

Duration of Vascular Access Usage and Patient Survival in the First Year of Hemodialysis

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Keywords. arteriovenous fistula, central venous catheters, renal dialysis, survival analysis, C5.0 algorithm, proportional hazard model

Introduction. The central venous catheter (CVC) has been shown to increase mortality in hemodialysis (HD) patients compared with the arteriovenous fistula (AVF). However, no study has examined the mortality of HD patients based on the time of conversion from the CVC to AVF. In this study, we investigated the association between patients' survival and length of time of using each access.

Methods. The C5.0 algorithm was used to find rules about the relationship between duration of the different access usage and survival. The cox model was applied to assess the association of the obtained duration categories and mortality.

Results. From 2367 adult patients who received maintenance HD from 2012 to 2014, 705 patients were eligible for the study. Using an AVF for more than 8 months and a CVC for less than 4.2 months had the highest one-year survival rate (91.8% and 87.4%). The hazard ratio (HR) for mortality of less than 2.8 months of AVF usage compared to the longest usage was 6.90 (95% CI: 4.60 - 10.30) before adjustment and 5.03 (95% CI: 3.20 - 8.00) after adjustment for all confounders. For the CVC, the ratio was 8.8 (95% CI: 6.00 - 13.00) when comparing more than 9.2 months of usage with the lowest usage duration before an adjustment and 6.00 (95% CI: 3.80 - 9.41) after adjustment.

Conclusion. Our results presented that regardless of the type of initial vascular access, limiting the length of the time using CVC as well as switching to AVF could significantly improve the survival of HD patients.

IJKD 2019;13:389-97
www.ijkd.org

INTRODUCTION

Patients with end-stage renal disease (ESRD) have a high risk of mortality¹ due to multiple factors such as underlying etiology of ESRD,² comorbid diseases such as diabetes,³⁻⁶ anemia,^{7,8} old age,^{2,4,9,10} and malnutrition.^{5,9} Type of vascular access has also a significant role in the mortality rate of patients undergoing hemodialysis (HD).¹¹⁻¹³ Previous studies have assessed the effect of initial vascular access type. These studies showed that the arteriovenous fistula (AVF), as the initial

vascular access type improves the survival rate of patients with ESRD compared with central venous catheters (CVCs).¹³⁻¹⁷ Hence, the AVF is considered the preferred access type for its lower mortality and complication rates.^{13,18,19}

Moreover, switching the access from a CVC to AVF or AV graft will improve short-term mortality risk.¹² In practice, many patients do not have AVF or graft at the time of starting HD and they have to insert a CVC to start emergency HD, and implanted an AVF or graft later. On the other hand, some

patients start HD with an AVF but have to switch to a CVC due to AVF dysfunction.

In the present study, we hypothesized that regardless of the initial vascular access, the amount of time a patient has used on a particular type of access is important in his outcome and survival. Thus, by the use of data mining methods, we have aimed to find the length of time each access has to be used to have a significant impact on survival. Access type may change over time, so we calculated the contribution of each vascular access type to the mortality of patients undergoing HD, considering the length of time each access type has been used through the first year of starting maintenance HD. This study is different from others in which they evaluated the effect of the type of initial access on mortality.

Data mining is an exploratory analysis done to discover hidden patterns and knowledge and gives new and unknown hypotheses. Decision tree analysis, a data mining technique, is used to extract implicit rules from various factors for predicting an outcome. Another usage of decision tree algorithms is to discretize data with appropriate thresholds for classification. In order words, numeric data is transformed into categorical data by splitting them into different ranges on the basis of historical data.²⁰

In the present study, the most prevalent and effective algorithm of the decision tree, the C5.0 algorithm,²¹ was used to find actionable rules about the relationship between the duration of using different vascular access types and survival in patients undergoing HD who were followed for at least 12 months. Extracted rules were tested by conventional statistical methods as a new hypothesis.

MATERIALS AND METHODS

Ethics Statement

The research ethics committee of the Shiraz University of Medical Sciences has approved this study (IRB code: IR.SUMS.REC.1394.S102). Since the data was analyzed anonymously, no informed consent was given and the ethics committee waived the requirement for informed consent.

Study Design

We conducted a retrospective analysis of 2367 adult patients undergoing HD who were registered

in the Shiraz University of Medical Sciences (SUMS) HD database (DB). This DB, provided by SUMS Special Diseases Affairs, contains all data related to patients on HD (clinical and demographical variables plus hemodialysis indices), starting from the initiation of HD until the death of the patient, transplantation, or switch to peritoneal dialysis. This DB, which was established in 2012, includes the data of patients from 34 HD centers affiliated with SUMS.

From the DB, data of patients older than 18 years of age were captured who initiated their first dialysis session from 2012 to 2014 and had at least 12 months of HD follow-up sessions. The follow-up period for each patient was from the first dialysis session and continued until the end of the twelfth month or until the death of the patient. Patients who underwent kidney transplantation within one year of dialysis initiation, died in the first three months, or were lost in the follow-up period were excluded. Finally, data of 705 patients were eligible to be assessed in this study.

The Duration of Each Vascular Access Type Usage

The access type may change over time after starting HD. Therefore, the contribution of major vascular access types was calculated throughout the 12 months of starting HD to assess the effect of the duration of each vascular access type on survival regardless of the initial access.

Since the ranges obtained from the analysis were for the proportion of the time (in percent) each vascular access type was used, they could be translated into the duration of time they were used in the form of months. Because of the limited usage of the AV graft in our study population, this access type was ignored. Moreover, considering the small number of patients that used tunneled CVCs, no rule was extracted from the C5.0 algorithm for this access type. However, significant time durations were obtained for the AVF and non-tunneled CVC. Hence, in this study, CVC refers to non-tunneled CVC. For all patients, HD was done using polysulfone dialysis membranes with bicarbonate dialysate and by a dialysate potassium concentration of 2 mEq/L.

Potential Confounding Factors

Based on previous studies,^{11,12,14,15} potential

confounding factors were considered in the analysis, which were available in the DB including sex, age, body mass index (BMI), the presence of anemia (hemoglobin [Hb] level below 10 g/dL), underlying etiology of ESRD, HD session indices including the flux type of the filters in terms of low flux/high flux (the contribution of each filter type in dialysis sessions), average systolic and diastolic blood pressure (SBP and DBP) in the first and fourth hours of hemodialysis, average pulse rate (the average of four pulse values throughout the four hours of each session), hemodialysis adequacy in terms of kt/v , monthly biochemical and hematological investigations including serum albumin, pre-dialysis blood urea nitrogen (pre-dialysis BUN), and post-dialysis BUN. For continuous variables, the averages of values during the follow-up period were calculated.

Statistical Analysis

We analyzed SUMS HD DB in a study and assessed data quality including outlier detection and missing handling.²² After preprocessing and cleaning the data, the decision tree algorithm of the IBM-SPSS Modeler 14.2 was used for prediction of mortality. Decision trees are expressive classification algorithms of data mining that can be used for extracting prediction rules and applied for evidence-based medicine.²³ One of the popular decision tree algorithms with accurate rule extraction and low error rate is the C5.0 algorithm,²⁴ which was used in this study. The C5.0 finds the cutoff value and patterns that most effectively predict mortality in patients with HD based on vascular access type. This algorithm discretized the vascular access durations in significant ranges. Finally, hidden rules on mortality risk prediction based on vascular access type were created through this analysis. The algorithm separated the patients into branches based on the ranges of vascular access usage.

Descriptive data are presented as mean \pm standard deviation (SD) and categorical variables were summarized as the percentage of total. Characteristics of patients according to mortality status (alive or deceased) were compared using the t-test for continuous variables and chi-square test for categorical features.

The statistical methods were used in complement with the C5.0 algorithm results. The cox proportional

hazard model was used for investigating the association between the duration of the AVF and CVC captured by data mining rules and mortality (0: alive, 1: deceased) by the hazard ratio (HR) and 95% confidence interval (CI). The Kaplan-Meier method was used for survival curves. *P* values $< .05$ were considered significant. The SPSS software, version 22 (IBM Inc.) was used for these analyses.

RESULTS

Baseline Characteristics

In this study, 705 patients undergoing HD with a mean \pm SD age of 58.61 ± 15.6 years and BMI of 22.7 ± 4.6 kg/m² were included in the analysis. Women comprised 40.9% ($n = 288$) of the study population. Baseline demographic data, laboratory variables, and HD session indices are listed in Table 1. The most common cause of ESRD was hypertension (30.3%) followed by diabetes mellitus (24.1%).

Minimum follow-up time in our study was 12 months. During the follow-up period, 150 (21.3%) patients died. Regarding vascular access type, during the 12 months of follow-up, on average, 60.5% of all HD sessions were reported to be done by the AVF, 25.4% by the non-tunneled CVC, and 12.4% by the tunneled CVC.

By comparing deceased patients with those who were alive, we found that while the average BMI, BUN, and Kt/V did not differ significantly, the average age, underlying etiology of ESRD, presence of anemia (Hb < 10 mg/dL), contribution of each type of vascular access (AVF, tunneled, or non-tunneled CVC), flux type of filter (high flux/low flux), average intradialytic pulse rate, SBP and DBP measurements, and serum albumin were significant variables. For patients who were alive until the end of the twelfth month, the AVF was used as the dominant vascular access (AVF: 67.5%, non-tunneled CVC: 19.9%, and tunneled CVC: 11% of sessions) in most sessions. However, for patients who died, the non-tunneled CVC has been used in most sessions (AVF: 34.4%, non-tunneled CVC: 45.8%, tunneled CVC: 18% of HD sessions) ($P < .001$, $P < .001$, and $P < .05$; respectively).

One-year Survival and the Duration of AVF Usage Based on C5.0 Algorithm Rules

Analyzing the relationship between one-year

Table 1. Baseline Characteristics of Patients Undergoing Hemodialysis According to Mortality Status

Characteristic	Total (n = 705)	Live (n = 555)	Dead (n = 150)	P
Age at Enrollment				
18 - 40	99 (14.0%)	81 (14.6%)	18 (12.0%)	
41 - 60	224 (31.8%)	191 (34.5%)	33 (22.0%)	< .05
61 - 70	181 (25.7%)	144 (25.9%)	37 (24.7%)	
> 70	201 (28.5%)	139 (25.0%)	62 (41.3%)	
Female Gender	288 (40.9%)	219 (39.5%)	69 (46.0%)	> .05
Underlying Etiology of ESRD				
Diabetes Mellitus	170 (24.1%)	138 (25.0%)	32 (21.2%)	
Hypertension	214 (30.3%)	178 (32.1%)	36 (24.0%)	
Hypertension and Diabetes	138 (19.6%)	114 (20.4%)	24 (16.0%)	
Glomerulonephritis	18 (2.6%)	14 (2.4%)	4 (2.6%)	< .05
Polycystic Kidney Disease	22 (3.1%)	17 (3.1%)	5 (3.2%)	
Nephrolithiasis	24 (3.4%)	18 (3.3%)	6 (4.0%)	
Urological Problems	15 (2.1%)	8 (1.4%)	7 (5.0%)	
Others	104 (14.8%)	68 (12.3%)	36 (24.0%)	
Anemia (Hb < 10 g/dL)	280 (39.7%)	187 (33.7%)	93 (62.0%)	< .001
BMI, kg/m ²	22.7 ± 4.6	22.8 ± 4.8	22.2 ± 4.2	> .05
AV fistula*	60.5 ± 36.0	67.5 ± 33.9	34.4 ± 34.7	< .001
Non-tunneled CVC	25.4 ± 27.0	19.9 ± 22.0	45.8 ± 33.4	< .001
Tunneled CVC	12.4 ± 24.3	11 ± 23.4	18 ± 26.8	< .05
High flux dialyzer (%)†	29.8 ± 20.0	31.6 ± 20.1	23.1 ± 18.3	< .001
Low Flux Dialyzer (%)†	68.4 ± 20.1	66.6 ± 20.2	75.0 ± 18.4	< .001
Pulse Rate (/min)	78.2 ± 4.1	78.0 ± 4.1	78.8 ± 4.0	< .05
Mean HD SBP, mmHg	131.6 ± 12.4	132.6 ± 12.0	127.5 ± 13.1	< .001
Mean HD DBP, mmHg	77.6 ± 5.9	77.9 ± 5.5	76.2 ± 7.0	< .05
Serum Albumin, gr/dL	3.8 ± 0.4	3.9 ± 0.4	3.5 ± 0.5	< .001
Post-BUN, mg/dL	20.1 ± 6.3	20.3 ± 6.3	19.5 ± 6.1	> .05
Pre-BUN, mg/dL	59.8 ± 14.5	59.7 ± 13.0	60.4 ± 19.1	> .05
KT/V	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	> .05

*The proportion of sessions done with each type of access.

†The proportion of sessions done with each type of filter.

Note: Categorical variables are mentioned as percentages, continuous variables are given as mean ± standard deviation.

Three Access types percentage mentioned in the table, 1.7% of all sessions were missing or graft that ignored.

Abbreviations: BMI, body mass index; CVC, central venous catheter; Mean HD SBP, the average of systolic blood pressure; Mean HD DBP; the average of diastolic blood pressure; Post-BUN, blood urea nitrogen immediately after hemodialysis; Pre-BUN, blood urea nitrogen before hemodialysis; KT/V, dialysis adequacy

Table 2. Extracted Rules of the C5.0 Algorithm for AVF Usage and One-year Survival

If	Then
Duration of AVF Usage ≤ 2.8	Survival rate is 55.6
2.8 < Duration of AVF Usage ≤ 6.6	Survival rate is 66.2
6.6 < Duration of AVF usage ≤ 8	Survival rate is 78.4
Duration of AVF usage > 8	Survival rate is 91.8

Note: Duration of AVF usage is mentioned as months.

survival and length of time each patient used an AVF as the main vascular access by the C5.0 algorithm resulted in four rules, shown in Table 2, as four distinct ranges of time with different survival rates (i.e., ≤ 2.8 months, 2.8 to 6.6 months, 6.6 to 8 months, and > 8 months). The survival rates

were 55.6%, 66.2%, 78.4%, and 91.8%; respectively (Figure 1).

One-year Survival and the Duration of CVC Usage Based on C5.0 Algorithm Rules

The relationship between the length of time each patient used a CVC and one-year survival resulted in four rules (Table 3) as four distinct ranges of time have different survival rates; i.e., ≤ 4.2 months, 4.2 to 5.4 months, 5.4 to 9.2 months, and > 9.2 months. The survival rates were 87.4%, 68.6%, 62.3%, and 33.3%; respectively (Figure 2).

The Kaplan-Meier results in Figure 3 for the AVF and in Figure 4 for the CVC are the same as

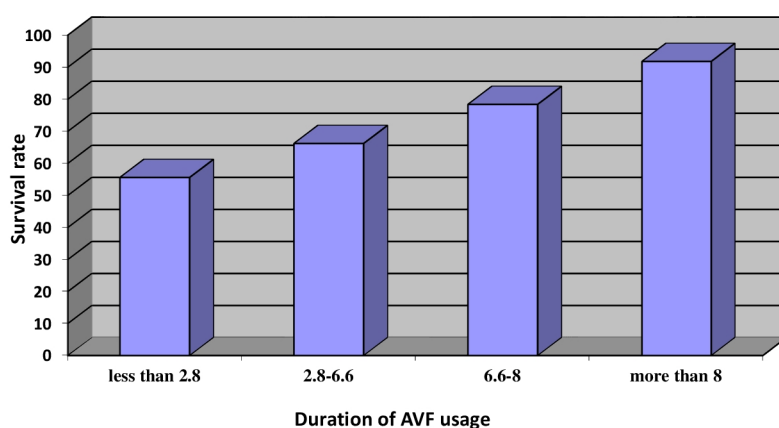


Figure 1. It shows Bar chart of one-year probability of survival (in percentage) according to the duration (in months) of using AVF as a vascular access.

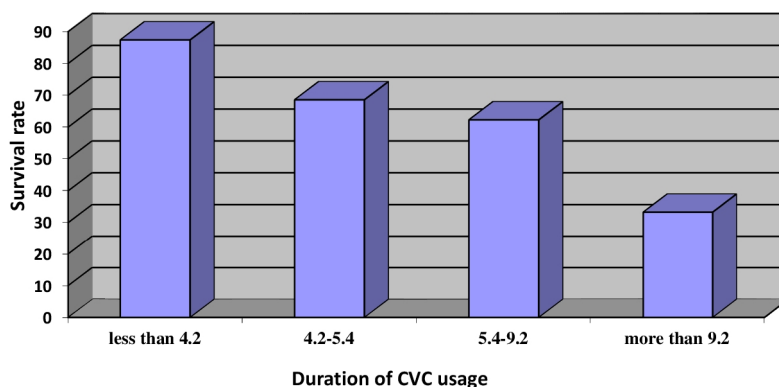


Figure 2. It determines Bar chart of one-year probability of survival (in percentage) according to the duration (in months) of using CVC as a vascular access.

Table 3. Extracted Rules of the C5.0 Algorithm for CVC Usage and One-year Survival

If	Then
Duration of CVC Usage ≤ 4.2	Survival rate is 87.4
$4.2 < \text{Duration of CVC Usage} \leq 5.4$	Survival rate is 68.6
$5.4 < \text{Duration of CVC Usage} \leq 9.2$	Survival rate is 62.3
Duration of CVC Usage > 9.2	Survival rate is 33.3

Note: Duration of CVC usage is mentioned as months.

the C5.0 algorithm survival probabilities, which were confirmed.

Risk of Mortality and the Duration of AVF Usage

In Table 4, the hazard ratios of HD patient mortality in the four categories of AVF usage (i.e., ≤ 2.8 months, 2.8 to 6.6 months, 6.6 to 8 months, and > 8 months) during the first year of HD treatment were compared. The hazard ratio for mortality in the mentioned AVF duration use ranges were 6.90 (95% CI: 4.60 - 10.30), 4.80 (95%

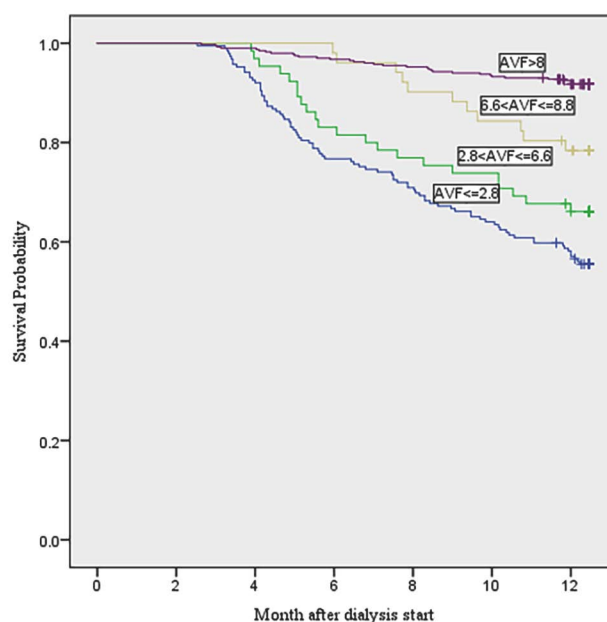


Figure 3. It mentions Kaplan-Meier survival curve according to the duration of using AVF (in months) as a vascular access.

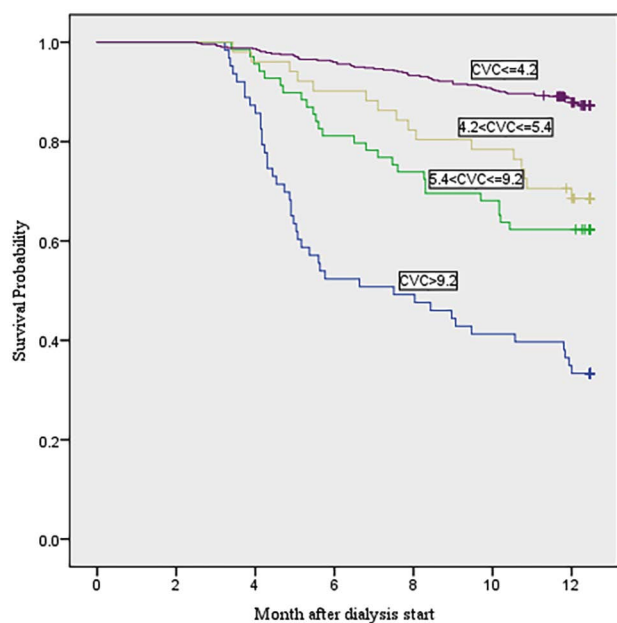


Figure 4. It shows Kaplan-Meier survival curve according to the duration of using CVC (in months) as a vascular access.

CI: 2.80 - 8.22), 2.71 (95% CI: 1.37 - 5.36), and 1.00 (reference); respectively.

As shown in Table 4, three steps of adjustments were applied to control the effect of confounding factors. After all adjustments (i.e., age, sex, the presence of anemia, BMI, underlying etiology of ESRD, HD session indices, biochemical and hematological investigations) the hazard ratios for the mentioned time periods were 5.03 (95% CI: 3.20 - 8.00), 3.80 (95% CI: 2.10 - 6.90), 2.03 (95% CI: 1.01 - 4.30), and 1.00 (reference); respectively. Between

the adjusted models, adding HD session indices (type of dialyzer, the average blood pressures and pulse rates, and kt/v) as confounding factors to the models was more effective in decreasing hazard ratios.

Risk of Mortality and the Duration of CVC Usage

As shown in Table 5, the hazard ratio for mortality in the four CVC duration use ranges (i.e., > 9.2 months, 5.4 to 9.2 months, 4.2 to 5.4 months, and ≤ 4.2 months) were 8.80 (95% CI: 6.00 - 13.00), 3.56 (95% CI: 2.26 - 5.61), 2.72 (95% CI: 1.60 - 4.71), and 1.00 (reference); respectively in the unadjusted model. After adjustment for all confounding variables, these results were 6.00 (95% CI: 3.80 - 9.41), 2.41 (95% CI: 1.45 - 4.02) and 2.33 (95% CI: 1.30 - 4.20).

DISCUSSION

A large number of patients undergoing HD die every year and the type of vascular access has an important role in hospitalization and mortality of these patients.¹

As an initial access and compared with patients using an AVF, previous studies have shown a higher mortality rate in patients using a CVC, which could be due to a higher rate of infection, more inflammation, and a higher rate of cardiovascular events.^{11,17,25,26} Our study was consistent with the previous studies regarding the higher mortality of patients using CVCs but from a different aspect. The present study has shown that in the first year

Table 4. Unadjusted and Adjusted HR (95% CI) of Mortality Based on the Duration of AVF

	≤ 2.8 months	2.8 to 6.6 months	6.6 to 8 months	≥ 8 months
Unadjusted	6.90 (4.60 - 10.30)	4.80 (2.80 - 8.22)	2.71 (1.37 - 5.36)	1.00 (reference)
Model 1 ^a	6.35 (4.10 - 9.84)	4.13 (2.30 - 7.50)	2.55 (1.23 - 5.30)	1.00 (reference)
Model 2 ^b	5.30 (3.40 - 8.30)	3.66 (2.02 - 6.65)	2.13 (1.02 - 4.45)	1.00 (reference)
Model 3 ^c	5.03 (3.20 - 8.00)	3.80 (2.10 - 6.90)	2.03 (1.01 - 4.30)	1.00 (reference)

^aAdjusted for age, sex, underlying etiology of ESRD, BMI, and presence of anemia

^bAdjusted for variables in model 1 plus type of dialyzer (high flux, low flux), the average blood pressures, pulse rates, and kt/v

^cAdjusted for variables in model 2 plus pre-BUN, post-BUN, and serum albumin

Table 5. Unadjusted and Adjusted HR (95% CI) of Mortality Based the Duration of CVC Use

	≥ 9.2 months	5.4 to 9.2 months	4.2 to 5.4 months	≤ 4.2 months
Unadjusted	8.80 (6.00 - 13.00)	3.56 (2.26 - 5.61)	2.72 (1.60 - 4.71)	1.00 (reference)
Model 1 ^a	7.10 (4.60 - 11.00)	3.00 (1.80 - 4.90)	2.43 (1.35 - 4.40)	1.00 (reference)
Model 2 ^b	6.20 (4.00 - 10.00)	2.52 (1.51 - 4.20)	2.35 (1.31 - 4.23)	1.00 (reference)
Model 3 ^c	6.00 (3.80 - 9.41)	2.41 (1.45 - 4.02)	2.33 (1.30 - 4.20)	1.00 (reference)

^aAdjusted for age, sex, underlying etiology of ESRD, BMI, and presence of anemia

^bAdjusted for variables in model 1 plus type of dialyzer (high flux, low flux), the average blood pressures, pulse rates, and kt/v

^cAdjusted for variables in model 2 plus pre-BUN, post-BUN, and serum albumin

of starting HD, as the contribution of the CVC as a vascular access increases, the mortality rate rises markedly. In contrast, as the contribution of the AVF increases, the survival rate of patients increases significantly.

For each type of vascular access (AVF and CVC) we categorized the durations into different ranges based on the mortality rate as an outcome, which was done using the C5.0 algorithm. Because of the small number of tunneled CVCs and AV grafts, just AVF and non-tunneled CVC were considered for analysis.

According to the results of the C5.0 algorithm, the survival benefit of using an AVF was more prominent when it was used for more than eight months in the first year. On the other hand, using a CVC for more than almost four months was associated with a significantly higher mortality rate. Although the association of access type duration with mortality declined with the adjustment of confounding factors, the survival advantage of the AVF and disadvantage of the CVC persisted even after adjusting for the potential confounders. Besides, with the passing of time, the survival disadvantage of non-users of AVFs increased dramatically to an almost five-fold mortality rate for patients who used an AVF for < 2.8 months compared to those with > 8 months. As the contribution of other accesses was negligible, it could be concluded that switching from a CVC to an AVF should be done as early as possible, particularly within the first four months of starting HD. It is noteworthy that using tunneled CVCs was not a common practice at the time of the study in the affiliated HD centers.

Our survey was in agreement with previous findings indicating that using CVC in comparison to AVF resulted in higher mortality in patients undergoing dialysis.^{11,12,15-17,19} Clinical practice guidelines recommend AVF as the preferred access type compared to the CVCs and AV graft because of the lower rate of morbidity and mortality.^{27,28} Moreover, a systematic review of the association between HD access type and clinical outcomes found that the use of AV grafts and CVCs led to higher risks of infection, hospitalization, and mortality as compared with AVF.²⁹ However, our findings emphasized the association between the mortality and the duration of use of the two main access types, which, to the researchers' best knowledge,

was not addressed in previous studies.

One of the strengths of our study is the adjustment for potential confounding factors such as age, underlying etiology of ESRD, BMI, the presence of anemia, serum albumin level, flux type of filters, blood pressure, and dialysis indices.

Our study adds to previous surveys on the association between the duration of use of each access type and HD patient mortality within the first year of starting HD. This study had some limitations. Some patients were ignored because of missing data. The cause of death (i.e. cardiovascular vs non-cardiac) was not available in the database. One of the other weaknesses of the study was the small number of patients using AV grafts and tunneled CVCs. Although the quality of data was checked and the out-of-acceptable range values were removed before the analysis, the quality of data could be affected by the manual entry of data by the HD staff. Besides the mentioned limitations, we did not have data on whether the patients had a planned start of HD with an AVF or an emergency start. Patients who have a timely referral to a nephrologist and already created an AVF before starting maintenance, have less morbidity and mortality.^{30,31}

CONCLUSION

In conclusion, our study has shown that regardless of the type of initial vascular access, the total amount of time on a particular type of access is also important in mortality. Our findings put emphasis on the role of early conversion of a CVC to an AVF on mortality and recommend restricting the duration of use of CVCs to less than four months because beyond that mortality will increase significantly.

ACKNOWLEDGEMENTS

The present article was extracted from Firouraghi's MSc. thesis in Medical Informatics, Faculty of Management and Medical Information Sciences, Shiraz University of Medical Sciences, Shiraz, Iran. The authors would like to thank the Research Vice-Chancellor of SUMS for financially supporting the research (Contract No. 94-7482), Center for Development of Clinical Research of Nemazee Hospital, and Dr. Nasrin Shokrpour for editorial assistance. In addition, the present study could not be done without the cooperation

of SUMS Special Diseases Affairs, especially Dr. Mohammadreza Morvaridi.

CONFLICT OF INTEREST

The authors declare no conflict of interest. The work presented here has not been published previously in whole or part, except in abstract format.

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Received March 2019
Revised May 2019
Accepted August 2019