Association of early loss of primary functional patency of arteriovenous access with mortality in incident hemodialysis patients

A nationwide population-based observational study

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Abstract

The long-term survival and life quality of hemodialysis (HD) patients depend on adequacy of dialysis via a well-functioning vascular access. Loss of primary functional patency (PFP) of an arteriovenous access (AVA) eventually happens in HD patients. The association between time to loss of PFP of AVAs and mortality in HD patients remains unclear. The retrospective nationwide population-based cohort study compared the hazards of mortality with time to loss of PFP. We enrolled 1618 adult incident HD patients who received HD via AVAs for at least 90 days between January 1, 2001 and December 31, 2013. They were divided into early (≤1 year) and late (>1 year) loss of PFP according to intervention-free intervals (time from first successful cannulation to percutaneous transluminal angioplasty [PTA]). Patients with early loss of PFP were older; had more clinic visits annually and higher Charlson comorbidity index scores; were associated with higher proportions of diabetes mellitus, coronary artery disease, heart failure, stroke, chronic obstructive pulmonary disease, cancer, and use of arteriovenous graft, diuretic, antidiabetic drugs, and aspirin (all \(P<.05\)). Kaplan–Meier analysis revealed the cumulative incidence of mortality was significantly higher in patients with early loss of PFP (log-rank test; \(P<.01\)). After adjustment, early loss of PFP was independently associated with a higher risk of mortality (adjusted hazard ratio, 1.21; 95% confidence interval, 1.01–1.45; \(P=.045\)). Regarding the impact of time to PTA on mortality, patients with intervention-free intervals of ≤3, 3 to 6, and 6 to 12 months had similar trends of lower survival. Early loss of PFP is an independent risk factor for mortality in chronic HD patients. A comprehensive strategy for maintaining PFP and reducing dysfunctional AVAs may be required.

Abbreviations: AVA = arteriovenous access, AVF = arteriovenous fistula, AVG = arteriovenous graft, ESRD = end-stage renal disease, HD = hemodialysis, NHI = National Health Insurance, NHIRD = The National Health Insurance Research Database, PFP = primary functional patency, PTA = percutaneous transluminal angioplasty.

Keywords: arteriovenous access, hemodialysis, mortality, primary functional patency

1. Introduction

Patients with end-stage renal disease (ESRD) require a vascular access for hemodialysis (HD). The survival and life quality of these patients depend on the adequacy of dialysis via a well-functioning vascular access.\[1\] Creating and maintaining a well-functioning vascular access is a critical challenge.

First, the high incidence of failure to mature of arteriovenous fistulas (AVFs) is an intractable problem after creation.\[2–4\] Second, even after maturation, the loss patency of AVFs still frequently occurs.\[5–7\] Compared with AVFs, the functional survival of arteriovenous grafts (AVGs) is much shorter.\[8\] The major causes of loss patency of arteriovenous access (AVA) are stenosis and thrombosis.\[9\] Percutaneous transluminal angioplasty (PTA) is a safe, effective, and standard treatment for stenotic lesions of AVAs.\[10,11\] In addition, it is also a salvage method for nonfunctional AVAs including nonmaturing AVFs\[12,13\] and thrombosed AVFs and AVGs.\[14–16\]

Primary functional patency (PFP) is defined as the interval from time of first successful cannulation for HD to any intervention to maintain or reestablish patency.\[17\] Accordingly, PFP reflects the functional period of AVA after first successful use. Vascular access dysfunction is associated with subsequent major adverse cardiovascular events in chronic HD patients,\[18\] but the
association between the PFP of AVAs and all-cause mortality in incident HD patients remains unclear. Therefore, we retrospectively evaluated the associations between the PFP of AVAs and all-cause mortality of incident HD patients in a large-scale nationwide cohort.

2. Methods

2.1. Data source

Taiwan’s National Health Insurance (NHI) program was implemented on March 1, 1995, and currently provides insurance coverage for >99% of the country’s total population. The National Health Insurance Research Database (NHIRD), which is managed by the Bureau of NHI, contains claims data and detailed information on health services; this includes demographic data, ambulatory care, and records of clinic visits, hospital admissions, dental services, operations, prescriptions, disease status, and dialysis history. Patients with ESRD who receive dialysis are issued catastrophic illness certificates, which allow the copayment for all ESRD-related care to be waived. Because all expenditures related to dialysis are fully reimbursed by the NHI system, the claims data provide a comprehensive data source for information on these patients. The present study obtained information on all dialysis patients registered in the Catastrophic Illness Dataset, which is a subset of the NHIRD for beneficiaries with a catastrophic illness profile. In the NHIRD, diseases are classified according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Because the data are de-identified and encrypted, this study was exempted from a full review and approved by the Institutional Review Board of Shin Kong Wu Ho-Su Memorial Hospital (approval number 20160910R).

2.2. Study design and cohort

Figure 1 shows the process of selecting patients for the study cohorts. From the Catastrophic Illness Dataset, we identified HD patients who had received HD therapy for at least 90 days between January 1, 1996, and December 31, 2013. For the 1996 to 2000 period, we used a look-back period to identify prevalent HD patients. This 5-year look-back period was used to determine whether a patient had any prior HD records and to reduce false incident cases. Among the patients who met these criteria, we excluded patients who did not have an AVA within 1 year of before or after the start of HD. Among HD patients who had an AVA created within 1 year of the start of HD, we excluded those who were aged <18 or >100 years, had died within 1 year or had a follow-up period of <1 year from first cannulation, had tunneled central venous catheters, had temporary double-lumen catheter placements or reconstruction of the access before PTA, had shifted to peritoneal dialysis or received a kidney transplant, had PTA history before the index date, or had missing information. The eligible incident HD patients whose AVA was created between 2001 and 2013 were enrolled in the study.

2.3. Outcome measures and comorbidity

Major comorbid diseases diagnosed before the index date were defined as baseline comorbidities according to the claims data. These comorbidities were identified by examining the ICD-9-CM codes (Table S1, http://links.lww.com/MD/C364) for hypertension, diabetes, hyperlipidemia, coronary artery disease, congestive heart failure (CHF), stroke, chronic obstructive pulmonary disease (COPD), malignancy, and peripheral arterial occlusive disease. Charlson comorbidity index (CCI) was used to quantify the baseline comorbidities. Long-term medications thought to be associated with all-cause mortality, including antihypertensive drugs such as angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers, beta blockers, calcium channel blockers, diuretics, antidiabetic drugs, statins, and aspirin, were also recorded.

To clarify the association between the PFP of AVAs and all-cause mortality in incident HD patients, the patients were divided into those who had an intervention-free interval of ≤1 year after commencing HD (early PFP loss) or not (late PFP loss). Time to death was defined as the duration from the index date to death. The study endpoints were death, withdrawal from the NHI program, or the end of 2013.

2.4. Statistical analysis

Demographic and clinical characteristics of the study cohort were summarized using proportions and the mean ± standard deviations. We used Chi-squared tests and t tests to compare categorical and continuous variables, respectively. The cumulative incidence of all-cause mortality was calculated using the Kaplan–Meier method, and pairs of groups were compared using log-rank tests. Cox proportional hazard models were used to estimate the relative risk of all-cause mortality in patients with the loss of PFP in ≤1 year compared with the control cohort. Confounders, including all the variables listed in Table 1, were adjusted in the multivariate Cox analysis to estimate the adjusted hazard ratios (aHRs). Comorbid diseases were modeled using nonreversible time-dependent binary covariates for the survival analyses, because these diseases may have been present at baseline or may have developed during the follow-up period. Additionally, subgroup analysis was performed to determine the interactive effects of comorbidities or medications and the loss of PFP on the risk of all-cause mortality. Furthermore, we conducted a series of analyses defining the early loss of PFP to minimize any misclassification bias, by using quantiles of intervention-free intervals of ≤3, 3 to 6, 6 to 12, and >12 months. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC). Two-tailed P-values of <.05 were considered statistically significant.

3. Results

3.1. Characteristics of the study population

Table 1 shows the characteristics of the study population. We enrolled 1618 incident HD patients whose AVA was created within 1 year of start of HD in the 2001 to 2013 period, and who received at least 90 days of HD therapy via AVAs. Among these patients, 860 had early PFP loss (intervention-free interval of ≤1 year), and the others had late PFP loss after commencing HD. The mean age of the patients was 63.25 ± 12.29 years. The mean follow-up periods were 3.88 ± 2.77 years in patients with early PFP loss, and 4.50 ± 3.01 years in those with late PFP loss. Patients with early loss of PFP were older and had a higher proportion of AVGs and more clinic visits (all P < .05). Furthermore, in these patients, the prevalence was higher for diabetes (P = .002), coronary artery disease (CAD; P = .021), CHF (P = .003), stroke (P = .04), COPD (P = .024), and cancer (P = .045). Finally, these patients had higher diuretic use (P = .02),...
3.2. Association of PFP of AVA with all-cause mortality

Table 2 shows the incidence of death and lists the crude HRs and aHRs for all-cause mortality in patients with the loss of PFP at ≤1 and >1 year after commencing HD. The incidence was 65.61 per 1000 person-years in patients with late PFP loss, and 92.92 per 1000 person-years in those with early PFP loss. Relative to patients with late PFP loss, the HR for all-cause mortality was 1.45 (95% confidence interval [CI], 1.21–1.73) in those with early PFP loss (P < .001). After adjustment for the variables listed in Table 1 and the variables of comorbidities and medications considered as time-dependent covariates, the early PFP loss remained a significant risk factor for all-cause mortality among the patients (aHRs, 1.23, 1.22, and 1.21; 95% CIs, 1.02–1.47, 1.02–1.46, and 1.01–1.45, respectively; all P < .05). The Kaplan–Meier curves for the cumulative incidence of all-cause mortality in patients with early and late PFP loss over the 13-year follow-up period are shown in Figure 2. Mortality was higher in patients with the early loss of PFP (log-rank test; P < .001).

3.3. Impact of time to PTA and mortality

Figure 3 shows the association of time to PTA with mortality. Compared with patients with an intervention-free interval of >1 year, those with an intervention-free interval of ≤3, 3 to 6, or 6 to
12 months remained at a significant risk of all-cause mortality (HRs, 1.48, 1.45, and 1.41; 95% CI, 1.17–1.87, 1.14–1.84, and 1.08–1.85, respectively; all P <.05). However, after adjustment for baseline and full covariates, the patients with an intervention-free interval of ≤3 months remained at a significant risk of all-cause mortality (aHRs, 1.28 and 1.27, respectively; all 95% CI, 1.01–1.61; all P <.05) and the patients with intervention-free intervals of 3 to 6, and 6 to 12 months had similar trends of lower survival.

### 3.4. Subgroup analysis

Table S2, http://links.lww.com/MD/C364, shows the subgroup analysis for the risk of all-cause mortality in patients with an arteriovenous accesses (AVAs).

| Variables | Early primary functional patency loss | Late primary functional patency loss | Total |
|-----------|--------------------------------------|-------------------------------------|-------|
| Male gender | 431 (50.12%) | 379 (50%) | 810 (50.06%) |
| Age | 64.6 ± 11.73 | 61.72 ± 12.75 | 63.25 ± 12.29 |
| Access type | Fistula | 698 (81.16%) | 678 (89.45%) | 1376 (85.04%) |
| Clinic visit frequency, visits per year | 40.85 ± 15.43 | 38.77 ± 15.95 | 39.87 ± 15.71 |
| Comorbidities | Hypertension | 797 (92.67%) | 703 (92.74%) | 1500 (92.71%) |
| Diabetes mellitus | 578 (67.21%) | 453 (59.76%) | 1031 (63.72%) |
| Hyperlipidemia | 362 (42.09%) | 297 (39.18%) | 659 (40.73%) |
| Diuretics | 593 (68.95%) | 481 (63.46%) | 1074 (66.38%) |
| ACEI or ARB | 616 (71.63%) | 525 (69.26%) | 1141 (70.52%) |
| Antihypertensive drugs | 763 (88.72%) | 661 (87.2%) | 1424 (88.01%) |
| Medications | 616 (71.63%) | 525 (69.26%) | 1141 (70.52%) |
| β blockers | 508 (59.07%) | 447 (58.97%) | 955 (59.02%) |
| Calcium-channel blockers | 678 (78.84%) | 597 (78.76%) | 1275 (78.8%) |
| Diuretics | 593 (68.95%) | 481 (63.46%) | 1074 (66.38%) |
| Antihypertensive drugs | 535 (62.21%) | 410 (54.09%) | 945 (58.41%) |
| 2–3 | 113 (13.14%) | 141 (18.6%) | 254 (15.7%) |
| 4–6 | 298 (34.65%) | 318 (41.99%) | 616 (38.07%) |
| ≥7 | 449 (52.21%) | 299 (39.45%) | 748 (46.23%) |
| Charlson comorbidity index score, CHF | 331 (38.49%) | 239 (31.53%) | 570 (35.23%) |
| CAD | 362 (42.09%) | 297 (39.18%) | 659 (40.73%) |
| Hypertension | 797 (92.67%) | 703 (92.74%) | 1500 (92.71%) |
| Diabetes mellitus | 578 (67.21%) | 453 (59.76%) | 1031 (63.72%) |
| Hyperlipidemia | 362 (42.09%) | 297 (39.18%) | 659 (40.73%) |
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| ≥7 | 449 (52.21%) | 299 (39.45%) | 748 (46.23%) |

**cHR = crude hazard ratio, CI = confidence interval, PY = person-years.**

| Events | PY | Incidence * | aHR (95% CI) | aHR (95% CI) | aHR (95% CI) | aHR (95% CI) |
|--------|----|------------|-------------|-------------|-------------|-------------|
| Early loss of PFP | 270 | 2905.81 | 92.92 (81.8 – 104.0) | 1.45 (1.21 – 1.73) | .000 | 1.23 (1.02 – 1.47) | .027 |
| Late loss of PFP | 224 | 3414.02 | 65.61 (57.0 – 74.2) | 1.22 (1.02 – 1.46) | .032 | 1.21 (1.01 – 1.45) | .045 |

*aHR* = adjusted hazard ratio, cHR = crude hazard ratio, CI = confidence interval, PY = person-years.
intervention-free intervals of ≤1 and >1 year after commencing HD. In the subgroup analysis, the aHRs for the all-cause mortality of patients with early PFP loss were higher among patients who were men, had AVFs, and had CCI scores of 0-1 (all $P < .05$). Figure 4 shows the subgroup analysis of comorbidities and medications associated with the risk of all-cause mortality in the same populations. In the subgroup analysis, higher aHRs for the all-cause mortality of patients with early PFP loss were observed among patients with and without diabetes mellitus or hypertension; without dyslipidemia, CAD, or stroke; with CHF; and among those who did not use statins but used aspirin (all $P < .05$). However, interactions between the PFP of AVAs and the aforementioned variables were nonsignificant (all $P > .05$).

### 4. Discussion

Vascular access is a lifeline for HD patients. The failure of vascular access, particularly the loss of functional patency of vascular access, is a cause of morbidity, discomfort, inconvenience, and increased costs.\[19\] The patient factors affecting the patency of AVF include age, diabetes, arteriosclerosis, vessel characteristics, smoking, and predialysis hypotension.\[20–22\] The primary and secondary patency rates for AVFs are superior to those for AVGs.\[23\] The high prevalence of comorbidities usually makes the creation of vascular access difficult, and many of these patients may have insufficient vasculature for maturation.\[23\]

In this population-based retrospective cohort study, patients with the early loss of PFP were older, had a higher proportion of AVGs, diabetes, CAD, CHF, stroke, COPD, and malignancy, and higher CCI scores. According to the United States Renal Data System 2015 annual data report, the survival of HD patients decreases with age, and diabetic HD patients have poorer survival than do those without diabetes.\[24\] Cancer, CHF, cardiovascular and cerebrovascular diseases, and COPD are the main causes of mortality. However, in the present study after adjustment for all confounders, the incident HD patients with AVAs who had early PFP loss were independently associated with an increased risk of mortality. Therefore, early stenotic or thrombosed vascular accesses were independently associated with mortality.

To evaluate the impact of time to PTA on mortality, we divided the patients with AVAs who had an intervention-free interval of ≤1 year into 3 groups according to the time to PTA (≤3, 3–6, and 6–12 months). The incident HD patients with an intervention-free interval of ≤3 months remained at a significant risk of all-cause mortality after adjustment for all covariates. Probably, incident HD patients with inadequate maturation of AVAs to maintain dialysis after successful cannulation have more influence on mortality. Moreover, similar trends of lower survival were observed among those with an intervention-free interval of 3 to 6 and 6 to 12 months. All in all, incident patients...
with inadequate maturation of AVAs to maintain HD therapy or early stenosis or thrombosis of AVAs had higher mortality.

In the present study, patients with late PFP loss had longer survival than did those with the early loss of primary patency. Mature AVAs with late stenosis or thrombosis probably had less influence on mortality than did early stenosis or thrombosis of AVAs. Therefore, the regular monitoring and surveillance of AVAs and vigorous improvement of their function in patients with the early loss of primary patency is necessary and beneficial.

The primary strengths of this study are the use of longitudinal population-based data, which are representative of the general population in Taiwan. However, this study has limitations. First, the NHIRD does not include detailed information on smoking habits, systolic or diastolic blood pressure, arterial or venous diameter of AVFs, anastomosis type of AVFs, far-infrared therapy, early referral, and access flow rates. These factors affect the patency of AVAs. Second, although PTA is efficacious in the correction of stenotic or thrombotic AVAs, no data regarding the characteristics of AVAs are available for after the intervention. Third, the results from a retrospective cohort study are of a lower statistical quality in comparison with prospective studies. Forth, information on the cause of death is not available within the NHIRD. Finally, because most of Taiwan’s population is of Chinese ethnicity, the results might not be generalizable to populations of other ethnic backgrounds.

In conclusion, this population-based retrospective cohort study revealed that the early loss of PFP of AVAs is an independent risk factor for the mortality of incident HD patients. Careful monitoring and surveillance of AVAs are required in these patients. The early detection and management of malfunctioning AVAs may be beneficial for decreasing mortality in incident HD patients.

Author contributions

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