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

Cheng-Chieh Yen [1], **Mei-Yin Liu** [2], **Po-Wei Chen** [3], **Peir-Haur Hung** [1], **Tse-Hsuan Su** Corresp., [4], **Yueh-Han Hsu** Corresp. [1, 5, 6]

[1] Division of Nephrology, Department of Internal Medicine, Ditmansion Medical Foundation Chia-Yi Christian Hospital, Chia-Yi City, Taiwan

[2] Health Center, Municipal Jingliau Junior High School, Tainan City, Taiwan

[3] Division of Cardiology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan City, Taiwan

[4] Department of Emergency Medicine, Chang Gung Memorial Hospital Linkou, Taoyuan City, Taiwan

[5] Department of Medical Research, China Medical University Hospital, China Medical University, Taichung City, Taiwan

[6] Department of Nursing, Min-Hwei College of Health Care Management, Tainan City, Taiwan

Corresponding Authors: Tse-Hsuan Su, Yueh-Han Hsu
Email address: Hsuan.ths@gmail.com, cych07023@gmail.com

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 had 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, were more likely to use erythropoiesis-stimulating agents but less likely to use renin–angiotensin–aldosterone system blockers. The patients with pre-HD AVA creation had a marginally lower rate of MACEs but a significant 35% lower rate of CHF hospitalization than those without creation (adjusted hazard ratio: 0.65 [95% confidence interval: 0.48–0.88]). In addition, the pre-HD AVA group exhibited an insignificantly lower rate of MACE-related mortality but a significantly 52% lower rate of all-cause mortality than the non-pre-HD AVA group (adjusted hazard ratio: 0.48 [95% confidence interval: 0.39–0.59]). 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

Authors

Cheng-Chieh Yen[1], Mei-Yin Liu[2], Po-Wei Chen [3], Peir-Haur Hung[1], Tse-Hsuan Su[4], Yueh-Han Hsu[1,5,6]

[1] Division of Nephrology, Department of Internal Medicine, Ditmansion Medical Foundation Chia-Yi Christian Hospital, Chia-Yi City, Taiwan

[2] Health Center, Municipal Jingliau Junior High School, Tainan City, Taiwan

[3] Division of Cardiology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan

[4] Department of Emergency Medicine, Chang Gung Memorial Hospital Linkou, Taoyuan City, Taiwan

[5] Department of Medical Research, China Medical University Hospital, China Medical University, Taichung City, Taiwan

[6] Department of Nursing, Min-Hwei College of Health Care Management, Tainan City, Taiwan

Corresponding Author

Tse-Hsuan Su, M.D., M.S.and Yueh-Han Hsu

Department of Emergency Medicine, Chang Gung Memorial Hospital Linkou, Taoyuan City, Taiwan

Division of Nephrology, Department of Internal Medicine, Ditmansion Medical Foundation Chia-Yi Christian Hospital, Chia-Yi City, Taiwan; Department of Medical Research, China Medical University Hospital, China Medical University, Taichung City, Taiwan; Department of Nursing, Min-Hwei College of Health Care Management, Tainan City, Taiwan

Tel: +886 3 328 1200 ext. 3523

Fax: +886 3 328 7715

Email: Hsuan.ths@gmail.com; cych07023@gmail.com

Abstract

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 had 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, were more likely to use erythropoiesis-stimulating agents but less likely to use renin–angiotensin–aldosterone system blockers. The patients with pre-HD AVA creation had a marginally lower rate of MACEs but a significant 35% lower rate of CHF hospitalization than those without creation (adjusted hazard ratio: 0.65 [95% confidence interval: 0.48–0.88]). In addition, the pre-HD AVA group exhibited an insignificantly lower rate of MACE-related mortality but a significantly 52% lower rate of all-cause mortality than the non-pre-HD AVA group (adjusted hazard ratio: 0.48 [95% confidence interval: 0.39–0.59]). 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.

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 relative risk of 5-year mortality(Robinson et al. 2016). Among the major causes of mortality, cardiovascular (CV) disease contributes nearly half of the events in this population(Collins et al. 2010). 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(Baek et al. 2015; Bradbury et al. 2007). Timely creation of arteriovenous access (AVA), such as native fistula or artificial graft, is one of the crucial methods of care planning. It prevents not only the complications from delayed dialysis but also catheter-related infectious events(Oliver et al. 2004). 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(Guyton & Sagawa 1961; Munclinger et al. 1987). London and colleagues reported that the arteriovenous shunt might result in chronic flow overload and cause cardiac hypertrophy(London et al. 1993). Nakhoul et al observed that nitric oxygen production was decreased in patients with arteriovenous fistula and contributed to pulmonary hypertension(Nakhoul et al. 2005). Korsheed and colleagues reported improved arterial stiffness, better ejection fraction, and lesser heart damage after native fistula creation(Korsheed et al. 2009; Korsheed et al. 2011). 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(MacRae et al. 2004; Reddy et al. 2017; Vizinho et al. 2014), while a national study using the United States Renal Data System showed that using pre-HD fistula was strongly associated with lower

CV mortality(Wasse et al. 2008). 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(Robinson et al. 2016). 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(Lin et al. 2018). 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(Hsu et al. 2018). 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(National Health Insurance Administration 2014). In this study, we used a representative subset of 1 million persons randomly sampled from the 24 million beneficiaries 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. 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 of 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. 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(Ravani et al. 2013). Pre-HD AVA

was defined as its creation date ≧ 1 month before the index date. Patients in whom AVA was created < 1 month prior to HD were excluded owing to their inappropriate access usage according to the guidelines(2006; Ishani et al. 2014). We further excluded patients who received implantation of HD catheters, namely tunneled and nontunneled catheters, before the index date.

Data and definitions of study variables

We analyzed the characteristics, comorbidities, and medicines of the included patients. Owing to the NHI charged its beneficiaries different amounts of insurance premiums according to their earnings, the socioeconomic status of patients was represented by their income, which was obtained according to the average insured payroll-related amounts. Comorbidities were defined as patients experiencing at least 1 hospitalization or 2 outpatient visits, which expressed in terms of the corresponding ICD-9-CM codes of any of the following illnesses, within the 1 year prior to the index date: hypertension (HTN), ischemic heart disease (IHD), congestive heart failure (CHF), cerebrovascular accident (CVA), peripheral vascular disease (PVD), dysrhythmia, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), peptic ulcer disease (PUD), liver disease, cancer, and dementia. Additionally, to denote the disease burdens we applied the Taiwan index, which is a comorbidity index for mortality prediction validated for Taiwanese patients with incident HD(Chen et al. 2014). Medicine including erythropoiesis-stimulating agent (ESA), antiplatelet agent, anticoagulant agent, angiotensin converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB) and statin was defined as more than 2 prescriptions during ambulatory visits within the 1 year prior to the index date and was expressed in terms of the anatomical therapeutic chemical classification system.

135 *Outcomes of study subjects*

136 Primary outcome of the present study was major adverse cardiovascular events (MACEs),
137 which was defined as ICD-9-CM-based hospitalization for acute myocardial infarction (AMI),
138 CVA, or CHF that occurred within the 1 year after the first HD session. Secondary outcomes
139 were all-cause mortality, MACE-related and bloodstream infection (BSI)-related mortality,
140 which was defined as overall death and death resulting from MACE and BSI in corresponding
141 ICD-9-CM codes, within the same follow-up period following the first dialysis. To validate the
142 findings, we performed multiple sensitivity analyses including exclusion patients without AVA
143 creation, exclusion of patients not receiving regular HD, and inclusion of patient receiving AVA
144 creation within 1 month.

145

146 *Statistical analysis*

147 We compared patient characteristics, comorbidities, and medical prescriptions between the
148 pre-HD AVA and non-pre-HD AVA groups. Continuous data were reported as a median or mean
149 and were analyzed using the Mann–Whitney test or independent t test as appropriate. Categorical
150 data were reported as percentages and were analyzed using the Chi-squared test. Since
151 management of chronic kidney disease changed over time, we included the year of starting HD
152 as a time indicator. We constructed our propensity score model using variables related to patient
153 characteristics, year of HD, comorbidities, and medical prescriptions, and calculated model using
154 the logistic regression method. We performed 1:1 matching using the nearest neighbor algorithm
155 without replacement and with a 0.05 caliper width to reduce imbalances between groups. After
156 matching, we used absolute standardized differences (ASD) to evaluate the balance between
157 groups. An ASD threshold of 10% was used to delineate good and poor balance(Austin 2008).

158 We evaluated the cause-specific mortality and overall mortality over 1 year using weighted

159 cumulative incidence curves considering competing risks of death. Event-time was measured
160 from the index date until the date of the event, 1 year after the index date, or the end of the study
161 (31/12/2013), whichever occurred earlier. We applied the Fine–Gray subdistributional hazard
162 models to calculate crude and adjusted hazard ratios (HRs). Robust sandwich variance was used
163 to correct the correlated data structure after matching(Austin 2014). Because the 1:1 propensity
164 score matching would reduce the sample size, we performed the inverse probability treatment
165 weighting (IPTW) of study subjects as another sensitivity analysis. Since extreme weights might
166 cause bias estimate in the marginal hazard ratio, we used IPTW in the subsample restricted to
167 patients with a propensity score between 0.1 and 0.9(Austin & Stuart 2017). A 2-tailed p value of
168 < 0.05 indicated statistical significance. SAS version 9.4 (SAS Institute, Inc.) was used for
169 analyses.

Results

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

The baseline characteristics of the recruited patients are presented in Table 1. The median age of patients with pre-HD AVA creation was lower than that of those without (66 years vs 71 years, ASD: 29.9%). No statistically significant difference was observed in terms of sex between the 2 groups. Considering comorbidities, the patients in the pre-HD AVA group had lower proportions of CVA, dysrhythmia, COPD, liver disease, and dementia than those in the non-pre-HD AVA group. The groups exhibited similar proportions of patients with IHD, CHF, PVD, and DM. The mean Taiwan index of pre-HD AVA group was significantly lower than that of the non-pre-HD AVA group (5.55 ± 4.0 vs 6.55 ± 4.4, ASD: 23%). Additionally, more patients with pre-HD AVA creation received ESAs than did those without pre-HD AVA creation (81.72% vs 34.81%, ASD: 108%), whereas less patients with pre-HD AVA received ACEIs and ARBs than did those without pre-HD AVA (60.57% vs 68.35%, ASD: 16.3%). The prescription of antiplatelet agent, anticoagulant agent or statin was similar among the groups.

Table 2 shows the primary and secondary outcomes of the pre-HD AVA and non-pre-HD AVA groups. The patients with pre-HD AVA creation had a lower rate of MACEs during the follow-up period than did those without pre-HD AVA creation (crude HR: 0.73 [95% confidence interval (CI): 0.6–0.89]), but the effect became nonsignificant after matching for age, sex, year of HD, comorbidities, and medicine (adjusted HR: 0.89 [95% CI: 0.71–1.11], $p = 0.29$, Figure 2). We further analyzed the MACEs separately and observed that patients with pre-HD AVA creation had a 35% lower CHF hospitalization rate after matching (adjusted HR: 0.65 [95% CI: 0.48–0.88], $p < 0.01$, Figure 3). We examined CHF hospitalization rate in the propensity-score-

194 matched groups, which showed a similar trend (adjusted HR: 0.63 [95% CI: 0.46–0.87], $p <$
195 0.01).

196 Regarding secondary outcomes, we revealed that patients in the pre-HD AVA group had a
197 52% lower rate of all-cause mortality (adjusted HR: 0.48 [95% CI: 0.39–0.59], $p < 0.001$, Figure
198 4), a marginally lower rate of MACE-related mortality (adjusted HR: 0.7 [95% CI: 0.45–1.08], p
199 = 0.1, Figure 5), and a 68% lower rate of BSI-related mortality (adjusted HR: 0.32 [95% CI:
200 0.22–0.46], $p < 0.001$, Supplementary Figure 1) than those in the non-pre-HD AVA group. We
201 next examined the outcomes in the propensity-score-matched groups. The patients with pre-HD
202 AVA creation exhibited a 54% lower rate of all-cause mortality (adjusted HR: 0.46 [95% CI:
203 0.36–0.59], $p < 0.001$), a 40% lower rate of MACE-related mortality (adjusted HR: 0.60 [95% CI:
204 0.38–0.96] , $p < 0.05$), and a 71% lower rate of BSI-related mortality (adjusted HR: 0.29 [95%
205 CI: 0.19–0.44], $p < 0.01$) than those without pre-HD AVA creation.

206 Sensitivity analyses of the outcomes were presented in Table 3. They revealed a
207 consistently lower CHF hospitalization rates, ranging from 29% to 43%, of patients receiving
208 pre-HD AVA creation. In addition, they exhibited a consistently lower BSI-related mortality
209 rates of patients in the pre-HD AVA group.

Discussion

In our nationally representative cohort, we observed that patients with pre-HD AVA creation had a 35% 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, had a higher percentage of ESAs but a lower percentage of ACEIs and ARBs usage (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(Kassahun 2018). Thus, patients who were young or had fewer comorbidities were willing to undergo pre-HD AVA surgery. Additionally, a different proportion of patients receiving ESAs and renin–angiotensin–aldosterone system blockers might imply more recruitment of pre-HD care, which promotes the possibility of dialysis access creation by education(Ishani et al. 2014).

Our study revealed a significantly lower CHF hospitalization rate within the first year of HD among the patients receiving pre-HD AVA creation (Figure 3). Consistent results were obtained for the other matched models (Table 2) and sensitivity analyses (Table 3). 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(Ori et al. 1996) and consequent fluid removal during HD sessions. The fluid status of most patients undergoing HD has been proved to achieve a new balance shortly(Alkhouli et al. 2015; Dal Canton et al. 1981). In the Dialysis Outcomes and Practice Patterns Study, Rayner and colleagues observed a low flow rate of the fistula in Japanese patients (Rayner et al. 2003), 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(Ori et al. 1996). 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(Sandhu et al. 2004). 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(MacRae et al. 2004). Other studies have adopted an opposite viewpoint on ejection fraction alteration following AVA creation(Iwashima et al. 2002; Korsheed et al. 2011; Ori et al. 1996). 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(Vizinho et al. 2014). 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(Reddy et al. 2017). 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 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 (Table 2, Figure 4). In addition to CV disease, catheter-associated infectious disease, mainly those transmitted through the bloodstream, is another major cause of mortality in patients undergoing dialysis. We assumed that the lower all-cause mortality might have been related to the 68% 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. Additionally, we also observed that the patients with pre-HD AVA creation had an insignificantly lower rate of MACE-related mortality compared with those without after propensity score matching (Table 2, Figure 5). 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(Banerjee et al. 2007; Lee et al. 2016; Zoccali et al. 2005). Because our groups had similar distributions of these diseases, our finding was in fair agreement with the literature.

This was a country-based study including all pre-HD patients underlined CKD matched for

age, sex, income, year of HD, comorbidities, and associated medicine. In Taiwan, the NHI Bureau has launched pay-for-performance program focusing on patients of glomerulus filtration rate < 45 ml/min/1.73m^2 from 2006. It is incentive payment for medical institution if recruited patients achieved the targets on blood pressure, glycated hemoglobin, nursing education, nutrition consult, and so on. Patients with ESRD have received comprehensive access evaluation by qualified nephrologists at outpatient clinics or during admissions. Most studies exploring the effects of pre-HD AVA creation on CV outcomes compared associated parameters before and after surgery(Dal Canton et al. 1981; Dundon et al. 2014; Iwashima et al. 2002; Korsheed et al. 2011; Munclinger et al. 1987; Ori et al. 2002; Ori et al. 1996; Reddy et al. 2017; Sandhu et al. 2004; Savage et al. 2002; Utescu et al. 2009; Vizinho et al. 2014). In addition, some compared the effects before dialysis initiation to exclude the impact of dialysis on CV performance(Dundon et al. 2014; Iwashima et al. 2002; Korsheed et al. 2011; Ori et al. 1996; Savage et al. 2002). 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(McIntyre 2009). 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 hazards of pre-HD AVA surgery.

This study had several limitations. First, the present study was an observational study, which non-observed confounders might restrict the inference. Second, the NHIRD is an

306 administrative database in which the identification of comorbidities is based solely on ICD-9-
307 CM codes rather than clinical criteria; misclassifications might thus have occurred, leading to
308 residual confounding. Additionally, we recruited our patients until the end of 2012 since the data
309 was valid until 31/12/2013 in LHID 2000. Third, patients could choose the preferred medical
310 providers for AVA creation or HD freely owing to high medical accessibility in Taiwan. It was
311 difficult to figure out the relationship between patients and medical providers, which have
312 influenced the timing of AVA creation. Fourth, the indications of CHF hospitalization are varied
313 among patients and medical facilities. However, the NHIRD does not provide objective
314 parameters of cardiac alteration, such as the level of natriuretic peptide, ejection fraction of
315 ventricles, or pulse wave velocity of vessels, which could support our findings. Fifth, our study
316 did not consider medications such as calcium channel blockers, beta blockers, or diuretics, which
317 have been shown to influence CV outcomes in patients undergoing HD(Georgianos & Agarwal
318 2016; Karaboyas et al. 2018). Lastly, it was difficult to distinguish the absolute effect of pre-HD
319 AVA on CV outcomes in combination with personal compliance and dialysis factors affecting
320 the CV system. Integrated trials comprising data and imaging should be further conducted to
321 corroborate our results.

Conclusions

In this population-based cohort study, patients with pre-HD AVA creation had a 35% lower CHF hospitalization rate and a 52% lower all-cause mortality rate than those without pre-HD AVA creation within the first year of HD. Marginal benefits were also observed in terms of MACEs and MACE-related mortality during the same follow-up period. Pre-HD AVA creation might be associated with better CV outcomes in the first year of HD and should be promoted in the pre-HD care focusing on patients with late-stage CKD.

Acknowledgements

We would like to thank Ching-Fang Tsai for the pretest of study design, and Professor Chih-Cheng Hsu for his experienced dehortation and encouragement throughout the study.

References

Introduction to the National Health Insurance Research Database (NHIRD), Taiwan. *Available at* http://nhird.nhri.org.tw/date_01_en.html (accessed 2017/11/01 2017).

2006. Clinical practice guidelines for vascular access. *Am J Kidney Dis* 48 Suppl 1:S248-273. 10.1053/j.ajkd.2006.04.040

Alkhouli M, Sandhu P, Boobes K, Hatahet K, Raza F, and Boobes Y. 2015. Cardiac complications of arteriovenous fistulas in patients with end-stage renal disease. *Nefrologia* 35:234-245. 10.1016/j.nefro.2015.03.001

Austin PC. 2008. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. *Stat Med* 27:2037-2049. 10.1002/sim.3150

Austin PC. 2014. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med* 33:1242-1258. 10.1002/sim.5984

Austin PC, and Stuart EA. 2017. The performance of inverse probability of treatment weighting and full matching on the propensity score in the presence of model misspecification when estimating the effect of treatment on survival outcomes. *Stat Methods Med Res* 26:1654-1670. 10.1177/0962280215584401

Baek SH, Ahn S, Lee SW, Park YS, Kim S, Na KY, Chae DW, Kim S, and Chin HJ. 2015. Outcomes of predialysis nephrology care in elderly patients beginning to undergo dialysis. *PLoS One* 10:e0128715. 10.1371/journal.pone.0128715

Banerjee D, Ma JZ, Collins AJ, and Herzog CA. 2007. Long-term survival of incident hemodialysis patients who are hospitalized for congestive heart failure, pulmonary edema, or fluid overload. *Clin J Am Soc Nephrol* 2:1186-1190. 10.2215/cjn.01110307

Bradbury BD, Fissell RB, Albert JM, Anthony MS, Critchlow CW, Pisoni RL, Port FK, and Gillespie BW. 2007. Predictors of early mortality among incident US hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clin J Am Soc Nephrol* 2:89-99. 10.2215/cjn.01170905

Chen JY, Tsai SH, Chuang PH, Chang CH, Chuang CL, Chen HL, and Chen PL. 2014. A comorbidity index for mortality prediction in Chinese patients with ESRD receiving hemodialysis. *Clin J Am Soc Nephrol* 9:513-519. 10.2215/cjn.03100313

Collins AJ, Foley RN, Herzog C, Chavers BM, Gilbertson D, Ishani A, Kasiske BL, Liu J, Mau LW, McBean M, Murray A, St Peter W, Guo H, Li Q, Li S, Li S, Peng Y, Qiu Y, Roberts T, Skeans M, Snyder J, Solid C, Wang C, Weinhandl E, Zaun D, Arko C, Chen SC, Dalleska F, Daniels F, Dunning S, Ebben J, Frazier E, Hanzlik C, Johnson R, Sheets D, Wang X, Forrest B, Constantini E, Everson S, Eggers PW, and Agodoa L. 2010. Excerpts from the US Renal

Data System 2009 Annual Data Report. *Am J Kidney Dis* 55:S1-420, a426-427. 10.1053/j.ajkd.2009.10.009

Dal Canton A, Maione S, Russo D, Teti C, Serino C, Gallo R, and Andreucci VE. 1981. Echocardiographic detection of cardiac effects of arterio-venous dialysis fistula. *Clin Exp Dial Apheresis* 5:259-267.

Dundon BK, Torpey K, Nelson AJ, Wong DT, Duncan RF, Meredith IT, Faull RJ, Worthley SG, and Worthley MI. 2014. The deleterious effects of arteriovenous fistula-creation on the cardiovascular system: a longitudinal magnetic resonance imaging study. *Int J Nephrol Renovasc Dis* 7:337-345. 10.2147/ijnrd.s66390

Georgianos PI, and Agarwal R. 2016. Pharmacotherapy of Hypertension in Chronic Dialysis Patients. *Clin J Am Soc Nephrol* 11:2062-2075. 10.2215/cjn.00870116

Guyton AC, and Sagawa K. 1961. Compensations of cardiac output and other circulatory functions in areflex dogs with large A-V fistulas. *Am J Physiol* 200:1157-1163. 10.1152/ajplegacy.1961.200.6.1157

Hsu CC, Hsiung CA, Wu MS, Huang SJ, Lin YC, Hsu YH, and Chiu YW. 2018. 2017 Annual Report on Kidney Disease in Taiwan. Maoli County, Taiwan: National Health Research Institutes.

Ishani A, Gilbertson DT, Kim D, Bradbury BD, and Collins AJ. 2014. Predialysis care and dialysis outcomes in hemodialysis patients with a functioning fistula. *Am J Nephrol* 39:238-247. 10.1159/000358843

Iwashima Y, Horio T, Takami Y, Inenaga T, Nishikimi T, Takishita S, and Kawano Y. 2002. Effects of the creation of arteriovenous fistula for hemodialysis on cardiac function and natriuretic peptide levels in CRF. *Am J Kidney Dis* 40:974-982. 10.1053/ajkd.2002.36329

Karaboyas A, Xu H, Morgenstern H, Locatelli F, Jadoul M, Nitta K, Dasgupta I, Tentori F, Port FK, and Robinson BM. 2018. DOPPS data suggest a possible survival benefit of renin angiotensin-aldosterone system inhibitors and other antihypertensive medications for hemodialysis patients. *Kidney Int* 94:589-598. 10.1016/j.kint.2018.03.013

Kassahun WT. 2018. The effects of pre-existing dementia on surgical outcomes in emergent and nonemergent general surgical procedures: assessing differences in surgical risk with dementia. *BMC Geriatr* 18:153. 10.1186/s12877-018-0844-x

Korsheed S, Burton JO, and McIntyre CW. 2009. Higher arteriovenous fistulae blood flows are associated with a lower level of dialysis-induced cardiac injury. *Hemodial Int* 13:505-511. 10.1111/j.1542-4758.2009.00384.x

Korsheed S, Eldehni MT, John SG, Fluck RJ, and McIntyre CW. 2011. Effects of arteriovenous fistula formation on arterial stiffness and cardiovascular performance and function. *Nephrol Dial Transplant* 26:3296-3302. 10.1093/ndt/gfq851

Lee T, Thamer M, Zhang Q, Zhang Y, and Allon M. 2016. Reduced Cardiovascular Mortality Associated with Early Vascular Access Placement in Elderly Patients with Chronic Kidney Disease. *Am J Nephrol* 43:334-340. 10.1159/000446159

Lin MY, Cheng LJ, Chiu YW, Hsieh HM, Wu PH, Lin YT, Wang SL, Jian FX, Hsu CC, Yang SA, Lee HL, and Hwang SJ. 2018. Effect of national pre-ESRD care program on expenditures and mortality in incident dialysis patients: A population-based study. *PLoS One* 13:e0198387. 10.1371/journal.pone.0198387

London GM, Marchais SJ, Guerin AP, Metivier F, and Pannier B. 1993. Cardiac hypertrophy and arterial alterations in end-stage renal disease: hemodynamic factors. *Kidney Int Suppl* 41:S42-49.

MacRae JM, Pandeya S, Humen DP, Krivitski N, and Lindsay RM. 2004. Arteriovenous fistula-associated high-output cardiac failure: a review of mechanisms. *Am J Kidney Dis* 43:e17-22.

McIntyre CW. 2009. Effects of hemodialysis on cardiac function. *Kidney Int* 76:371-375. 10.1038/ki.2009.207

Munclinger M, Nemecek K, Serf B, Vondracek V, and Hrudova J. 1987. Effect of arteriovenous fistula creation and maturation on rest hemodynamics in patients with end-stage renal disease. *Nephron* 46:105-106. 10.1159/000184321

Nakhoul F, Yigla M, Gilman R, Reisner SA, and Abassi Z. 2005. The pathogenesis of pulmonary hypertension in haemodialysis patients via arterio-venous access. *Nephrol Dial Transplant* 20:1686-1692. 10.1093/ndt/gfh840

National Health Insurance Administration MoHaW, Taiwan, R.O.C. 2014. National Health Insurance Annual Report 2014-2015.122.

Oliver MJ, Rothwell DM, Fung K, Hux JE, and Lok CE. 2004. Late creation of vascular access for hemodialysis and increased risk of sepsis. *J Am Soc Nephrol* 15:1936-1942.

Ori Y, Korzets A, Katz M, Erman A, Weinstein T, Malachi T, and Gafter U. 2002. The contribution of an arteriovenous access for hemodialysis to left ventricular hypertrophy. *Am J Kidney Dis* 40:745-752. 10.1053/ajkd.2002.35685

Ori Y, Korzets A, Katz M, Perek Y, Zahavi I, and Gafter U. 1996. Haemodialysis arteriovenous access--a prospective haemodynamic evaluation. *Nephrol Dial Transplant* 11:94-97.

Ravani P, Palmer SC, Oliver MJ, Quinn RR, MacRae JM, Tai DJ, Pannu NI, Thomas C, Hemmelgarn BR, Craig JC, Manns B, Tonelli M, Strippoli GF, and James MT. 2013. Associations between hemodialysis access type and clinical outcomes: a systematic review. *J Am Soc Nephrol* 24:465-473. 10.1681/asn.2012070643

Rayner HC, Pisoni RL, Gillespie BW, Goodkin DA, Akiba T, Akizawa T, Saito A, Young EW, and Port FK. 2003. Creation, cannulation and survival of arteriovenous fistulae: data from the Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 63:323-330. 10.1046/j.1523-

1755.2003.00724.x

Reddy YNV, Obokata M, Dean PG, Melenovsky V, Nath KA, and Borlaug BA. 2017. Long-term cardiovascular changes following creation of arteriovenous fistula in patients with end stage renal disease. *Eur Heart J* 38:1913-1923. 10.1093/eurheartj/ehx045

Robinson BM, Akizawa T, Jager KJ, Kerr PG, Saran R, and Pisoni RL. 2016. Factors affecting outcomes in patients reaching end-stage kidney disease worldwide: differences in access to renal replacement therapy, modality use, and haemodialysis practices. *Lancet* 388:294-306. 10.1016/s0140-6736(16)30448-2

Sandhu JS, Wander GS, Gupta ML, Aulakh BS, Nayyar AK, and Sandhu P. 2004. Hemodynamic effects of arteriovenous fistula in end-stage renal failure. *Ren Fail* 26:695-701.

Savage MT, Ferro CJ, Sassano A, and Tomson CR. 2002. The impact of arteriovenous fistula formation on central hemodynamic pressures in chronic renal failure patients: a prospective study. *Am J Kidney Dis* 40:753-759. 10.1053/ajkd.2002.35686

Utescu MS, LeBoeuf A, Chbinou N, Desmeules S, Lebel M, and Agharazii M. 2009. The impact of arteriovenous fistulas on aortic stiffness in patients with chronic kidney disease. *Nephrol Dial Transplant* 24:3441-3446. 10.1093/ndt/gfp276

Vizinho RS, Santos C, Lucas C, Adragao T, and Barata JD. 2014. Effect of the arteriovenous access for hemodialysis on subendocardial viability ratio, pulse pressure and hospitalizations. *J Nephrol* 27:563-570. 10.1007/s40620-014-0056-1

Wasse H, Speckman RA, and McClellan WM. 2008. Arteriovenous fistula use is associated with lower cardiovascular mortality compared with catheter use among ESRD patients. *Semin Dial* 21:483-489. 10.1111/j.1525-139X.2008.00467.x

Zoccali C, Tripepi G, and Mallamaci F. 2005. Predictors of cardiovascular death in ESRD. *Semin Nephrol* 25:358-362. 10.1016/j.semnephrol.2005.05.002

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.

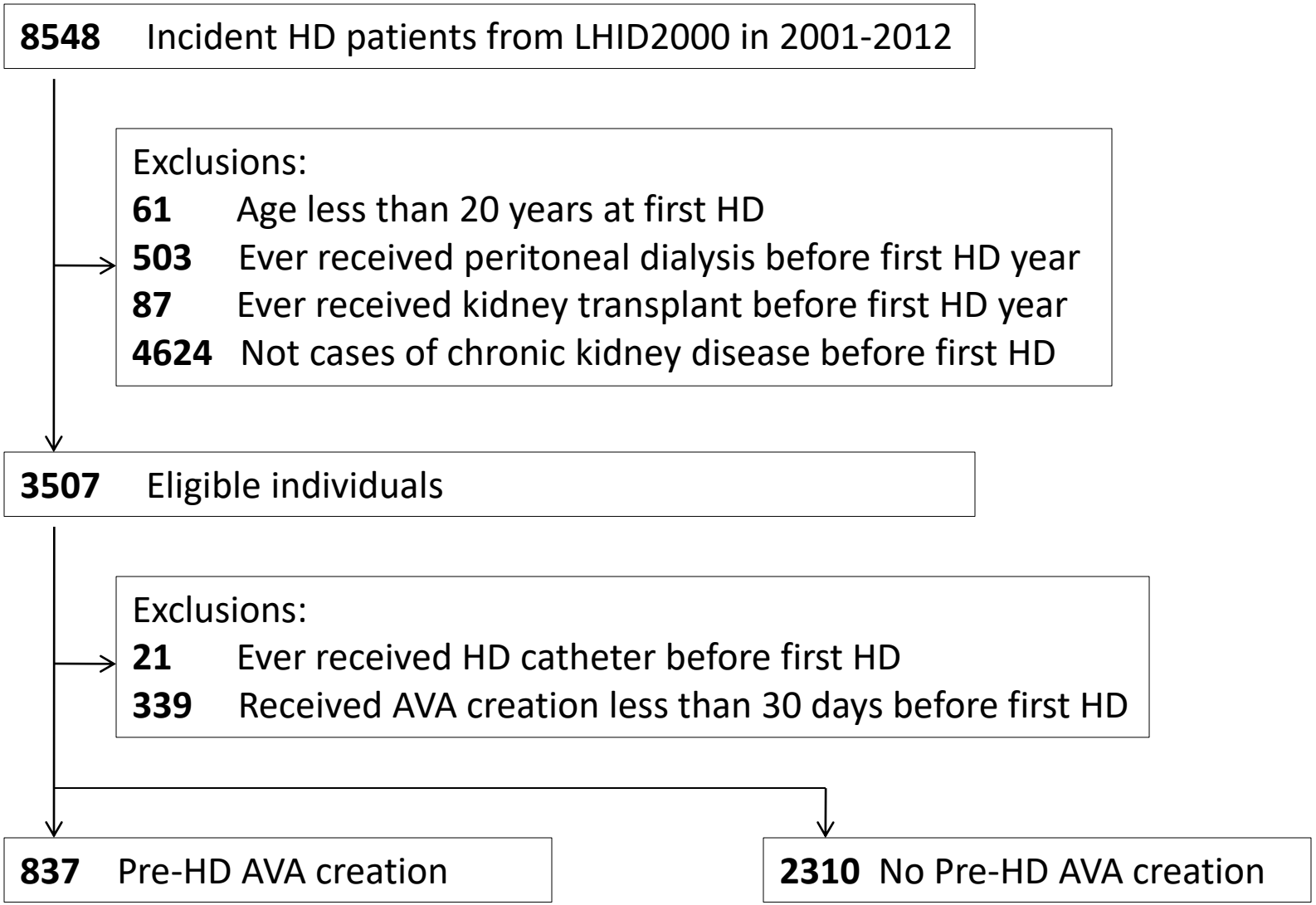
8548 Incident HD patients from LHID2000 in 2001-2012
Exclusions:
61 Age less than 20 years at first HD
503 Ever received peritoneal dialysis before first HD year
87 Ever received kidney transplant before first HD year
4624 Not cases of chronic kidney disease before first HD
3507 Eligible individuals
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 in patients with and without prehemodialysis arteriovenous access creation.

MACEs: major adverse cardiovascular events; Pre-HD AVA: prehemodialysis arteriovenous access.

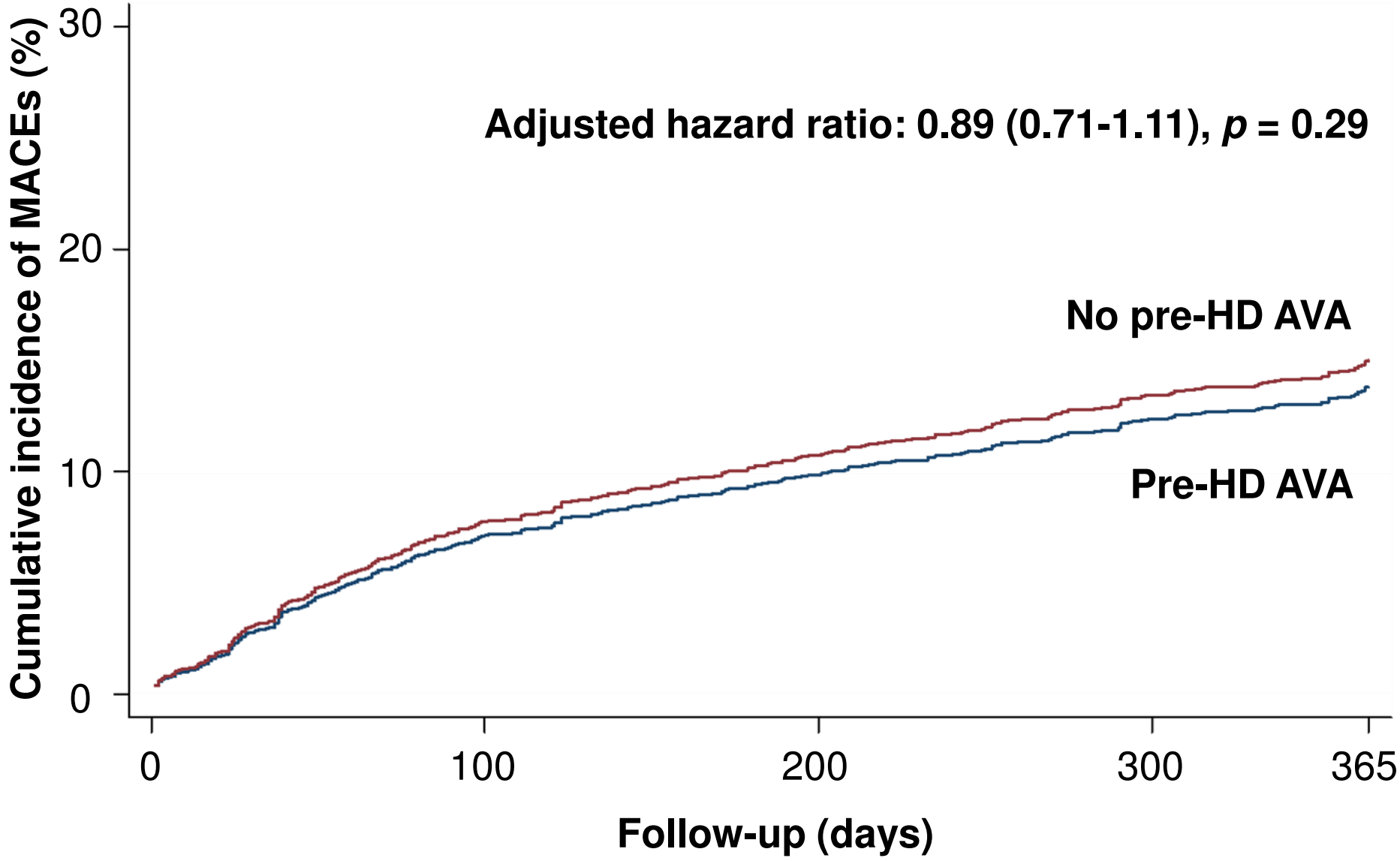
Cumulative incidence of MACEs (%)
30
20
10
0
Adjusted hazard ratio: 0.89 (0.71-1.11), p = 0.29
No pre-HD AVA
Pre-HD AVA
0
100
200
300
365
Follow-up (days)

Figure 3(on next page)

Cumulative incidence of congestive heart failure in patients with and without prehemodialysis arteriovenous access creation.

CHF: congestive heart failure; Pre-HD AVA: prehemodialysis arteriovenous access.

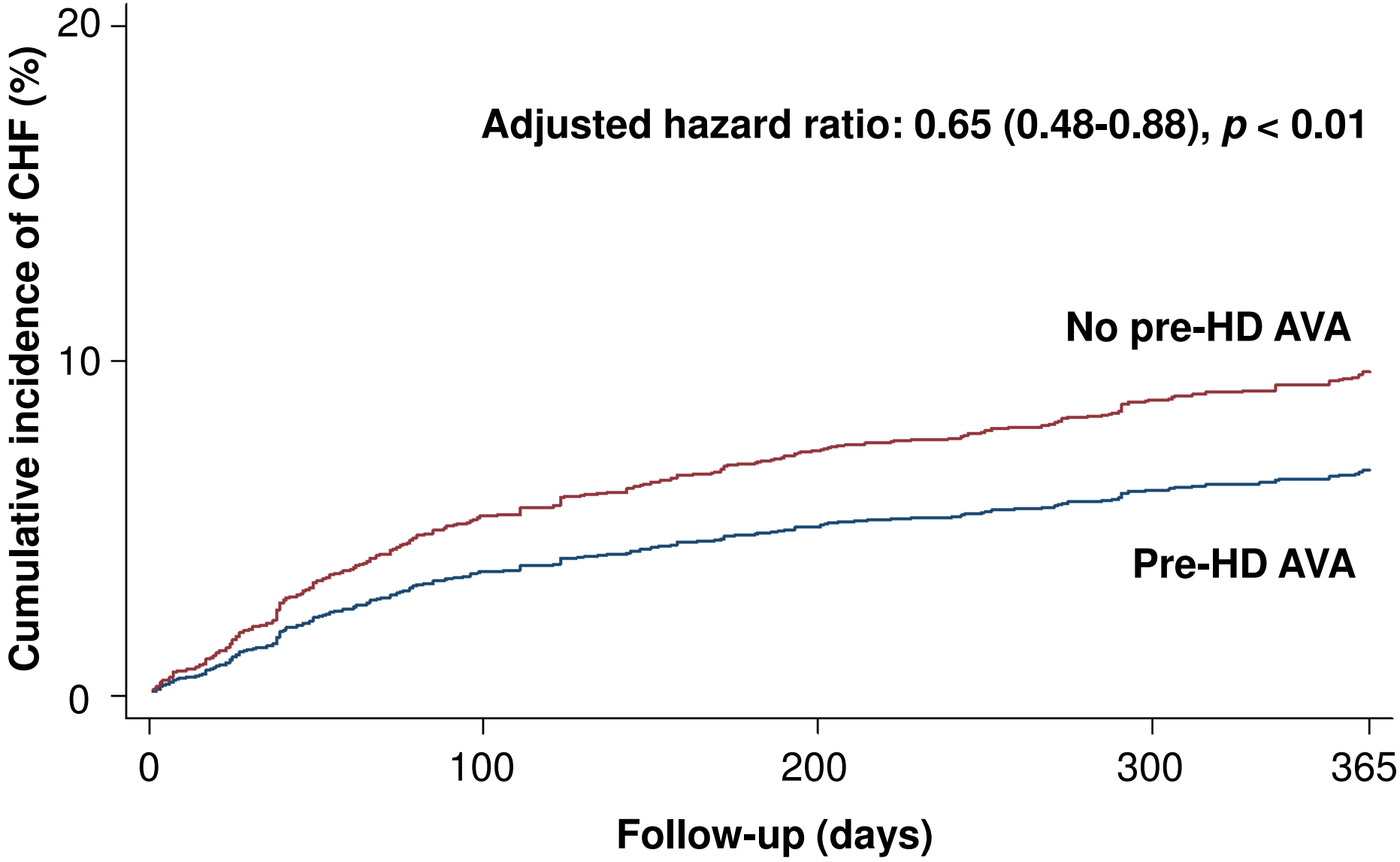
Adjusted hazard ratio: 0.65 (0.48-0.88), p < 0.01
No pre-HD AVA
Pre-HD AVA
Cumulative incidence of CHF (%)
20
10
0
0
100
200
300
365
Follow-up (days)

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.

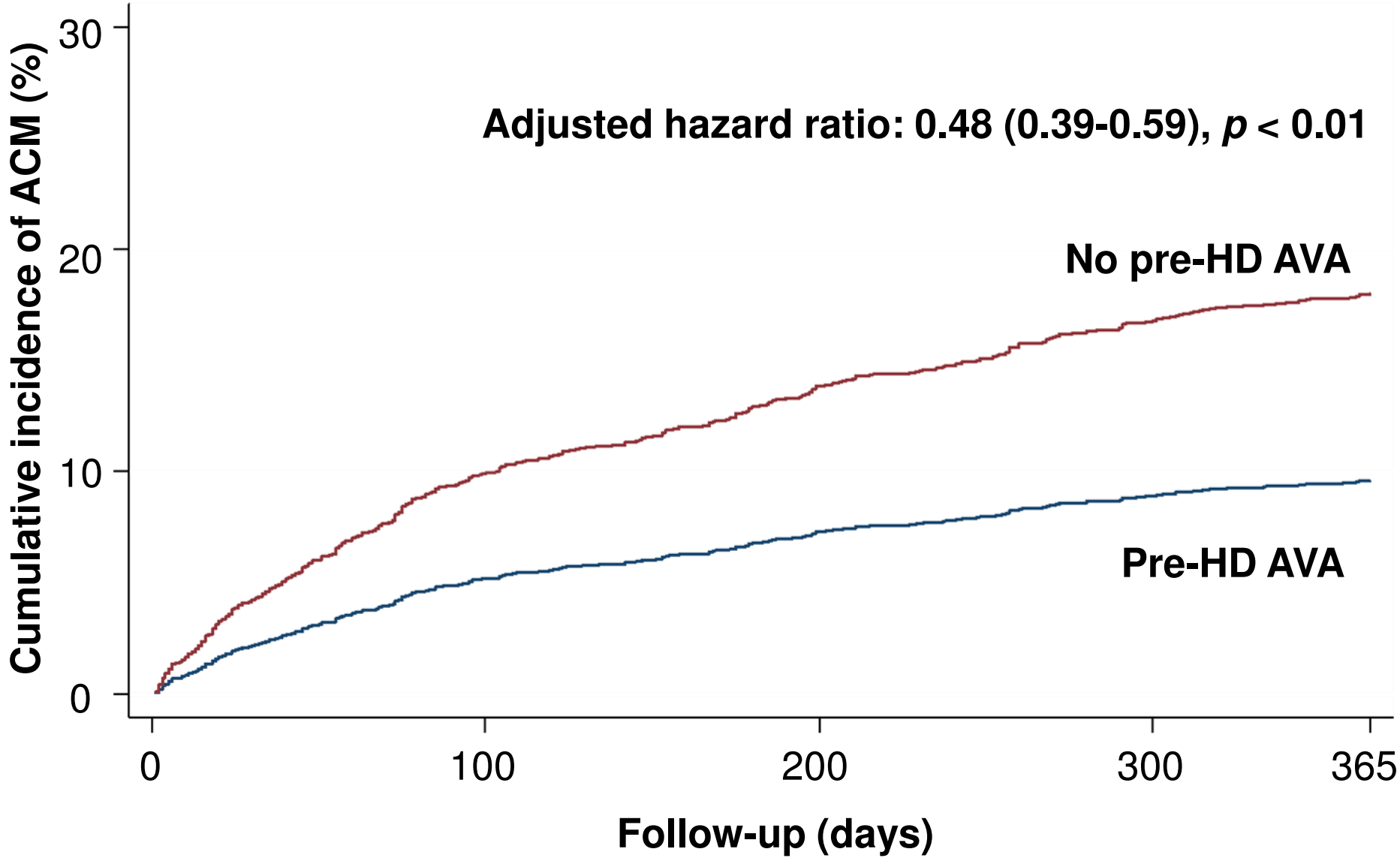
Cumulative incidence of ACM (%)
30
20
10
0
Adjusted hazard ratio: 0.48 (0.39-0.59), p < 0.01
No pre-HD AVA
Pre-HD AVA
0
100
200
300
365
Follow-up (days)

Figure 5(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.

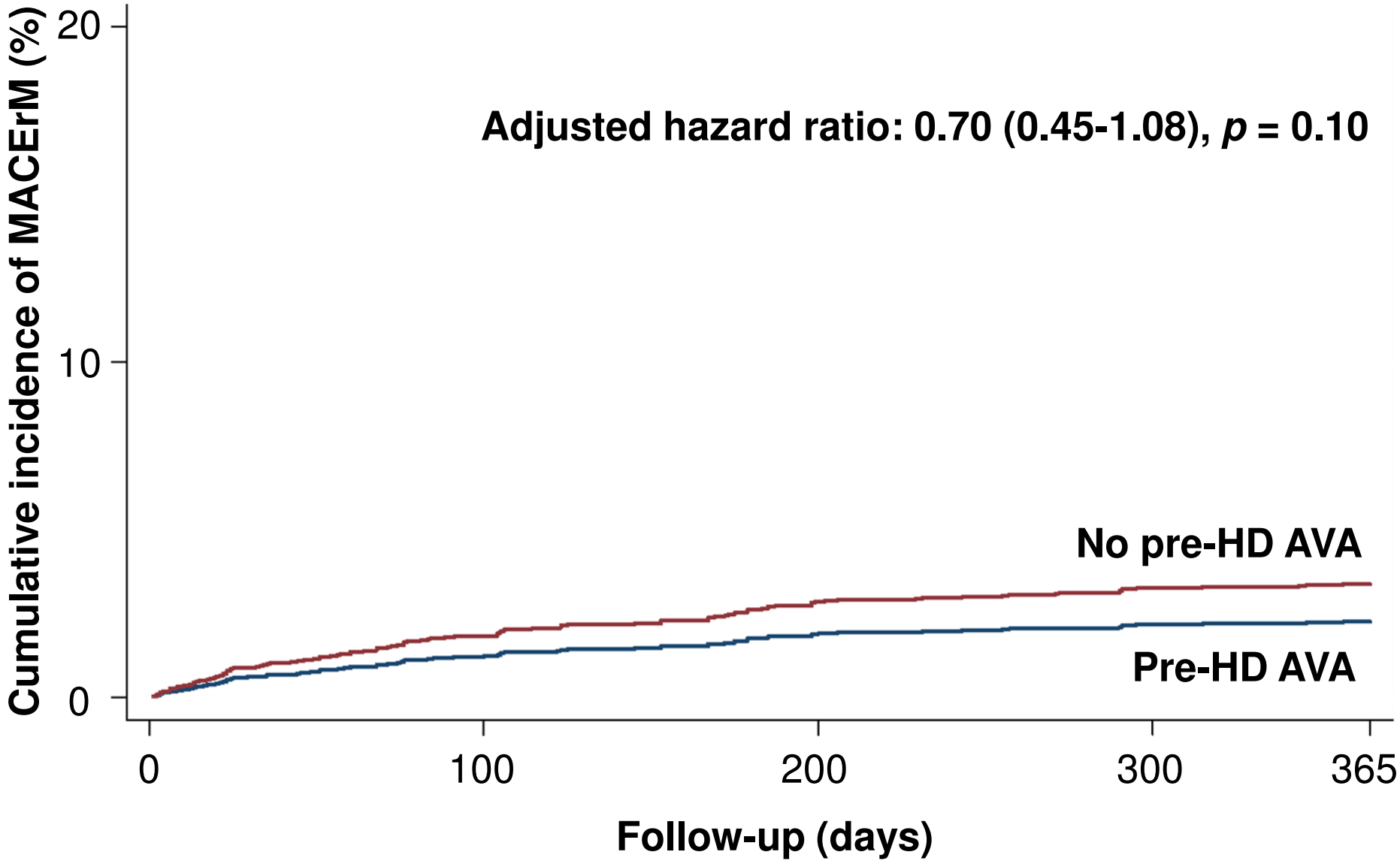
Cumulative incidence of MACErM (%)
20
10
0
Adjusted hazard ratio: 0.70 (0.45-1.08), p = 0.10
No pre-HD AVA
Pre-HD AVA
0
100
200
300
365
Follow-up (days)

Table 1(on next page)

Characteristics of patients with and without prehemodialysis arteriovenous access

	Unmatched			Matched		
	Pre-HD AVA (N = 837)	No pre-HD AVA (N = 2310)	ASD (%)	Pre-HD AVA (N = 792)	No pre-HD AVA (N = 792)	ASD (%)
Age, years						
Median (IQR)	66 (56-74)	71 (59-79)	29.9*	67 (56-75)	66 (55-75)	2.42
Sex, male (%)	440 (52.57)	1157 (50.09)	4.96	401 (50.63)	423 (53.41)	5.56
Income, NTD/year			15.3*			1.83
Dependent	296 (35.36)	878 (38.01)		284 (35.86)	288 (36.36)	
1-19999	206 (24.61)	700 (30.30)		197 (24.87)	197 (24.87)	
20000-39999	275 (32.86)	645 (27.92)		259 (32.70)	261 (32.95)	
≥40000	60 (07.17)	87 (03.77)		52 (06.57)	46 (05.81)	
Comorbidities						
HTN	712 (85.07)	1899 (82.21)	7.73	670 (84.60)	673 (84.97)	1.05
IHD	218 (26.05)	649 (28.10)	4.61	197 (24.87)	200 (25.25)	0.87
CHF	393 (46.95)	1150 (49.78)	5.66	364 (45.96)	364 (45.96)	0.00
CVA	76 (09.08)	363 (15.71)	20.2*	75 (09.47)	76 (09.60)	0.42
PVD	45 (05.38)	152 (06.58)	5.07	40 (05.05)	47 (05.93)	3.88
Dysrhythmia	50 (05.97)	226 (09.78)	14.1*	49 (06.19)	44 (05.56)	2.68
DM	461 (55.08)	1303 (56.41)	2.60	429 (54.17)	440 (55.56)	2.79
COPD	81 (09.68)	379 (16.41)	20.0*	78 (09.85)	82 (10.35)	1.67
PUD	186 (22.22)	569 (24.63)	5.69	175 (22.10)	172 (21.72)	0.91
Liver disease	65 (07.77)	252 (10.91)	10.0*	65 (08.21)	56 (07.07)	4.27
Cancer	74 (08.84)	233 (10.09)	4.25	71 (08.96)	69 (08.71)	0.80
Dementia	20 (02.39)	124 (05.37)	15.4*	20 (02.53)	17 (02.15)	2.50
Taiwan index (mean±SD)	5.55 ± 4.00	6.55 ± 4.40	23.0*	5.52 ± 4.02	5.52 ± 4.04	0.09
Medicine						
ESAs	684 (81.72)	804 (34.81)	108.*	639 (80.68)	635 (80.18)	1.27
Antiplatelets	537 (64.16)	1563 (67.66)	7.30	505 (63.76)	505 (63.76)	0.00
Anticoagulants	75 (08.96)	161 (06.97)	7.35	53 (06.69)	51 (06.44)	1.00
ACEI / ARBs	507 (60.57)	1579 (68.35)	16.3*	485 (61.24)	500 (63.13)	3.90
Statins	262 (31.30)	665 (28.79)	5.48	244 (30.81)	247 (31.19)	0.81

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: ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; 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%

1

Table 2(on next page)

Clinical outcomes of patients with and without prehemodialysis arteriovenous access

	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)	0.93 (0.73-1.18)	0.94 (0.74-1.21)
CHF	0.52 (0.40-0.68)***	0.65 (0.48-0.88)**	0.63 (0.46-0.86)**	0.63 (0.46-0.87)**
Secondary outcomes				
All-cause mortality	0.28 (0.23-0.34)***	0.48 (0.39-0.59)***	0.47 (0.37-0.60)***	0.46 (0.36-0.59)***
MACE-related mortality	0.37 (0.25-0.55)***	0.70 (0.45-1.08)	0.59 (0.37-0.93)*	0.60 (0.38-0.96)*
BSI-related mortality	0.21 (0.15-0.30)***	0.32 (0.22-0.46)***	0.30 (0.20-0.45)***	0.29 (0.19-0.44)**

[a]Adjusted for age, sex, income, year of hemodialysis, comorbidities, and medicine; [b]adjusted for age, sex, income, year of hemodialysis, Taiwan index, hypertension, dementia, and medicine. 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. Abbreviations: BSI: bloodstream infection; CHF: congestive heart failure; HR: hazard ratio; MACEs: major adverse cardiovascular events. *$p < 0.05$; **$p < 0.01$; ***$p < .001$

1

Table 3(on next page)

Sensitivity analyses of clinical outcomes of patients with and without prehemodialysis arteriovenous access

	SA1[b]	SA2[c]	SA3[d]	SA4[e]
Primary outcomes				
MACEs, aHR[a]	0.77 (0.62-0.97)*	0.82 (0.64-1.05)	0.90 (0.74-1.10)	0.88 (0.69-1.13)
CHF, aHR	0.57 (0.42-0.77)***	0.60 (0.43-0.84)**	0.69 (0.53-0.91)**	0.71 (0.51-0.98)*
Secondary outcomes				
All-cause mortality, aHR	0.94 (0.72-1.22)	0.65 (0.46-0.91)*	0.50 (0.42-0.60)***	0.47 (0.36-0.61)***
MACE-related mortality, aHR	0.93 (0.56-1.56)	0.79 (0.42-1.49)	0.65 (0.43-0.97)*	0.70 (0.43-1.17)
BSI-related mortality, aHR	0.60 (0.39-0.92)*	0.38 (0.21-0.67)***	0.34 (0.25-0.47)***	0.29 (0.19-0.46)***

[a]Adjusted for age, sex, income, year of hemodialysis, comorbidities, and medicine; [b]exclusion of patients not receiving arteriovenous access in the first year of dialysis; [c]exclusion of patients not receiving regular hemodialysis. [d]inclusion of patients receiving arteriovenous access less than 1 month before the first hemodialysis; [e]inverse probability of treatment weighting of study subjects. Abbreviations: aHR: adjusted hazard ratio; BSI: bloodstream infection; CHF: congestive heart failure; MACEs: major adverse cardiovascular events; SA: sensitivity analysis. *$p < 0.05$; **$p < 0.01$; ***$p < .001$

1