a potential predictor of AVF failure. In the present study, IHD was found to be associated with poor AVF survival only by univariate analysis. The differences between the present study and the study of Twine et al.<sup>16)</sup> might be because of the differences in IHD severity. In the study of Twine et al.,<sup>16)</sup> the median age of patients was 69 years, which was greater than the median patient age of 60 years observed in the present study. Older patients are more likely than younger patients to experience a longer duration of IHD symptoms. Given that atherosclerosis is a systemic disease that develops not only in coronary arteries but also in other vessel beds, including AVF blood vessels,<sup>27)</sup> patients with a longer duration of IHD would be more prone to AVF stenosis than patients with shorter disease duration. In addition to IHD, two studies found that a relationship exists between malignant neoplasm and the risk of AVF loss.<sup>7,8)</sup> On the contrary, this study did not observe such a finding. The possible cause for the conflicting results was the dissimilarities of the types and stages of cancer in the present study and the two other studies. Further research with more strict inclusion criteria for cancer patterns is needed to ascertain such an association.

Prior CVC placement is another issue of concern because the rates of CVC use remains high in many countries. This study found that a history of CVC placement was a poor prognostic predictor of AVF survival. This finding was consistent with the results of previous studies that showed frequent AVF failure in patients with prior CVC placement or prolonged use of CVCs.<sup>8,9,11</sup> The explanation for such a finding is that CVC placement can elicit systemic inflammation,<sup>28</sup> which has been suggested to be involved in the pathogenesis of intimal hyperplasia formation and subsequent AVF stenosis.<sup>29</sup>

The three prognostic predictors of AVF survival observed in the present study were old age, DM, and prior CVC placement. In clinical practice, the use of only one clinical parameter (i.e., old age or DM or prior CVC use) to assess AVF survival might be irrational because the prognostic performance of each parameter would be suboptimal. Furthermore, no study has developed a prognostic rule to predict five-year AVF survival. The author then incorporated these three significant parameters into a prognostic model to assess the five-year survival of AVFs. This prognostic model is simple, practical to use, and can assist the surgeon in deciding the right choice of vascular access device for each patient. For example, a patient aged 55 years old who has no history of DM or prior CVC placement would have a prognostic score of 0 with an expected 5-year AVF survival rate of 60%. In this case, an AVF should be the suitable vascular access for this patient. On the contrary, a patient aged 85 years old who has a history of DM and prolonged use of CVC would have a prognostic score of 5 with an expected 5-year AVF survival rate of only 2.9%. This patient is at risk for further interventions, which could increase risks of morbidity and mortality. Therefore, an AVG might be more appropriate than an AVF in this scenario.

Despite its feasibility for clinical application, the prognostic model developed herein was incorporated from retrospective data. Hence, some information, including vessel diameter, which might affect AVF patency, was unavailable. Nevertheless, in the author's institution, surgeons usually selected patients whose venous and arterial diameters were greater than 2 mm and who were good candidates for the operation. Furthermore, the patients included in this study were only those who had been followed up at the author's institution for at least five years or until AVF failure. It is unknown whether patients who had follow-up visits elsewhere would have the same results. Lastly, this study was a monocentric study. Therefore, the prognostic model needs to be externally validated in other settings to confirm its generalizability.

This study has several strengths. First, this is the first study that developed a prognostic rule to assess the fiveyear survival of radiocephalic or brachiocephalic AVFs, which are commonly performed in current vascular surgery practice. Second, the prognostic model included only basic data that could be obtained from history taking. Therefore, it yielded advantages over models that included ultrasound or intraoperative parameters in terms of being free of charge and being available to predict AVF survival before the operation occurs. Third, this prognostic model was derived from data of Thai people; therefore, this model might be better suited for Asian population than prognostic tools that include the data of other racial groups. Nevertheless, the author could not make any definite conclusion regarding the clinical application of this prognostic model because data from this study were limited to a homogeneous population from a single hospital.

# Conclusion

The five-year survival rate of AVFs among Thai ESRD patients was modest at 34.5%. A prognostic model including old age, DM, and prior CVC placement could help clinicians assess the five-year AVF survival in each patient and suggest the appropriate type of vascular access. However, given that this study was conducted in a single center, further studies are warranted to corroborate the findings in other institutions in the country or in other Asian groups.

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# **Disclosure Statement**

The author has no conflict of interest.

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