Kidney Diseases

Research Article

Kidney Dis
DOI: 10.1159/000529802

Received: September 8, 2022
Accepted: February 13, 2023
Published online: March 3, 2023

Clinical Outcomes in Patients on Hemodialysis with Congestive Heart Failure

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Keywords
Congestive heart failure · Mortality · Cardiovascular death · Hemodialysis · DOPPS

Abstract
Introduction: Congestive heart failure (CHF) is one of the common complications in patients with end-stage kidney disease. In the general population, CHF increases the risk of the death. However, there is no well-designed relevant study in the Chinese hemodialysis (HD) population addressing the risks associated with CHF. The aim of this study was to explore the impact of CHF on clinical outcomes in HD patients. ***Methods:*** Data from a prospective cohort study, the China Dialysis Outcomes and Practice Patterns Study (DOPPS) 5 (2012–2015), were analyzed. Demographic data, comorbidities, lab data, and death records were extracted. CHF was defined by the diagnosis records upon study inclusion. Our primary outcome was all-cause and cardiovascular (CV) mortality; secondary outcomes were all-cause and cause-specific hospitalization risk. Associations between CHF and outcomes were evaluated using Cox regression models. Stepwise multivariate logistic regression was used to identify the related risk factors, and subgroup analyses were carried out. ***Results:*** Of 1,411 patients without missing CHF history information, 24.1% (340) had CHF diagnosis at enrollment. The overall mortality rates were 21.8% versus 12.0% ($p < 0.001$) in patients with and without CHF during follow-up, respectively. CHF was associated with higher all-cause mortality (adjusted HR: 1.72, 95% confidence interval [CI]: 1.17–2.53, $p = 0.006$), and the association with CV death was of similar magnitude (HR: 1.60, 95% CI: 0.91–2.81, $p = 0.105$). CHF patients had more episodes of hospitalization due to heart failure (HR: 2.93, 95% CI: 1.49–5.76, $p < 0.01$). However, compared with patients without CHF, the all-cause hospitalization risk was not much higher in CHF patients (HR: 1.09, 95% CI: 0.90–1.33, $p = 0.39$). Subgroup analysis found that the effect of CHF on all-cause mortality was stronger for male patients, patients with residual renal function, the elderly (≥60 years of age), patients with arteriovenous

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fistulae vascular accesses, nondiabetic patients, low-flux dialyzer users, and inadequately dialyzed patients (standardized Kt/V <2). ***Conclusion:*** In HD patients, CHF was found to be associated with a higher risk of all-cause mortality and cause-specific hospitalization risk. Further research is needed to identify opportunities to improve care for HD patients combined with CHF.

Introduction

Hemodialysis (HD) is a unique treatment modality which offers a life-sustaining treatment option for patients with end-stage kidney disease (ESKD). There are approximately 3 million HD patients worldwide [1]. This number is estimated to reach 5.4 million by 2030 [1]. In 2016, there were about 578,000 dialysis patients in China [2]. It has been reported that the prevalence of HD patients increased to 692,736 cases at the end of 2020 [3].

Despite advancements in medical technologies, the mortality of HD patients is still unacceptably high compared with the general population [4, 5]. Cardiovascular diseases (CVDs) (including myocardial infarction, heart failure [HF], and stroke) are the leading causes of death in dialysis-dependent ESKD patients, accounting for approximately 40% of mortality [4]. Congestive HF (CHF) is a final common clinical pathway for several diseases, such as coronary artery disease, high blood pressure (BP), and diabetes, and for adults with other cardiovascular (CV) and kidney disease risk factors. With the deterioration of renal function, the chance of CHF increases, which varies among the modalities of kidney replacement therapy, including transplantation [6, 7]. HD patients are at 12–36 times higher risk for the development of CHF [7, 8]. It has been reported that the prevalence of HF was as high as 33%–40% in Medicare ESKD patients in the USA [9, 10]. ESKD and HF have the same traditional common causes. ESKD patients also have nontraditional risk factors unique to chronic kidney disease, such as inflammation, anemia, and disorders of bone and mineral metabolism [6, 7, 11, 12]. The concurrent presence of both conditions tends to accelerate the progression of each of them and increases the risks of the hospitalization, rehospitalization, need for intensive care or dialysis, and death [6, 7]. Recurrent CHF for prevalent HD patients has been shown to be an independent adverse prognostic factor. However, limited progress has been made in the improvement of the survival of patients with combined HF and chronic dialysis, which warrants further research.

Little is known about the prevalence and the outcomes in patients with combined CHF and HD in the Chinese population. Thus, we analyzed a large group of patients in the China Dialysis Outcomes and Practice Patterns Study (DOPPS). We mainly investigated the association between CHF and all-cause mortality, CV mortality, and all-cause and cause-specific hospitalization risks.

Materials and Methods

Study Design and Subjects

The DOPPS (www.dopps.org) is an international prospective cohort study of 18-year-old or older patients receiving in-center HD treatment [13, 14]. China joined DOPPS in 2011. China DOPPS randomly selected an average of 30 patients from 15 dialysis facilities in Beijing, Shanghai, and Guangzhou. This has been described in previous publications [15–17]. 1,427 patients participated in China DOPPS 5 (2012–2015). Of the 1,427 patients, 16 patients were excluded from the present analysis as their CHF history information was missing. Baseline demographic and clinical data were collected at the initiation of DOPPS 5.

The data underlying this article cannot be shared publicly, due to privacy concerns for the individuals who participated in the study. The data will be shared upon reasonable request to the DOPPS project; see https://www.dopps.org/PartnerwithUs.aspx for more information. The study was approved by the Ethics Committee of Peking University People's Hospital (ethical approval number: 2018PHB028-01). Other participating subcenters also obtained Ethics Committee approval documents prior to the start of clinical trials. All patients provided written, informed consent. The authors confirm that all the methods used in this study comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration.

Patient Groups

Participants were divided into 2 groups according to their CHF diagnosis records. Patients with diagnosed CHF were assigned as the CHF group and patients without the diagnosis as the non-CHF group.

Outcomes

The primary end-point was all-cause and CV mortality. The secondary end-point event was all-cause and cause-specific hospitalization risk during the follow-up period.

CV mortality was defined by the primary death records in the dataset. The following diagnoses in the primary death records were considered CV mortality: atherosclerotic heart disease, cardiac arrest, cardiac arrhythmia, cardiomyopathy, cerebrovascular accident (including intracranial hemorrhage), CHF, hemorrhage from ruptured vascular aneurysm, ischemic brain damage/anoxic encephalopathy, acute myocardial infarction, pulmonary embolus, stroke, and valvular heart disease. We also wanted to explore possible impact factors of CHF and the effect of CHF on all-cause mortality across clinically relevant subgroups.

Statistical Analysis

Continuous variables were represented as mean ± SD or median (25th, 75th percentile) for variables with skewed or otherwise non-normal distributions. Categorical variables were expressed as percentages. We stratified data by CHF and non-CHF groups. Differences in the mean and the median among groups were evaluated using ANOVA and nonparametric tests, respectively. Categorical data were compared using the χ^2 test.

Survival curves were produced by the Kaplan-Meier method. We used Cox proportional hazards models to assess the association between the CHF status and all-cause mortality, CV mortality, and hospitalization risks. All Cox models accounted for facility clustering effects by using the robust sandwich covariance estimate. Survival time for Cox models of all-cause mortality was the time from the study entry to the end of the study or to death, whichever occurred first. A similar calculation was made for the CV mortality risk. The non-CHF group was taken as the reference group for all the analyses. We produced Cox regression models with five incremental levels of covariate adjustment to show the effects of adjusting for each group of covariates.

Model 1: unadjusted; model 2: adjusted for age, sex, body mass index, dialysis vintage; model 3: model 2 variables plus comorbidities (diabetes, coronary artery disease, other CVDs, cerebrovascular disease, hepatitis B and C, cancer [non-skin], peripheral vascular disease, lung disease, hypertension, psychiatric disorder, gastrointestinal bleeding, recurrent cellulitis, fracture, neurologic disease); model 4 (case-mix + laboratory): model 3 plus hemoglobin, albumin, white blood cells, pre-dialysis serum potassium, and pre-dialysis serum creatinine; model 5: model 4 plus intradialytic weight loss, fistula use, primary kidney disease, standardized Kt/V (stdKt/V), urine output <200 mL/d. Intradialytic weight loss was defined as the value from pre-dialysis weight minus post-dialysis weight for the 2nd dialysis session of the week.

We examined proposed clinically relevant variables by univariate logistic regression models, and relatively significant variables ($p < 0.15$) were added stepwise into a multivariate logistic regression analysis to identify the impact factors of CHF. Comorbidities were categorized into yes or no variables. Dialysis adequacy was divided into 2 groups according to the stdKt/V (<2 or ≥2) which is more precise, especially for patients not dialyzed thrice per week. Odds ratios and 95% confidence intervals (CIs) were calculated for each variable.

We performed the MI procedure to impute missing data, and continuous and categorical variables were imputed 25 times by fully conditional specification regression and logistic regression, respectively. The imputed datasets were analyzed using the MI Analyze procedure in SAS/STAT 9.4. The percentages of missing data for most variables were <10%, except for single-pooled Kt/V (62.7%). A p value of < 0.05 was considered statistically significant. All statistical analyses were performed with SAS, version 9.4 (SAS institute, Cary, NC, USA).

Results

Demographic Data and Clinical Characteristics

1,411 (98.9%) patients had baseline CHF status records. In the study cohort, male patients accounted for 54.9% of the patients. The median age was 60.0 (49.0, 71.0) years, and median dialysis vintage was 2.6 (0.9, 5.4) years. The median follow-up period was 1.9 (1.2, 2.1) years. A flowchart of the follow-up results is presented in Figure 1. The baseline characteristics of HD patients are shown in Table 1. The prevalence of CHF was 24.1%. Patients with CHF tended to be older, with lower albumin and creatinine, lower fistular usage, and with more frequent diabetes and CVD burdens (Table 1).

Associations between CHF and Outcomes

Among the 1,411 included patients, 203 (14.4%) died; 103 (7.3%) of these died from CVD. CV death constituted half of the patients' mortality. The mortality risk was higher in patients with CHF compared with patients without CHF (21.8% vs. 12.6%). At the end of the follow-up, patients that survived had lower CHF diagnoses than patients who died (22.0% vs. 36.5%). The distribution of the primary causes of death is shown in Table 2. According to the results of the Kaplan-Meier analysis, patients with CHF had significantly higher risk of all-cause mortality and CV-related deaths (log-rank test; $p < 0.01$; Fig. 2a and b). In the fully adjusted Cox model, CHF was associated with higher all-cause mortality after adjusting for covariates (HR: 1.72, 95% CI: 1.17–2.53, $p = 0.006$, Fig. 3). The association with CV death was of similar magnitude, though not reaching the statistical significance level of 0.05 (HR: 1.60, 95% CI: 0. 91–2.81, $p = 0.105$). CHF patients had more episodes of hospitalization due to CHF (HR: 2.93, 95% CI: 1. 49–5.76, $p < 0.01$). However, the all-cause hospitalization risk was similar in the two groups (HR: 1.09, 95% CI: 0.90–1.33, $p = 0.39$).

Impact Factors of CHF

Data for pre-dialysis diastolic BP (DBP) was also included after the univariate regression analysis and was further divided into 4 groups: <65 mm Hg, 65–74 mm Hg, 75–84 mm Hg, and ≥85 mm Hg. Stepwise multivariate logistic regression showed that coronary heart disease and diabetes comorbidity are independent risk factors of CHF, whereas higher pre-dialysis DBP and stdKt/V are reversely associated with CHF risk (Table 3).

Subgroup Analysis

CHF was associated with all-cause mortality for male patients, patients with relatively shorter dialysis vintage (≤5 years), with residual renal function (urine output ≥ 200 mL/d), with arteriovenous fistulae as their blood access, nondiabetic or hypertensive patients, and low-flux dialyzer users (Table 4).

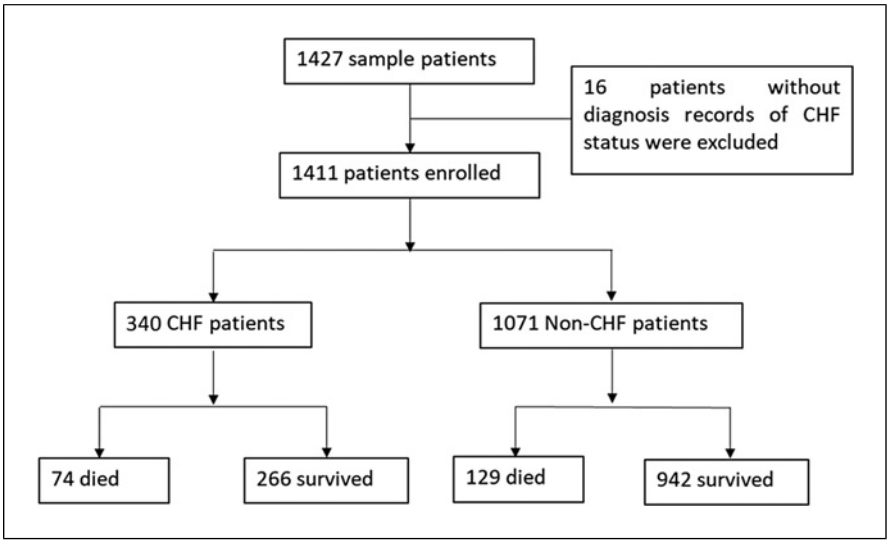

Fig. 1. Patients and follow-up flowchart for this cohort.

Discussion

In this large prospective cohort study of HD patients, we found that the combination of HD with CHF was positively associated with all-cause mortality. This result is in line with similar observations that were made in incident dialysis patients in the USA [10]. In a historic cohort study of more than 1,900 patients enrolled in the US Renal Data System Dialysis Morbidity and Mortality Study Wave 2, the incidence of HF was 71 per 1,000 person-years, with an 83% mortality rate at 3 years [18, 19]. CV mortality in our study was the leading cause of death, accounting for half of patients' mortality, which was consistent with previous findings [4]. The association between CHF and CV mortality followed a similar trend yet was not statistically significant after adjustments. We propose that this might be due to the small number of event cases. A larger sample size is needed to further analyze this issue. To the best of our knowledge, this is the first study focused on investigating the association between CHF and mortality in the Chinese dialysis population, and the findings of the present paper expand upon our prior knowledge.

Studies have shown that HD patients with CHF have a higher hospitalization risk [18, 20]. However, in our study, the all-hospitalization risk was similar among HD patients with and without CHF. This might be partly due to different criteria and policies in place for hospital admission in different countries and areas. Therefore, this analysis could be biased. Not surprisingly, we found that HF-related hospitalization risk is higher for CHF patients. In some studies, researchers have found that repeated hospitalization for CHF patients was associated with a higher mortality risk [21–24]. Whether this is true for Chinese HD patients with CHF needs further research.

It is estimated that around 40% of patients on HD have CHF [6, 9], which is higher than what we reported here. Our reported prevalence rate could underestimate the real condition in this cohort. In our database, we did not collect echocardiography, B-type natriuretic peptide (BNP), or N-terminal pro-BNP, which could detect asymptomatic HF patients, thus causing an underestimation for the prevalence rate of CHF. The prevalence also varies among different dialysis populations with different ethnicities, underlying CHF causes, ESKD primary diseases, patients' complications, medical conditions, and dialysis practice patterns as well [7]. Another possible reason could be the constantly changing HF definition and diagnosis criteria, which could lead to some differences in the disease prevalence figures [6, 9, 25, 26].

The recognized risk factors for HF in chronic kidney disease and ESKD include long-standing hypertension, salt and water retention causing excessive preload, and cardiomyopathic factors including left ventricular hypertrophy and fibrosis and other novel possible risk factors like fibroblast growth factor 23 [6, 7, 11, 12]. In the present study, we found that comorbidity of coronary heart disease or diabetes was an independent risk factor for CHF, which is consistent with previous findings [6, 7, 9, 11]. We also found that pre-dialysis DBP was negatively related with CHF risks. In the general population, the Framingham Heart Study showed that each component of BP, including systolic, diastolic, and pulse

Table 1. Baseline characteristics of HD patients with and without CHF

Variables	All (n = 1,411)	CHF (n = 340)	Non-CHF (n = 1,071)	p value
Demographics				
Age, years	60.0 (49.0, 71.0)	63.0 (52.0, 74.0)	59.0 (49.0, 70.0)	<0.01
Males, %	54.9	56.5	54.3	0.53
Dialysis vintage, years	2.6 (0.9, 5.4)	2.5 (1.0, 5.3)	2.6 (0.8, 5.5)	0.89
BMI	21.9±3.71	22.0±3.63	21.9±3.74	0.05
Urine output >200 mL/day, %	31.8	30.6	32.1	0.64
Primary kidney diseases, %				
Glomerulonephritis	39.3	31.5	41.8	<0.01
Diabetic nephropathy	23.5	37.6	19.0	
Hypertensive nephropathy	15.5	17.6	14.8	
Others	21.6	13.2	24.3	
Laboratory tests				
Hgb, g/dL	10.6 (9.4, 11.7)	10.7 (9.1, 11.8)	10.6 (9.5, 11.7)	0.67
Alb, g/dL	4.0 (3.7, 4.2)	3.9 (3.6, 4.1)	4.0 (3.7, 4.2)	<0.01
White blood cells, 10^9/L	6.0 (4.9, 7.3)	6.1 (5.0, 7.3)	6.0 (4.8, 7.3)	0.24
Creatine, mg/dL	10.1 (8.0, 12.5)	9.6 (7.5, 12.1)	10.3 (8.1, 12.6)	<0.01
Potassium, mmol/L	5.0±0.8	5.0±0.8	4.9±0.9	0.53
Dialysis prescription				
spKt/V	1.4 (1.2, 1.6)	1.3 (1.2, 1.5)	1.4 (1.2, 1.6)	0.20
stdKt/V	2.0±0.35	2.0±0.37	2.0±0.35	0.05
Dialysis <3 times/week (%)	21.4	19.4	22.0	0.32
Intradialytic weight loss (%)	2.4 (1.6, 3.1)	2.5 (1.8, 3.2)	2.3 (1.6, 3.1)	0.05
Fistula use, %	84.9	78.8	86.8	<0.01
Low-flux dialyzer, %	73.6	72.8	76.0	0.26
Comorbidities, %				
Diabetes	27.6	42.4	22.9	<0.01
Coronary artery disease	25.2	44.7	19.0	<0.01
Other CV diseases	21.1	47.4	12.8	<0.01
Cerebrovascular disease	14.5	26.8	10.6	<0.01
Hypertension	86.0	90.6	84.6	0.02
Peripheral vascular disease	9.1	19.1	5.9	<0.01
Hepatitis	13.0	11.8	13.4	0.63
Lung disease	5.0	10.3	3.3	<0.01
Cancer (non-skin)	3.9	3.5	4.0	0.92
Gastrointestinal bleeding	2.4	3.5	2.1	0.24
All-cause death	14.4	21.8	12.0	<0.01
Cardiac/vascular death	7.3	11.8	5.9	<0.01

CHF, congestive heart failure; BMI, body mass index; Hgb, hemoglobin; Alb, albumin; spKt/V, single-pooled Kt/V; stdKt/V, standardized Kt/V.

Table 2. The distribution of primary causes of death

Causes of deaths, n (%)	All
Cardiac/vascular	103 (50.7)
Liver disease	2 (1.0)
Infection	33 (16.3)
Gastrointestinal	8 (3.9)
Metabolic	6 (3.0)
Other	19 (9.4)
Unknown	32 (15.8)

pressure, was associated with a risk for incident CHF, and pulse and systolic pressure conferred a greater risk than diastolic pressure [27] Furthermore, BP has been found to be positively associated with the risk of death from HF, where randomized trials have demonstrated that this association is causal [12, 28]. A meta-analysis of all the major BP-lowering trials has shown that a 10-mm Hg reduction in systolic BP lowers the risk of HF by 28% (95% CI: 22–33) [12, 29]. However, there is a phenomenon called "decapitated hypertension," which means that patients who have had hypertension at the

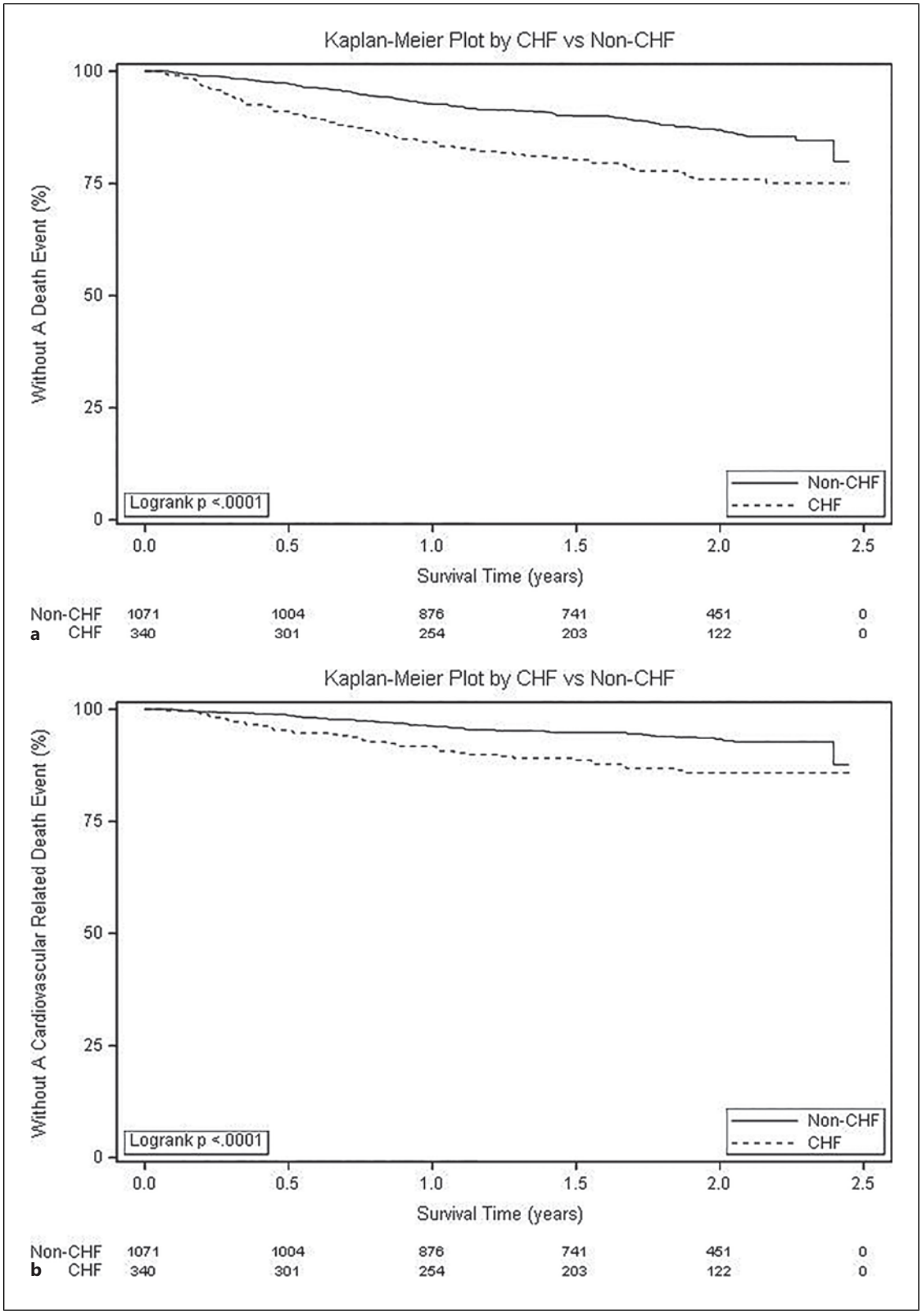

Fig. 2. Kaplan-Meier curves for CHF and non-CHF groups in HD patients. **a** Survival curves of all-cause mortality. **b** Survival curves of CV mortality between two groups. HD, hemodialysis; CHF, congestive heart failure; non-CHF, without congestive heart failure.

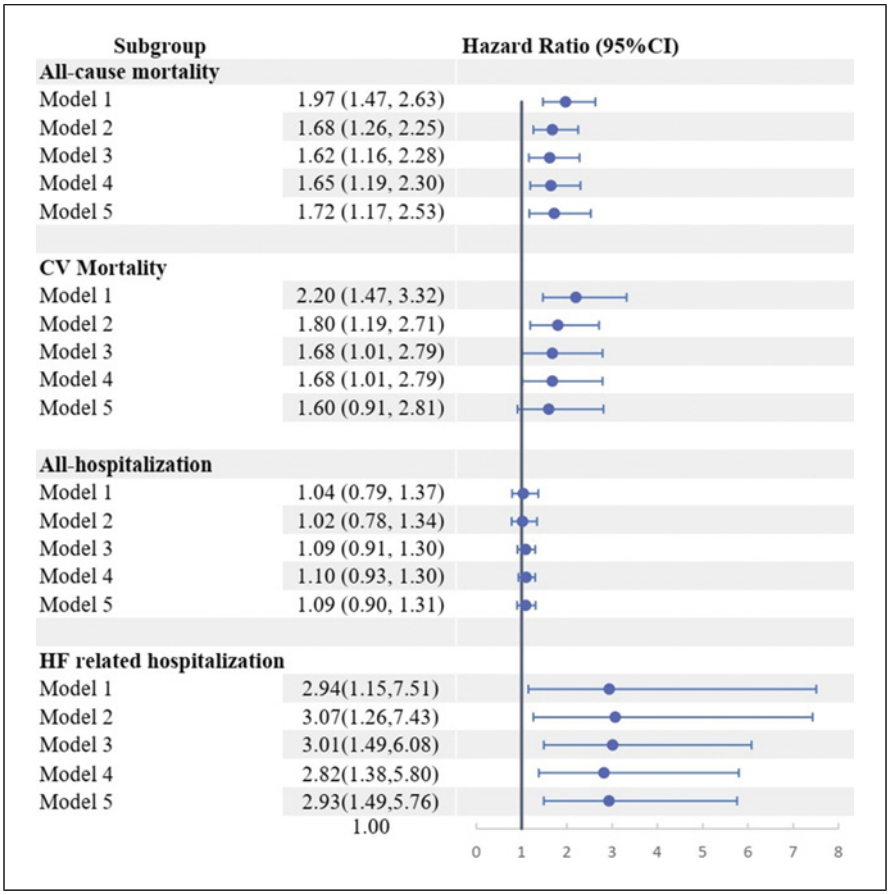

Fig. 3. Associations between the CHF status (yes vs. no) and all-cause mortality, CV mortality, and hospitalization risk in different Cox regression models. Notes: Model 1: unadjusted; model 2: adjusted for age, gender, BMI, dialysis vintage; model 3: model 2 variables plus comorbidities (diabetes, coronary artery disease, CHF, other CV diseases, cerebrovascular disease, hepatitis B and C, cancer [non-skin], peripheral vascular disease, lung disease, hypertension, psychiatric disorder, gastrointestinal bleeding, recurrent cellulitis, fracture, neurologic disease); model 4: model 3 plus hemoglobin, albumin, white blood cells, potassium, and serum creatinine; model 5: model 4 plus intradialytic weight loss, fistula use, primary kidney disease, standard Kt/V, urine output >200 mL/d. CHF, congestive heart failure; non-CHF, without congestive heart failure; BMI, body mass index.

Table 3. Stepwise multivariate logistic regression for risk factors of CHF

Variables	ORs	95% CI	*p* value
Coronary heart disease	4.17	2.77–6.23	<0.01
Diabetes	1.68	1.10–2.57	0.02
Pre-dialysis DBP	0.62	0.40–0.94	0.02
stdKt/V	0.50	0.28–0.88	0.01

OR, odds ratio.

outset progressively develop normal and even low BP as HF worsens and becomes more severe [30]. Hence, BP paradox in patients with HF appears. Both lower SBP and DBP were associated with a significant risk of adverse outcomes in patients with HF [30–32]. Our findings suggest that pre-dialysis DBP was adversely associated with CHF risk. The lower DBP could be due to pump failure for some CHF patients per the "decapitated hypertension" phenomenon. Therefore, higher DBP might be less associated with the risk of CHF. Moreover, understanding BP and CHF risk could be very complicated for HD patients compared with non-HD patients. Because usually they have pre- and post-dialysis BP measurements, including SBP and DBP, which might be imprecise estimates of real BP control for this population [33]. The current opinion is to use 44-h ambulatory BP monitoring and home BP measurements to define and monitor patients' BP, which might be a more reliable indicator for HD patients [34, 35]. This finding is complex and needs further prospective cohort studies.

For the first time, we identified dialysis adequacy (stdKt/V) as a potential impact factor of CHF. Dialysis adequacy directly reflects the removal of uremic toxins and is associated with inflammation, anemia, and nutritional status [36], which might serve as risk factors of CVD. Studies have shown that dialysis dose or adequacy or even the blood flow rate were associated with mortality or cause-specific mortality [17, 37–41]. However, how dialysis adequacy is associated with CHF is worthy of further research.

Why the effect of CHF on all-cause mortality was more prominent in some subgroups was complicated. In

Table 4. Effect of CHF on all-cause mortality across clinically relevant subgroups

Variables	Hazard ratios	95% CI	*p* value
Age, years			
<60	1.19	0.55–2.59	0.66
≥60	1.74	0.97–3.12	0.06
Gender			
Male	2.23	1.41–3.55	<0.01
Female	1.20	0.69–2.12	0.52
Dialysis vintage, years			
>5	0.80	0.31–2.08	0.65
≤5	1.94	1.28–2.94	<0.01
Blood access type			
Arteriovenous fistulae	1.79	1.23–2.62	<0.01
Catheter and others	1.09	0.34–3.45	0.89
Urine output			
<200 mL/d	1.26	0.85–1.86	0.25
≥200 mL/d	4.29	2.00–9.23	<0.01
Diabetes			
Yes	1.65	0.72–3.75	0.23
No	1.54	0.99–2.38	0.05
Hypertension			
Yes	1.77	1.21–2.57	<0.01
No	1.03	0.25–4.21	0.97
Dialyzer type			
High-flux	2.60	0.89–7.62	0.08
Low-flux	1.58	1.10–2.26	0.01

general HF patients, it has been shown that there are sex disparities: men are predisposed to HF with reduced ejection fraction, whereas women predominantly have HF with preserved ejection fraction [42–44]. Sex differences are also notable in the penetrance of genetic cardiomyopathies, risk factors, and so on [42, 43, 45]. However, there is no specific relative study for dialysis patients yet. The fact that arteriovenous fistulae usage could induce or deteriorate HF in dialysis patients has been well recognized [6, 46]. Patients with more urine production (≥200 mL/d) were more likely to also have CHF. This might be due to their reluctance to remove adequate water during dialysis treatments. Patients want to preserve their residual renal function, and some of them may have inadequate water removal from dialysis and hence are overhydrated. Low-flux dialyzer users might be at higher mortality risk when combined with CHF. Low-flux dialyzers could not clear large middle molecules including cytokines, adipokines, hormones, and other proteins. These molecules are implicated in chronic inflammation, atherosclerosis, structural heart disease, and secondary immunodeficiency which might have a role in inducing vascular calcification, CVD, and hence HF [47, 48]. Why the effect was stronger in other patient groups also needs further study.

Our study has several limitations. First, as noted before, this is an observational study, which might have inherent shortcomings, such as selection bias and confounding factors. Second, the study suffered from lack of additional measurements of echocardiography and serum biomarkers, especially left ventricular ejection factor and BNP measures. However, the cutoff value and meaning for biomarkers like BNP or NT-proBNP are still controversial in HD patients. Third, CHF diagnosis for a patient was based upon medical record abstraction, which could be misclassified for a patient. Fourth, patients were from 3 big cities in China, not including patients from rural and sub-urban areas, which suggests that the conclusions should be restricted to a similar patient population and should be cautiously expanded to other populations. In addition, we could not perform analyses related to drug usage. Nevertheless, we believe these factors should not affect our conclusions regarding our main findings.

Conclusion

In this prospective cohort study, the prevalence of CHF was identified to be around one quarter, and all-cause mortality in patients with combined CHF and HD was found to be higher. CHF was associated with increased risk of all-cause mortality and cause-specific hospitalization risk in HD patients. The associations were not affected by adjustment for several potential confounding factors. Thus, CHF was found to be an outcome predictor for HD patients, and measures should be adopted to improve care for these patients to improve their survival.

Acknowledgments

We thank all colleagues participating in our study for their arduous work and all the patients for their cooperation.

Statement of Ethics

The study was approved by the Ethics Committee of Peking University People's Hospital (ethical approval number: 2018PHB028-01). Other participating subcenters also obtain Ethics Committee approval documents prior to the start of clinical trials. All patients signed the written informed consent.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Funding Sources

The Dialysis Outcomes and Practice Patterns Study (DOPPS) Program in China is supported by Vifor Fresenius Renal Pharma, Sanofi Renal, Nipro Trading (Shanghai) Co., Ltd, 3SBio Inc., B. Braun, and CEMMA MEDICAL. None of these entities had any role in the study design, data collection, analysis, interpretation, and writing of the report. None of the support provided by these entities imposed any restriction on the publications of the results. This article was supported by Beijing Natural Science Foundation (No 7222201), and the grant recipient is Li ZUO.

Author Contributions

X.Z. and L.Z. contributed to conception and design of the research. X.Z., L.G., and Q.N. analyzed the data. X.Z., Q.N., Z.N., and L.Z. interpreted the results of the experiments. X.Z. wrote the draft manuscript. L.G., F.F.H., X.L., X.C., Y.C., J.Z., K.M., Z.N., and L.Z. edited and revised the manuscript. Z.N. and L.Z. has primary responsibility for the final content. All the authors have read and approved the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the DOPPS project; see https://www.dopps.org/PartnerwithUs.aspx for more information.

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