Prehemodialysis arteriovenous access creation Is associated with better cardiovascular outcomes in patients receiving hemodialysis: A population-based cohort study

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Background. Cardiovascular disease contributes to nearly half of the mortalities in patients with end-stage renal disease. Patients who received prehemodialysis arteriovenous access (pre-HD AVA) creation have divergent cardiovascular outcomes.

Methods. We conducted a population-based cohort study by recruiting incident patients receiving HD from 2001 to 2012 from the Taiwan National Health Insurance Research Database. Patients' characteristics, comorbidities, and medicines were analyzed. The primary outcome of interest was major adverse cardiovascular events (MACEs), defined as hospitalization due to acute myocardial infarction, stroke, or congestive heart failure (CHF) occurring within the first year of HD. Secondary outcomes included MACE-related mortality and all-cause mortality in the same follow-up period.

Results. The patients in the pre-HD AVA group were younger, had a lower burden of underlying diseases, and were more likely to use erythropoiesis-stimulating agents. The patients with pre-HD AVA creation had a marginally lower rate of MACEs but a significantly 34% lower rate of CHF hospitalization than those without creation (adjusted hazard ratio: 0.66 [95% confidence interval: 0.49–0.89]). In addition, the pre-HD AVA group exhibited a nonsignificantly lower rate of MACE-related mortality but a significantly 52% lower rate of all-cause mortality than the non-pre-HD AVA group. Sensitivity analyses obtained consistent results.

Conclusions. Pre-HD AVA creation is associated with a lower rate of CHF hospitalization and overall death in the first year of dialysis.

Prehemodialysis Arteriovenous Access Creation Is Associated With Better Cardiovascular Outcomes in Patients Receiving Hemodialysis: A Population-Based Cohort Study

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Abstract

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Results. The patients in the pre-HD AVA group were younger, had a lower burden of underlying diseases, and were more likely to use erythropoiesis-stimulating agents. The patients with pre-HD AVA creation had a marginally lower rate of MACEs but a significantly 34% lower rate of CHF hospitalization than those without creation (adjusted hazard ratio: 0.66 [95% confidence interval: 0.49–0.89]). In addition, the pre-HD AVA group exhibited a nonsignificantly lower rate of MACE-related mortality but a significantly 52% lower rate of all-cause mortality than the non-pre-HD AVA group. Sensitivity analyses obtained consistent results.

Conclusions. Pre-HD AVA creation is associated with a lower rate of CHF hospitalization and overall death in the first year of dialysis.

Keywords

Congestive heart failure, Hemodialysis, Major adverse cardiovascular events, Mortality, Prehemodialysis arteriovenous access, Taiwan

Introduction

End-stage renal disease (ESRD) has become a major public health issue because of its prevalence in more than 2 million people worldwide and increasing incidence. Compared with general cohorts, patients with ESRD have a higher mortality rate (>50% within 5 years)(1). Among the major causes of mortality, cardiovascular (CV) disease contributes nearly half of events in this population(2). Therefore, identifying management of CV complications is essential.

Pre-hemodialysis (pre-HD) care has been proved to ameliorate the outcomes of patients with ESRD maintained on HD(3, 4). Timing of arteriovenous access (AVA) creation is one of the crucial methods in care planning. It prevents not only the complications of delayed dialysis but also catheter-related infectious events(5). However, CV outcomes following pre-HD AVA surgery are currently divergent. Once pre-HD AVA is created, cardiac output increases and leads to functional and structural changes of the heart, lungs and vasculature(6, 7). London and colleagues reported that the arteriovenous shunt might result in chronic flow overload and cause cardiac hypertrophy(8). Nakhoul et al observed that nitric oxygen production was decreased in patients with arteriovenous fistula and contributed to pulmonary hypertension(9). Korsheed and colleagues reported improved arterial stiffness, better ejection fraction, and lesser heart damage after native fistula creation(10, 11). Variation in laboratory and imaging parameters makes it difficult to predict the clinical outcomes. Several small-scale studies have reported negative clinical CV results following fistula creation(12-14), while a national study using the United States Renal Data System showed that pre-HD fistula use was strongly associated with lower CV mortality(15). At present, only a few large-scale studies have explored the association between AVA creation and CV-related hospitalization.

Although ESRD is reported to have the highest prevalence in Taiwan compared with other countries, the 5-year-survival rate of patients with ESRD seems better in Taiwan(1). The Taiwan

pre-ESRD pay-for-performance program, involving education and promotion of pre-HD AVA establishment, might have contributed to the higher survival rate(16). In Taiwan, more than half of the patients undergoing dialysis received access surgery before their first dialysis session, and access creation had been completed in more than 80% of them before their chronic dialysis sessions(17). Our study investigated the association between timing of AVA creation and CV outcomes in patients who underwent HD. We hypothesized that pre-HD AVA creation improves the CV outcomes of patients undergoing HD.

Materials and Methods

Data source

We conducted a retrospective cohort study by using the Taiwan National Health Insurance Research Database (NHIRD), which is a national population-based database, provided by Taiwan National Health Insurance (NHI). The NHI is a single-payer, universal and compulsory healthcare program initiated in 1995 and covers 99.9% of Taiwanese residents(18). In this study, we used a representative subset of 1 million persons randomly sampled from the 24 million beneficiares from the Taiwan NHI between 2000 and 2013. No significant difference was observed between the subset and NHIRD in the distribution of sex, age, and average insured payroll-related amount(19). All identities in the NHIRD are encrypted to guarantee patient privacy. This study was approved by the Institutional Review Board of Ditmanson Medical Foundation Chia-Yi Christian Hospital in Taiwan (CYCH-IRB No. 2018054). Informed consent was waived owing to the absence of interference in decision-making processes for medical care.

Study design, identification and grouping of study subjects

We identified patients with chronic kidney disease (CKD) who began HD sessions during 2001 to 2012 by using the NHI procedure codes of receiving HD in the LHID2000. The day of first HD session was employed as the index date. CKD was defined as patients receiving at least 2 outpatient diagnoses according to International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes within the 1 year prior to the index date. Patients were excluded if they were aged <20 years, had ever received peritoneal dialysis, or had kidney transplantation before or during their first year of HD. We combined patients receiving native fistula and artificial graft for analysis because of their similar CV results(20). Patients in whom AVA was created <1 month prior to the index date were excluded owing to their inappropriate

106 access usage according to the guidelines(21, 22). We further excluded patients who received
107 implantation of HD catheters, namely tunneled and nontunneled catheters, before the index date.
108
109 Data and definitions of study variables
110 We analyzed the characteristics, comorbidities, and medicines of the included patients.
111 Comorbidities were defined as patients experiencing at least 1 hospitalization or 2 ambulatory
112 visits within the 1 year prior to the index date due to the corresponding ICD-9-CM codes of any
113 of the following illnesses: hypertension (HTN), ischemic heart disease (IHD), congestive heart
114 failure (CHF), cerebrovascular accident (CVA), peripheral vascular disease (PVD), dysrhythmia,
115 diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), peptic ulcer disease
116 (PUD), liver disease, cancer, and dementia. Additionally, to denote the disease burden we
117 applied the Taiwan index, which is a comorbidity index for mortality prediction validated for
118 Taiwanese patients with incident HD(23). Medicine usage including erythropoiesis-stimulating
119 agent (ESA), antiplatelet agent, and anticoagulant agent was defined as more than 2 prescriptions
120 during ambulatory visits within the 1 year prior to the index date and was expressed in terms of
121 the anatomical therapeutic chemical classification system.
122
123 Outcomes of study subjects
124 Primary outcome of the present study was major adverse cardiovascular events (MACEs),
125 which was defined as ICD-9-CM-based hospitalizations for acute myocardial infarction (AMI),
126 CVA, or CHF that occurred within the 1 year after the first HD session. To validate the findings
127 regarding CHF hospitalization rate, we performed sensitivity analyses excluding patients without
128 AVA creation and patients not receiving regular HD in the first year of HD. Secondary outcomes
129 were MACE-related and blood stream infection (BSI)-related mortality, which was defined as

death resulting from MACE and BSI in corresponding ICD-9-CM codes, respectively, and all-cause mortality within the same follow-up period following the first dialysis.

Statistical analysis

We compared patient characteristics, comorbidities, and medical prescriptions between the pre-HD AVA and non-pre-HD AVA groups. Continuous data were reported as a median or mean and were analyzed using the Mann–Whitney test or independent t test as appropriate. Categorical data were reported as percentages and were analyzed using the Chi-squared test. We constructed our propensity score model using variables related to patient characteristics, comorbidities, and medical prescriptions, and calculated model using the logistic regression method. We performed 1:1 matching using the nearest neighbor algorithm without replacement and with a .05 caliper width to reduce imbalances between groups. After matching, we used absolute standardized differences (ASD) to evaluate the balance between groups. An ASD threshold of 10% was used to delineate good and poor balance.

We evaluated the cause-specific mortality and overall mortality over 1 year using weighted cumulative incidence curves considering competing risks of death. We applied subdistributional hazard models to calculate crude and adjusted hazard ratios (HRs). Robust sandwich variance was used to correct the correlated data structure after matching. A 2-tailed P value of $<.05$ indicated statistical significance. SAS version 9.4 (SAS Institute, Inc.) was used for analyses.

149 **Results**

150 Figure 1 illustrates the research design and sampling strategy. Overall, this study analyzed
151 3147 patients—837 patients (26.6%) receiving pre-HD AVA creation and 2310 patients (73.4%)
152 not receiving pre-HD AVA creation.

153 The baseline characteristics of the recruited patients are presented in Table 1. The median
154 age of patients with pre-HD AVA creation was lower than that of those without (66 years vs 71
155 years, ASD: 29.9%). No obvious difference was observed in terms of sex between the 2 groups.
156 Considering comorbidities, the patients in the pre-HD AVA group had lower proportions of
157 CVA, dysrhythmia, COPD, liver disease, and dementia than those in the non-pre-HD AVA
158 group. The groups exhibited similar proportions of patients with IHD, CHF, PVD, and DM. The
159 mean Taiwan index of pre-HD AVA group was significantly lower than that of the non-pre-HD
160 AVA group (5.55 ± 4.0 vs 6.55 ± 4.4, ASD: 23%). Additionally, more patients with pre-HD
161 AVA creation received ESA than did those without pre-HD AVA creation (81.72% vs 34.81%,
162 ASD: 108%), whereas the prescription of antiplatelet agent or anticoagulant agent was similar
163 among the groups.

164 Table 2 shows the primary and secondary outcomes of the pre-HD AVA and non-pre-HD
165 AVA groups. The patients with pre-HD AVA creation had a lower rate of MACEs during the
166 follow-up period than did those without pre-HD AVA creation (15.29% vs 20.00%, crude HR:
167 0.73 [95% confidence interval (CI): 0.6–0.89]), but the effect became nonsignificant after
168 matching for age, sex, comorbidities, and medicine (adjusted HR: 0.89 [95% CI: 0.71–1.11], P =
169 .3, Figure 2). We further analyzed the MACEs separately and observed that patients with pre-HD
170 AVA creation had a 34% lower CHF hospitalization rate after matching (adjusted HR: 0.66
171 [95% CI: 0.49–0.89], $P < .01$, Figure 2). We validated the findings of CHF hospitalization rate
172 by sensitivity analyses. A significantly lower CHF hospitalization rates, ranging from 38% to

53%, was observed in the pre-HD AVA group, which was similar to the previous results.

Regarding secondary outcomes, we revealed that patients in the pre-HD AVA group had a marginally lower rate of MACE-related mortality (adjusted HR: 0.7 [95% CI: 0.45–1.08], $P = .1$, Figure 3), a 69% lower rate of BSI-related mortality (adjusted HR: 0.31 [95% CI: 0.22–0.46], $P < .01$, Supplementary Figure 1), and a 52% lower rate of all-cause mortality (52%; adjusted HR: 0.48 [95% CI: 0.39–0.6], $P < .01$, Figure 4) than those in the non-pre-HD AVA group. We next examined the outcomes in the propensity-score-matched groups. The patients with pre-HD AVA creation exhibited a nonsignificantly lower rate of MACEs (adjusted HR: 0.91 [95% CI: 0.70–1.17]), a 29% lower rate of CHF hospitalization (adjusted HR: 0.71 [95% CI: 0.5–1.0]), a marginally lower rate of MACE-related mortality (adjusted HR: 0.64 [95% CI: 0.39–1.07]), a 71% lower rate of BSI-related mortality (adjusted HR: 0.29 [95% CI: 0.19–0.42]), and a 54% lower rate of all-cause mortality (adjusted HR: 0.46 [95% CI: 0.36–0.58]) than those without pre-HD AVA creation. These results were consistent with those of the original cohort.

Discussion

In our nationally representative cohort, we observed that patients with pre-HD AVA creation had a 34% lower CHF hospitalization rate and 52% lower all-cause mortality rate than those without during the first year of HD—significant differences. Additionally, we disclosed a marginally lower rate of MACEs and MACE-related mortality during the same follow-up period. Pre-HD AVA creation might be associated with better CV outcomes within the first year of HD.

In this study, the patients with pre-HD AVA creation were younger, had a lesser burden of comorbidities, and had a higher percentage of ESA use (Table 1). Age is a well-established factor affecting postsurgery prognosis. The significantly lower Taiwan index of the pre-HD AVA group indicated the lower disease burden of the patients in the pre-HD AVA group compared with the non-pre-HD AVA group. We also observed that the patients without pre-HD AVA creation were significantly more likely to have CVA, dysrhythmia, COPD, or liver disease than those with pre-HD AVA creation, and those diseases might reflect higher neurologic, respiratory, and coagulatory risks during the operation. In one previous study, patients with dementia had a greater risk of early death and fatal complications postoperatively(24). Thus, patients who were young or had fewer comorbidities were willing to undergo pre-HD AVA surgery. Additionally, a higher proportion of patients receiving ESA might imply more recruitment of pre-HD care, which promotes the possibility of dialysis access creation by education(22).

Our study revealed a significantly lower CHF hospitalization rate within the first year of HD among the patients receiving pre-HD AVA creation (Table 2). Consistent results were obtained for the other matched models. Patients who undergo AVA surgery before HD might avoid delayed HD, thus preventing exacerbated fluid overload and increased CHF risk. The increased cardiac preload after AVA surgery is compensated by a corresponding decrease in

peripheral vascular resistance following surgery(25) and consequent fluid removal during HD sessions. The fluid status of most patients undergoing HD has been proved to achieve a new balance shortly(26, 27). In the Dialysis Outcomes and Practice Patterns Study, Rayner and colleagues observed a low flow rate of the fistula in Japanese patients (28), which might be related to low-caliber vessels in the Asian population. The degree of CV damage due to blood volume following AVA creation might differ according to vascular characteristics. Several studies have supported our findings of CV benefits following pre-HD AVA creation: Ori et al conducted an echocardiographic study to observe cardiac performance before and after AVA creation. A gentle volume overload developed postoperatively but was offset by decreased vascular resistance. The shortening and ejection fractions of the left ventricle were improved 2 weeks after the AVA operation(25). Sandhu and colleagues observed that none of 17 patients receiving native fistula before HD developed CHF during the 6 weeks following surgery. They concluded that the postoperative changes in cardiac index, stroke volume, and vascular resistance were physically minimal and without extra loading of patients' hemodynamics(29). Thus, CHF might not occur or worsen after AVA creation. Further investigation is warranted to clarify the causality of AVA in CV outcomes.

Some studies have obtained contrasting results from ours: MacRae et al noted that a patient undergoing HD developed cardiac failure under a high-flow arteriovenous fistula and concluded that the high fistula flow caused myocardium decompensation with a decline in the ejection fraction(12). Other studies have adopted an opposite viewpoint on ejection fraction alteration following AVA creation(10, 25, 30). Vizinho and colleagues reported that pre-HD AVA creation was associated with a decrease in the subendocardial viability ratio, which predicted a poorer outcome regarding CV hospitalization(13). Nevertheless, a small sample size and lack of CV comorbidity adjustments limit the relevance of their speculation. Reddy et al traced CV changes

of patients following native shunt creation for 2.6 years and observed that remodeling and dysfunction of the right ventricle developing after shunt operation and dialysis initiation caused increased risks of CHF and death(14). However, the absence of controls and uncertainty in the effect of AVA and dialysis on cardiac dysfunction made the supposition inconclusive. More large-scale and close-matching studies should be planned to confirm the relationship.

Considering secondary outcomes, we observed that the patients with pre-HD AVA creation had a nonsignificantly lower rate of MACE-related mortality compared with those without after propensity score matching (Table 2, Figure 3). We believe that this type of mortality is mainly affected by the underlying diseases of patients rather than AVA surgery. The literature has suggested that HTN, IHD, CHF, and DM influence the CV mortality rate for patients undergoing HD(31-33). Because our groups had similar distributions of these diseases, our finding was in fair agreement with the literature. We also evaluated the effect of pre-HD AVA creation on overall mortality and disclosed a 52% lower rate of all-cause mortality in the pre-HD AVA group. In addition to CV disease, catheter-associated infectious disease, mainly those transmitted through the blood stream, is another major cause of mortality in patients undergoing dialysis. Because the difference in MACE-related mortality between the pre-HD AVA and non-pre-HD AVA groups was nonsignificant, we assumed that the lower all-cause mortality might have been related to the 69% reduction in the rate of BSI-related mortality in the pre-HD AVA group (Table 2, Supplementary Figure 1), which was due to lesser usage of HD catheters.

This was a country-based study including all pre-HD patients underlined CKD matched for age, sex, income, comorbidities, and associated medicine. Most studies exploring the effects of pre-HD AVA creation on CV outcomes compared associated parameters before and after surgery(7, 10, 13, 14, 25, 26, 29, 30, 34-37). In addition, some compared the effects before dialysis initiation to exclude the impact of dialysis on CV performance(10, 25, 30, 35, 37).

However, selection bias would have been unavoidable in these studies because patients with pre-HD AVA creation tend to be compliant in medical practice, which would affect their overall outcomes. Furthermore, excluding the dialysis effect appears impractical considering the goal of AVA preparation. Moreover, dialysis is a well-known risk factor of cardiac injury, and its vintage was positively associated with the degree of injury(38). Once the AVA was used for dialysis, evaluating the CV prognoses in combination with HD was difficult. We followed up for 1 year after HD initiation because we assumed that the effect of pre-HD AVA creation would be offset by a longer period of HD. Our study provides another perspective regarding evaluation of the benefits and hazrads of pre-HD AVA surgery.

This study had several limitations. First, the NHIRD is an administrative database in which the identification of comorbidities is based solely on ICD-9-CM codes rather than clinical criteria; misclassifications might thus have occurred, leading to residual confounding. Second, the indications of CHF hospitalization vary among patients and medical facilities. However, the NHIRD does not provide objective parameters of cardiac alteration, such as the level of natriuretic peptide, ejection fraction of ventricles, or pulse wave velocity of vessels, which could support our findings. Third, our study did not consider medications such as rennin–angiotensin–aldosterone system inhibitors, calcium channel blockers, beta blockers, or diuretics, which have been shown to influence CV outcomes in patients undergoing HD(39-41). Lastly, it was difficult to distinguish the absolute effect of pre-HD AVA on CV outcomes in combination with personal compliance and dialysis factors affecting the CV system. Integrated trials comprising data and imaging should be further conducted to corroborate our results.

279 **Conclusions**

280 In this population-based cohort study, patients with pre-HD AVA creation had a 34% lower
281 CHF hospitalization rate and a 52% lower all-cause mortality rate than those without pre-HD
282 AVA creation within the first year of HD. Marginal benefits were also observed in terms of
283 MACEs and MACE-related mortality during the same follow-up period. Pre-HD AVA creation
284 might be associated with better CV outcomes in the first year of HD and should be promoted in
285 patients with late-stage CKD.

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Figure 1(on next page)

Overall Flow Diagram of the Research Design and Sampling Strategy.

AVA: arteriovenous access; HD: hemodialysis; LHID2000: Longitudinal Health Insurance Database 2000, a validated subgroup extracted from the Taiwan National Health Insurance Research Database.

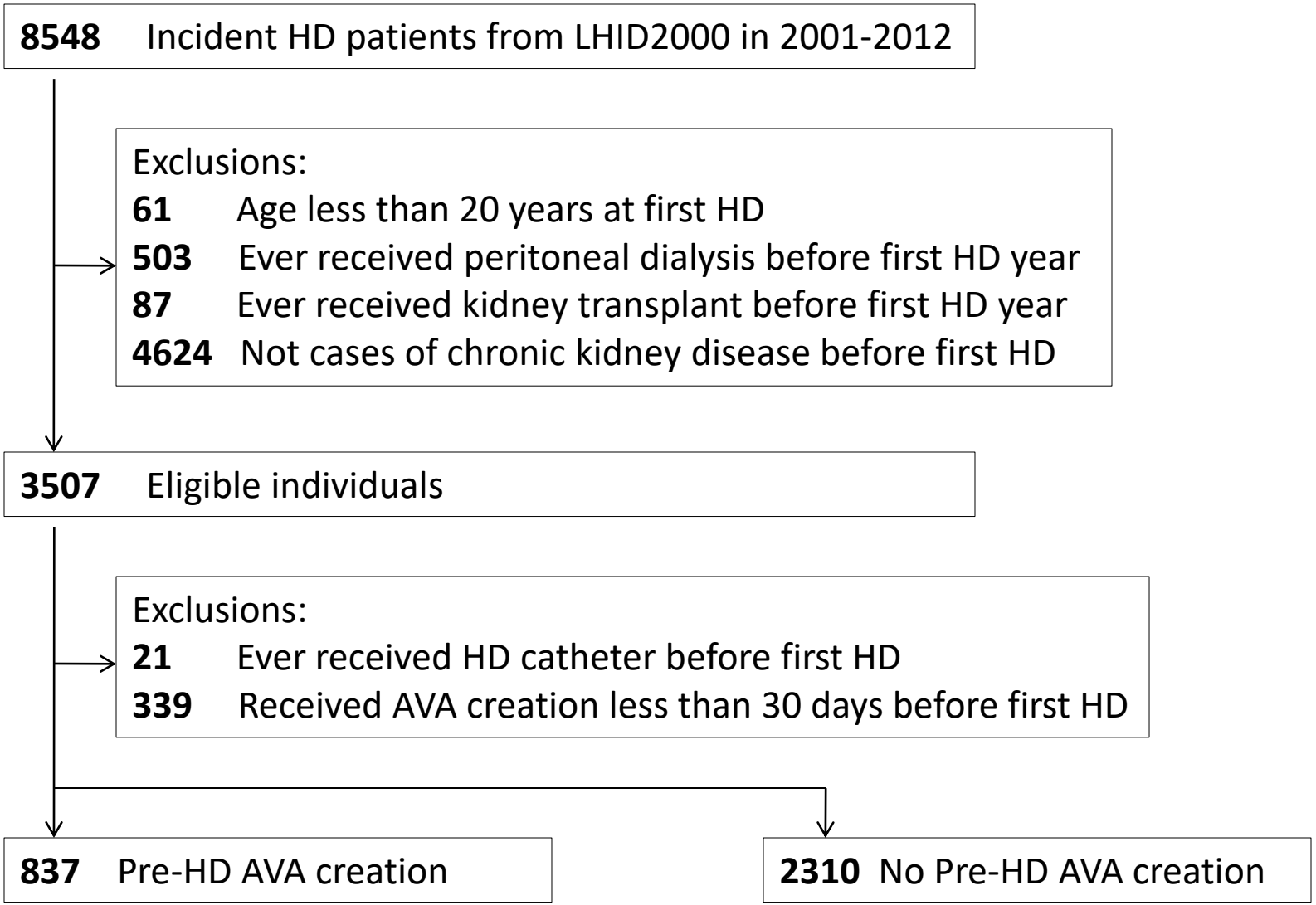
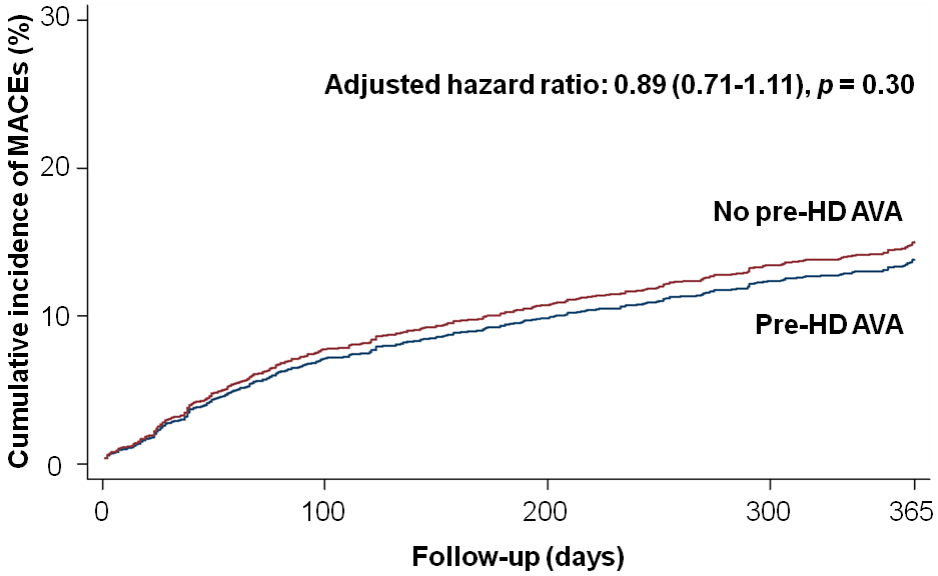

8548 Incident HD patients from LHID2000 in 2001-2012
Exclusions:
61 Age less than 20 years at first HD
503 Ever received peritoneal dialysis before first HD year
87 Ever received kidney transplant before first HD year
4624 Not cases of chronic kidney disease before first HD
3507 Eligible individuals
Exclusions:
21 Ever received HD catheter before first HD
339 Received AVA creation less than 30 days before first HD
837 Pre-HD AVA creation
2310 No Pre-HD AVA creation

Figure 2(on next page)

Cumulative Incidence of Major Adverse Cardiovascular Events (left) and Congestive Heart Failure (right) in Patients with and without Prehemodialysis Arteriovenous Access Creation.

CHF: congestive heart failure; MACEs: major adverse cardiovascular events; Pre-HD AVA: prehemodialysis arteriovenous access.


Cumulative incidence of MACEs (%)
30
20
10
0
Adjusted hazard ratio: 0.89 (0.71-1.11), p = 0.30
No pre-HD AVA
Pre-HD AVA
0
100
200
300
365
Follow-up (days)

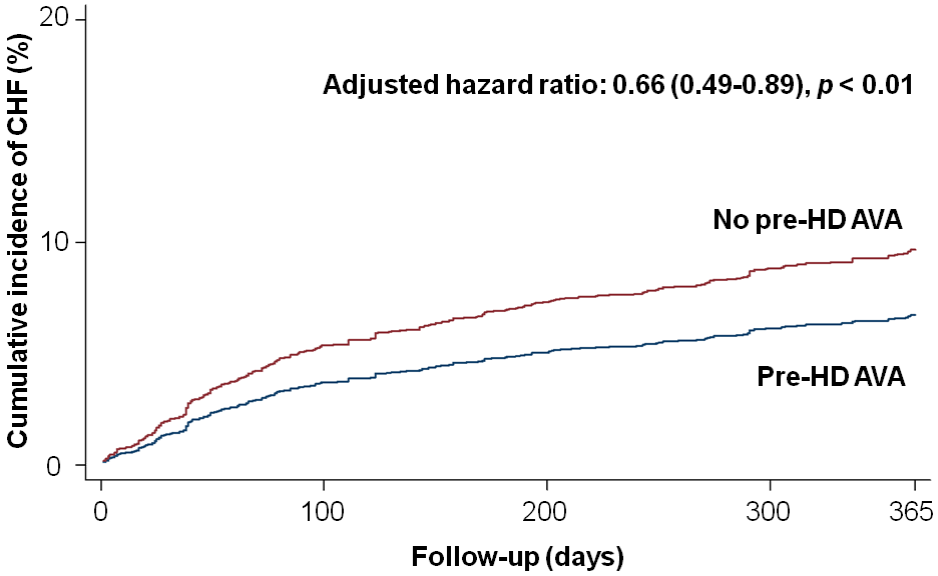

Cumulative incidence of CHF (%)
20
10
0
Adjusted hazard ratio: 0.66 (0.49-0.89), p < 0.01
No pre-HD AVA
Pre-HD AVA
0
100
200
300
365
Follow-up (days)

Figure 3(on next page)

Cumulative Incidence of Major Adverse Cardiovascular Event-Related Mortality in Patients with and without Prehemodialysis Arteriovenous Access Creation.

MACErM: major adverse cardiovascular event-related mortality; Pre-HD AVA: prehemodialysis arteriovenous access.

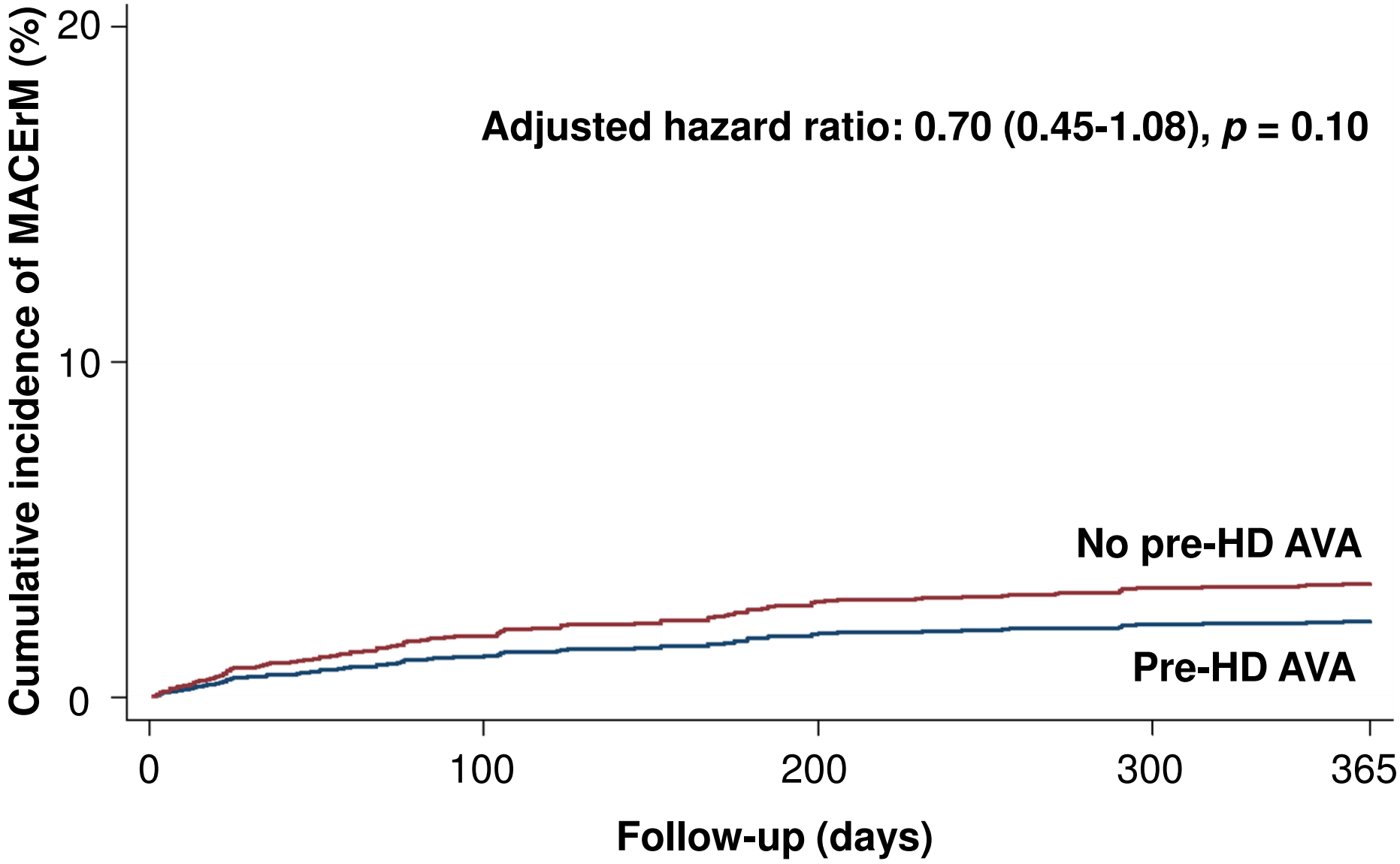

Cumulative incidence of MACErM (%)
20
10
0
Adjusted hazard ratio: 0.70 (0.45-1.08), p = 0.10
No pre-HD AVA
Pre-HD AVA
0
100
200
300
365
Follow-up (days)

Figure 4(on next page)

Cumulative Incidence of All-Cause Mortality in Patients with and without Prehemodialysis Arteriovenous Access Creation.

ACM: all-cause mortality; Pre-HD AVA: prehemodialysis arteriovenous access.

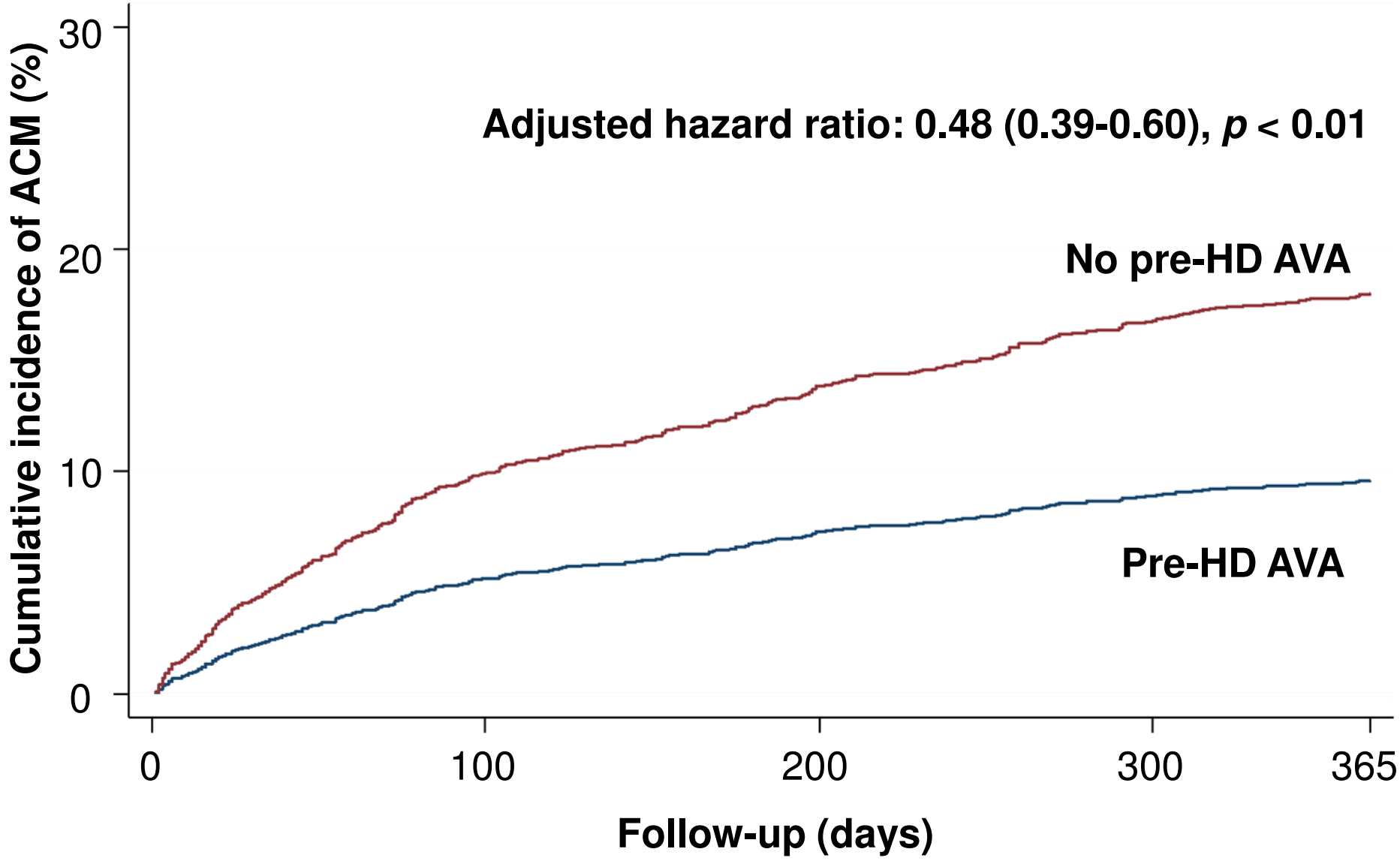

Cumulative incidence of ACM (%)
30
20
10
0
Adjusted hazard ratio: 0.48 (0.39-0.60), p < 0.01
No pre-HD AVA
Pre-HD AVA
0
100
200
300
365
Follow-up (days)

Table 1(on next page)

Characteristics of Patients with and without Prehemodialysis Arteriovenous Access Creation

	Unmatched			Matched		
	Pre-HD AVA (N = 837)	No pre-HD AVA (N = 2310)	ASD (%)	Pre-HD AVA (N = 807)	No pre-HD AVA (N = 807)	ASD (%)
Age, years						
Median (IQR)	66 (56-74)	71 (59-79)	29.9*	67 (56-75)	65 (55-75)	5.70
Sex, male (%)	440 (52.57)	1157 (50.09)	4.96	413 (51.18)	416 (51.55)	0.74
Income, NTD/year			15.3*			1.54
Dependent	296 (35.36)	878 (38.01)		289 (35.81)	284 (35.19)	
1-19999	206 (24.61)	700 (30.30)		198 (24.54)	208 (25.77)	
20000-39999	275 (32.86)	645 (27.92)		264 (32.71)	271 (33.58)	
≥40000	60 (7.17)	87 (3.77)		56 (6.94)	44 (5.45)	
Comorbidities						
HTN	712 (85.07)	1899 (82.21)	7.73	684 (84.76)	683 (84.63)	0.34
IHD	218 (26.05)	649 (28.10)	4.61	208 (25.77)	198 (24.54)	2.00
CHF	393 (46.95)	1150 (49.78)	5.66	373 (46.22)	379 (46.96)	1.49
CVA	76 (9.08)	363 (15.71)	20.2*	75 (9.29)	69 (8.55)	2.60
PVD	45 (5.38)	152 (6.58)	5.07	43 (5.33)	38 (4.71)	2.80
Dysrhythmia	50 (5.97)	226 (9.78)	14.1*	49 (6.07)	41 (5.08)	4.32
DM	461 (55.08)	1303 (56.41)	2.60	435 (53.90)	454 (56.26)	4.73
COPD	81 (9.68)	379 (16.41)	20.0*	80 (9.91)	79 (9.79)	0.41
PUD	186 (22.22)	569 (24.63)	5.69	179 (22.18)	180 (22.30)	0.29
Liver disease	65 (7.77)	252 (10.91)	10.0*	65 (8.05)	66 (8.18)	0.45
Cancer	74 (8.84)	233 (10.09)	4.25	73 (9.05)	67 (8.30)	2.64
Dementia	20 (2.39)	124 (5.37)	15.4*	20 (2.48)	19 (2.35)	0.80
Taiwan index (mean±SD)	5.55±4.00	6.55±4.40	23.0*	5.53±4.01	5.50±4.04	0.79
Medicine						
ESA	684 (81.72)	804 (34.81)	108.*	654 (81.04)	652 (80.79)	0.63
Antiplatelets	537 (64.16)	1563 (67.66)	7.30	515 (63.82)	508 (62.95)	1.80
Anticoagulants	75 (8.96)	161 (6.97)	7.35	58 (7.19)	53 (6.57)	2.44

Income was divided into 4 strata according to insurance fees: dependent (patient's medical expenditure was taken charge of the government), <20 000 New Taiwan Dollars (NTD) per month, 20 000–40 000 NTD per month, and >40 000 NTD per month.
The Taiwan index is a weighted comorbidity score of IHD × 1 + CHF × 3 + CVA × 4 + PVD × 2 + COPD × 3 + PUD × 2 + Liver disease × 4 + Dysrhythmia × 3 + Cancer × 6 + DM × 3
Abbreviations: ASD: absolute standard mean difference; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; DM: diabetes mellitus; ESA: erythropoiesis-stimulating agent; HTN: hypertension; IHD: ischemic heart disease; IQR: interquartile range; Pre-HD AVA: prehemodialysis arteriovenous access; PUD: peptic ulcer disease; PVD: peripheral vascular disease; SD: standard deviation.
*ASD ≥ 10%

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Table 2(on next page)

Clinical Outcomes of Patients with and without Prehemodialysis Arteriovenous Access Creation

	Unmatched		Matched	
	Crude HR	Adjusted HR[a]	Crude HR	Adjusted HR[b]
Primary outcomes				
MACEs	0.73 (0.60-0.89)**	0.89 (0.71-1.11)	0.91 (0.71-1.16)	0.91 (0.70-1.17)
CHF	0.52 (0.40-0.68)***	0.66 (0.49-0.89)**	0.70 (0.51-0.98)*	0.71 (0.50-1.00)*
sensitivity analysis 1[c]	0.47 (0.36-0.62)***	0.57 (0.42-0.78)***	0.59 (0.43-0.80)***	0.58 (0.42-0.80)***
sensitivity analysis 2[d]	0.52 (0.39-0.71)***	0.61 (0.43-0.85)**	0.62 (0.44-0.88)**	0.62 (0.44-0.88)**
Secondary outcomes				
MACE related mortality	0.37 (0.25-0.55)***	0.70 (0.45-1.08)	0.65 (0.40-1.06)	0.64 (0.39-1.07)
BSI related mortality	0.21 (0.15-0.30)***	0.31 (0.22-0.46)***	0.32 (0.22-0.47)***	0.29 (0.19-0.42)***
All-cause mortality	0.28 (0.23-0.34)***	0.48 (0.39-0.60)***	0.49 (0.38-0.62)***	0.46 (0.36-0.58)***

[a]Adjusted for age, sex, income, comorbidities, and medicine usage; [b]adjusted for age, sex, income, Taiwan index, hypertension, dementia, and medicine usage. The Taiwan index is a comorbidity index employed for mortality prediction that has been validated for Taiwanese patients undergoing hemodialysis as having adequate reclassification ability; [c]exclusion of patients not receiving AVA in the first year of dialysis; [d]exclusion of patients not receiving regular hemodialysis.

Abbreviations: BSI: blood stream infection; CHF: congestive heart failure; HR: hazard ratio; MACEs: major adverse cardiovascular events.

*$P < .05$; **$P < .01$; ***$P < .001$

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