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FULL RESEARCH PAPER
Congenital heart disease

Advanced heart failure in adult congenital heart disease: the role of renal dysfunction in management and outcomes

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Aims Previous studies in adult congenital heart disease (CHD) have demonstrated a link between renal dysfunction and mortality. However, the prognostic significance of renal dysfunction in CHD and decompensated heart failure (HF) remains unclear. We sought to assess the association between renal dysfunction and outcomes in adults with CHD presenting to our centre with acute HF between 2010 and 2021.

Methods and results This retrospective analysis focused on the association between renal dysfunction, pre-existing and on admission, and outcomes during and after the index hospitalization. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2. Cox regression analysis was used to identify the predictors of death post-discharge. In total, 176 HF admissions were included (mean age 47.7 ± 14.5 years, 43.2% females). One-half of patients had a CHD of great complexity, 22.2% had a systemic right ventricle, and 18.8% had Eisenmenger syndrome. Chronic kidney disease was present in one-quarter of patients. The median length of intravenous diuretic therapy was 7 (4–12) days, with a maximum dose of 120 (80–160) mg furosemide equivalents/day, and 15.3% required inotropic support. The in-hospital mortality rate was 4.5%. The 1- and 5-year survival rates free of transplant or ventricular assist device (VAD) post-discharge were 75.4% [95% confidence interval (CI): 69.2–82.3%] and 43.3% (95% CI: 36–52%), respectively. On multivariable Cox analysis, CKD was the strongest predictor of mortality or transplantation/VAD. Highly complex CHD and inpatient requirement of inotropes also remained predictive of an adverse outcome.

Conclusion Adult patients with CHD admitted with acute HF are a high-risk cohort. CKD is common and triples the risk of death/transplantation/VAD. An expert multidisciplinary approach is essential for optimizing outcomes.

Lay summary

- Renal dysfunction was associated with more advanced disease, higher diuretic doses, and a longer hospital inpatient stay.
- Chronic kidney disease was common and tripled the risk of death, transplantation, or ventricular assist device.
- Renal dysfunction in adults with congenital heart disease and heart failure should prompt intensified monitoring, optimization of medical therapy, and collaborative management with renal physicians.

Keywords Adult congenital heart disease • Heart failure • Renal failure • Chronic kidney disease • Bayesian analysis

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Previous presentations: Some of the results of this study have been previously reported in the form of an abstract (https://doi.org/10.1093/eurheartj/ehac544.1819).

Introduction

The congenital heart disease (CHD) population is estimated at 12 million.[1,2] Adults account for two-thirds of cases of CHD and there has been a disproportionate increase in the prevalence of complex CHD. Despite vast improvements in survival afforded by stepwise advances in surgical, medical, and perioperative care, adults with CHD often have residual lesions, including valve dysfunction, shunts, surgical scarring, and myocardial fibrosis or dysfunction. These may result in arrhythmias, heart failure, and pulmonary vascular disease, and extra-cardiac organ dysfunction. Renal dysfunction is one such extra-cardiac sequela, prevalent in adults with CHD, and even mild renal impairment is a marker of adverse prognosis in unselected patients.[3] In acquired heart failure, the presence of renal impairment is associated with increased mortality and morbidity, but the role of acute and chronic kidney disease (CKD) in adults with CHD admitted with decompensated heart failure is not well-established.[4]

In this study, we sought to assess the association of renal dysfunction, along with other clinical variables, with outcomes, in adults with CHD presenting with acute decompensated heart failure requiring intravenous diuresis, in a large tertiary centre.

Methods

Data were collected retrospectively on consecutive patients above the age of 17 years, who presented with heart failure requiring intravenous diuretic therapy to a tertiary adult CHD centre in the UK between 1 January 2010 and 1 April 2021. The first presentation with heart failure over this period was included. Patients were identified, and demographic and clinical information were extracted, from the Royal Brompton and Harefield Hospitals Clinical Informatics Department, which included curated data from the clinical data warehouse, enriched with manual data collection from individual hospital records. Clinical details of the index hospitalization, including biochemistry and echocardiographic data, were assessed. Survival status was retrieved from the Primary Care Mortality Database in October 2021. The study was approved by the UK Health Research Authority (IRAS Project ID 275809) and based on data collected for routine clinical care and administrative purposes, and therefore did not require individual consent.

Patients admitted for ≤3 days or treated exclusively with oral diuretics were excluded as were patients with genetic aortopathies (e.g. Marfan's syndrome, Loeys–Dietz syndrome). Congenital heart disease complexity was determined for each patient on the basis of the anatomic classification defined in the American Heart Association/American College of Cardiology adult CHD guidelines.[5] Chronic kidney disease referred to CKD Stages III–V and was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, on a blood test taken >3 months pre-admission where available, using the simplified Modification of Diet in Renal Disease (MDRD) equation.[6] Chronic kidney disease was not assumed in patients who did not have a baseline blood test. Renal dysfunction on admission was defined as an eGFR <90 mL/min/1.73 m^2 (any) or <60 mL/min/1.73 m^2 (moderate–severe). Resting cyanosis was defined as oxygen saturation <90%. All diuretic doses are given in milligram furosemide equivalents.

Statistical analysis

Statistical analyses were performed using *R* version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as mean ± standard deviation or median (interquartile range). Categorical variables are presented as number (percentage). The denominator for percentages was the total number of patients with available data for each variable analysed. Comparisons between groups were performed using the Wilcoxon rank sum test for continuous variables and the χ^2 test for categorical variables. The relationship between hospital length of stay and clinical variables was assessed using a generalized linear model with a gamma distribution. Survival analysis was performed for the endpoint of all-cause mortality, heart or heart–lung transplantation, or placement of long-term mechanical circulatory support/ventricular assist device (VAD). Patients surviving to hospital discharge without the need for heart transplantation or VAD were included in the survival cohort. Patients were censored if they were alive at the end of the study (1 June 2022). Transplant/VAD-free survival differences in Kaplan–Meier survival curves were evaluated using the Logrank test. Univariable Cox regression analysis was used to assess the relationship between baseline clinical variables and transplant/VAD-free survival. Missing data were imputed using multiple imputation by chained equations (package 'mice') to generate 10 imputed data sets. Multiplicative terms were created prior to multiple imputation, whereas log transformation of skewed variables was performed post-imputation. Collinearity testing was undertaken pre- and post-multiple imputation (collinearity indicated by a variance inflation factor <3). Variables with high missingness (>20%) were not imputed or included in the subsequent analysis, apart from serum b-type natriuretic peptide (BNP) concentration as a sensitivity analysis. Multivariable Cox regression analysis was performed on each imputed data set and pooled estimates generated. Full Bayesian criterion-based model selection and model averaging on imputed data were undertaken using the Cox proportional hazards model (package 'mami').[7,8] Posterior effect probabilities were reported for each variable to judge the posterior probability that the Hazard in the Cox regression model for a variable was not 1, taking model selection uncertainty into account. As part of a sensitivity analysis, BNP levels were multiply imputed and included in the multivariable model, model selection, and averaging. A two-sided *P*-value of <0.05 was considered indicative of statistical significance.

Results

Baseline characteristics

A total of 176 heart failure admissions fulfilled the inclusion criteria. Mean age was 47.7 ± 14.5 years and 76 (43.2%) were females. One half of patients (89, 50.6%) had CHD of great complexity. Definitive repair of CHD had been performed in less than half of the patients (81, 46.0%), while 46 (26.1%) had undergone palliative intervention and 49 (27.8%) were unoperated. The most frequent underlying forms of CHD were: tetralogy of Fallot (24, 13.6%), transposition of the great arteries after atrial switch operation (19, 10.8%), isolated ventricular septal defect [18, 10.2%, of whom 9 (50%) patients had Eisenmenger syndrome], or univentricular physiology after Fontan-type surgery (17, 9.7%; see Supplementary material online, *Table S1*). Eisenmenger syndrome was present in 33 (18.8%) patients, 39 (22.2%) had a systemic right ventricle, and 67 (38.1%) had resting cyanosis. A genetic syndrome was present in 14 (8.0%) patients, most commonly Down syndrome (5, 2.8%) and DiGeorge syndrome (3, 1.7%). Almost two-thirds of patients (111, 63.1%) had a history of atrial tachycardia or atrial fibrillation.

A history of CKD was present in a quarter of patients (43, 24.4%), but only a minority had previously required renal replacement therapy (6, 3.4%) or renal transplantation (0.6%). Adults with a history of CKD were older at the time of admission than those without CKD (56.0 ± 12.8 vs. 45.7 ± 14.2 years, $P < 0.001$), and were more likely to have a history of systemic hypertension (18.6 vs. 5.3%, $P = 0.02$) and cyanosis (53.5 vs. 33.1%, $P = 0.03$; *Table 1*). Cardiovascular risk factors for acquired heart disease were present in a minority of patients: 21 (12.1%) patients with diabetes mellitus and 15 (8.6%) systemic hypertension; the latter was more common in older patients (61.5 ± 9.4 vs. 46.8 ± 14.3 years, $P < 0.001$).

Assessment on admission

Most patients (107, 60.8%) were admitted with fluid overload as the main reason for hospitalization. Other reasons for admission included arrhythmia (27, 15.4%), infective endocarditis (6, 3.4%), and other infections (29, 16.5%) requiring intravenous diuresis following hospitalization.

Biochemical and echocardiographic admission data are summarized in *Table 2*. Of patients in whom serum BNP was measured on admission, 73 (64.6%) had a severely raised BNP >400 ng/L and 31 (27.4%) very severely raised BNP >1000 ng/L. BNP levels were higher in

Table 1 Baseline clinical and demographic characteristics in patients with and without chronic kidney disease

	All ($n = 176$)	No CKD ($n = 133$)	CKD ($n = 43$)	*P*-value
Male sex, *n* (%)	100 (56.8)	74 (55.6)	26 (60.5)	0.71
Age on admission, years	47.7 ± 14.5	45.2 ± 14.2	55.6 ± 12.8	**<0.001**
Complexity, *n* (%)				0.33
Complex	89 (50.6)	64 (48.1)	25 (58.1)	
Moderate	87 (49.4)	69 (51.9)	18 (41.9)	
Eisenmenger syndrome, *n* (%)	33 (18.8)	21 (15.8)	12 (27.9)	0.12
Systemic right ventricle, *n* (%)	39 (22.2)	30 (22.6)	9 (20.9)	0.99
Univentricular physiology, *n* (%)	25 (14.2)	16 (12)	9 (20.9)	0.23
Repaired CHD, *n* (%)	81 (46)	67 (50.4)	14 (32.6)	0.06
Unoperated CHD, *n* (%)	49 (27.8)	34 (25.6)	15 (34.9)	0.32
History of arrhythmia, *n* (%)	111 (63.1)	78 (58.6)	33 (76.7)	0.05
Diabetes mellitus, *n* (%)	21 (12.1)	13 (9.9)	8 (18.6)	0.21
Systemic hypertension, *n* (%)	15 (8.6)	7 (5.3)	8 (18.6)	**0.02**
Resting cyanosis, *n* (%)	67 (38.1)	44 (33.1)	23 (53.5)	**0.03**
Arrhythmia triggering admission, *n* (%)	27 (15.4)	23 (17.4)	4 (9.3)	0.3
Maintenance loop diuretics, *n* (%)	128 (72.7)	89 (66.9)	39 (90.7)	**0.004**
Maintenance loop diuretic dose, mg[a]	80 (40–100)	40 (40–80)	80 (40–160)	**<0.001**
ACEI/ARB on admission, *n* (%)	84 (47.7)	58 (43.6)	26 (60.5)	0.08
MRA on admission, *n* (%)	77 (43.8)	52 (39.1)	25 (58.1)	**0.04**
Beta-blocker on admission, *n* (%)	91 (51.7)	67 (50.4)	24 (55.8)	0.66
Digoxin on admission, *n* (%)	17 (9.7)	15 (11.3)	2 (4.7)	0.33

Bold font is representative of statistical significance ($P < 0.05$).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CHD, congenital heart disease; CKD, chronic kidney disease; MRA, mineralocorticoid receptor antagonist.
[a]Maintenance loop diuretic dose reported only for patients on diuretics in milligram furosemide equivalents.

Table 2 Biochemistry and echocardiographic parameters on heart failure admission in patients with and without chronic kidney disease

	All ($n = 176$)	No CKD ($n = 133$)	CKD ($n = 43$)	*P*-value
Sodium, mmol/L	136 (133–138)	136 (134–138)	135 (132–137)	**0.04**
Creatinine, mg/dL	1 (0.8–1.4)	0.9 (0.7–1.2)	1.7 (1.4–2)	**<0.001**
BNP, ng/L	574 (244–1136.2)	496 (236–898)	888 (487–1643.8)	**0.01**
Albumin, g/L	38 (33–41)	38 (33–41.3)	36 (33–41)	0.32
ALT, IU/L	19 (14.5–29)	20 (15–30.5)	17 (13–21)	**0.01**
Bilirubin, μmol/L	20 (13–30)	21 (13–31)	19 (14–26)	0.5
Systemic ventricular dilatation, *n* (%)	33 (20.6)	20 (16.5)	13 (33.3)	**0.04**
Systemic ventricular dysfunction, *n* (%)	36 (22.4)	22 (18.2)	14 (35)	**0.046**
Subpulmonary ventricular dilatation, *n* (%)	75 (52.4)	53 (48.2)	22 (66.7)	0.1
Subpulmonary ventricular dysfunction, *n* (%)	69 (48.3)	47 (42.7)	22 (66.7)	**0.03**
Pulmonary hypertension, *n* (%)	35 (28.2)	31 (32.6)	4 (13.8)	**0.01**
TAPSE, cm	1.4 (1.1–1.7)	1.4 (1.1–1.7)	1.4 (1.05–1.65)	0.8
RA area, cm^2	26.5 (17.9–33.6)	25.5 (16.6–32.3)	30.6 (23.2–38.5)	**0.005**
LA area, cm^2	23.2 (15.9–31.6)	22.5 (15.8–31.6)	25 (17.2–31.7)	0.39
RA/LA area ratio	1.1 (0.9–1.6)	1.1 (0.8–1.52)	1.2 (1–1.6)	**0.09**
S/D ratio	1.3 (1–1.6)	1.3 (1–1.7)	1.3 (1.05–1.6)	0.49
Presence of shunt, *n* (%)	83 (52.5)	57 (48.3)	26 (65)	0.1
Pericardial effusion, *n* (%)	14 (9)	13 (11)	1 (2.6)	0.21

Bold font is representative of statistical significance ($P < 0.05$).
ALT, alanine aminotransferase; BNP, b-type natriuretic peptide; CKD, chronic kidney disease; LA, left atrial; RA, right atrial; S/D ratio, right ventricular systolic to diastolic duration ratio.

patients with a history of CKD than those without [888 (487–1644) vs. 496 (236–898) ng/L, $P = 0.01$].

Overall, two-thirds (118, 67.0%) of patients had evidence of renal dysfunction on admission (MDRD eGFR <90 mL/min/1.73 m^2, Supplementary material online, *Table S2*); 59 (33.5%) had at least moderate renal dysfunction (eGFR <60 mL/min/1.73 m^2). Patients with any renal dysfunction were older than those without (51.6 ± 13.3 vs. 39.7 ± 13.7 years, $P < 0.001$) and were more likely to have a history of arrhythmia (72.9 vs. 43.1%, $P < 0.001$), but did not differ from those without renal dysfunction in terms of diabetes mellitus or systemic hypertension. Admission BNP was higher in patients with renal dysfunction [574 (236–1032) vs. 352 (148–505), $P = 0.01$]. Patients with renal dysfunction were more likely to have at least moderate systemic (27.8 vs. 11.3%, $P = 0.03$) or subpulmonary ventricular (56.1 vs. 31.1%, $P = 0.009$) dysfunction. They were also more likely to have systemic ventricular dilatation (23.4 vs. 15.1%, $P = 0.3$) or a larger right atrial area [28 (20–34) vs. 20 (15–34) cm^2, $P = 0.03$].

The vast majority of patients (144, 81.8%) were on at least 1 conventional heart failure therapy prior to the index heart failure admission: 84 (47.7%) patients were on an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, 91 (51.7%) received a beta-blocker, 77 (43.8%) a mineralocorticoid receptor antagonist, 17 (9.7%) digoxin, and 2 (1.1%) sacubitril-valsartan. One half (50.0%) of patients were taking at least 2 heart failure therapies and 19.3% were taking 3 or more heart failure therapies. Almost three quarters (128, 72.7%) of patients were on a loop diuretic pre-admission at a median dose of 80 (40–100) mg furosemide equivalents. Patients with CKD were more likely to be on at least one heart failure agent (95.3 vs. 77.4%, $P = 0.02$), as well as a loop diuretic pre-admission (90.7 vs. 66.9%, $P = 0.004$), at a higher maintenance dose [80 (40–160) vs. 40 (40–80) mg furosemide equivalents, $P < 0.001$]. Patients on loop diuretics pre-admission were more likely to be older ($P < 0.001$), have CHD of great complexity ($P = 0.02$), a systemic right ventricle ($P = 0.04$), resting cyanosis ($P = 0.04$), or systemic ventricular dysfunction ($P = 0.04$).

Inpatient management

The median length of intravenous diuretic therapy was 7 (4–12) days, with a maximum dose of 120 (80–160) mg furosemide equivalents/day; 35 (24.3%) patients required a maximum diuretic dose >160 mg furosemide equivalents/day. Patients with renal dysfunction required higher doses of intravenous loop diuretic [140 (80–200) vs. 80 (40–160) mg furosemide equivalents, $P = 0.006$]. Patients with higher daily diuretic requirements had a larger right atrial area [30.0 (26.0–42.5) vs. 23.0 (16.6–32.0) cm^2, $P = 0.006$], required more often inotropic support (42.9 vs. 7.3%, $P < 0.001$), and a longer hospital admission [21 (12–37) vs. 10 (7–17) days, $P < 0.001$].

Other heart failure therapies were uptitrated during admission in three quarters (128, 75.7%) of patients. Spironolactone was the most frequent newly introduced or uptitrated agent (102, 60.4%). Moreover, patients with a history of CKD were less likely to undergo uptitration of spironolactone (42.9 vs. 66.1%, $P = 0.01$). Spironolactone was downtitrated or stopped in few (8, 4.7%) patients, who were more likely to have an eGFR <60 mL/min/1.73 m^2 on admission (12.3 vs. 0.9%, $P = 0.004$).

During the index admission, 27 (15.3%) patients required inotropic support: the majority received dopamine (11, 6.2%), followed by milrinone (9, 5.1%) and dobutamine (8, 4.5%). The median duration of inotropic support was 7 (2–15) days and 14 (8.0%) required escalation to high dependency or intensive care. There was a trend for more frequent inotropic support in patients with renal dysfunction than in those with normal renal function (19.5 vs. 6.9%, $P = 0.05$). Five patients (2.8%) received renal replacement therapy in the form of temporary filtration [duration 50.5 (29.2–81.0) hours].

Length of hospital stay and in-hospital mortality

The median length of hospital stay was 13 (8–20) days. Patients with a BNP >400 ng/L ($P = 0.009$), a higher peak serum creatinine ($P = 0.002$), or any renal dysfunction on admission ($P = 0.04$), had a longer hospital stay. In-hospital mortality in the overall cohort was 4.5%.

Mortality and predictors of outcome following hospitalization with decompensated heart failure in adult congenital heart disease

During a median follow-up of 2.9 (1.1–6.2) years (cumulative follow-up time of 641.2 patient-years), 96 (57.5%) patients died, 7 (4.2%) were transplanted (5 orthotopic heart, 1 heart–lung, 1 heart–liver), and 1 (0.6%) patient received a VAD. In addition, 71 (42.5%) patients were rehospitalized for heart failure, and 15 (9.0%) required renal replacement therapy. On Kaplan–Meier analysis, the 1-, 3-, and 5-year transplant/VAD-free survival for the overall study population was 75.4% [95% confidence interval (CI) 69.2–82.3%], 55.9% (95% CI 48.8–64.1%), and 43.3% (95% CI 36–52%), respectively (*Figure 1*). At 1, 3, and 5 years, freedom from death, transplantation/VAD, or heart failure rehospitalization was 60.5% (95% CI 53.5–68.4%), 41.1% (95% CI 34.2–49.5%), and 31.8% (95% CI 25.1–40.3%), respectively.

On univariable Cox regression analysis, CKD was related to a greater than three-fold increased risk of death or transplantation/VAD [hazard ratio (HR) 3.64, 95% CI 2.41–5.48, $P < 0.001$, *Figure 2A*]. A greater than two-fold increase in risk was also identified for patients with renal dysfunction (eGFR <90 mL/min/1.73 m^2) on admission (HR 2.33, 95% CI 1.45–3.74, $P < 0.001$, *Figure 2B*). When admission creatinine was analysed as a continuous variable, a 53% increase in the risk of death or transplantation/VAD post-discharge was identified for each 1 mg/dL increase in serum creatinine concentration (HR 1.53, 95% CI 1.22–1.92, $P < 0.001$, *Figure 3*).

Several other variables were identified as predictors of death or transplantation/VAD after discharge from hospital (*Figure 4*), including older age, greatly complex CHD, history of arrhythmia, presence of moderate–severe systemic ventricular dysfunction, subpulmonary ventricular dilatation, higher right atrial area, number of conventional heart failure therapies on admission, use of loop diuretics pre-admission, and diuretic dose. Moreover, a longer duration of intravenous loop diuretics (>7 days), higher maximum daily diuretic dose, need for inotropes during admission, and peak inpatient creatinine concentration were also related to death or transplantation/VAD. Finally, a BNP >400 ng/L was also associated with an increased risk of an adverse outcome post-discharge (HR 2.64, 95% CI 1.52–4.58, $P < 0.001$), but was measured in a subset (64.1%) of patients and so was not tested in the multivariable model.

On multivariable Cox analysis after multiple imputation, CKD, greatly complex CHD, and inpatient requirement of inotropic support remained predictive of mortality or transplantation/VAD (*Table 3*). Bayesian model averaging and selection were undertaken on multiply imputed data: CKD was the strongest predictor of outcome (HR 2.8, 95% CI 1.82–4.31) with a posterior effect probability of 1. As part of a sensitivity analysis of multiply imputed data including serum BNP concentration, CKD remained a predictor of death or transplantation/VAD (HR 2.6, 95% CI 1.6–4.26, posterior effect probability 0.99).

Discussion

Adults with CHD admitted with heart failure are a high-risk population, with a long hospitalization time and an increased risk of death, transplantation/VAD or rehospitalization post-discharge. Both a history of

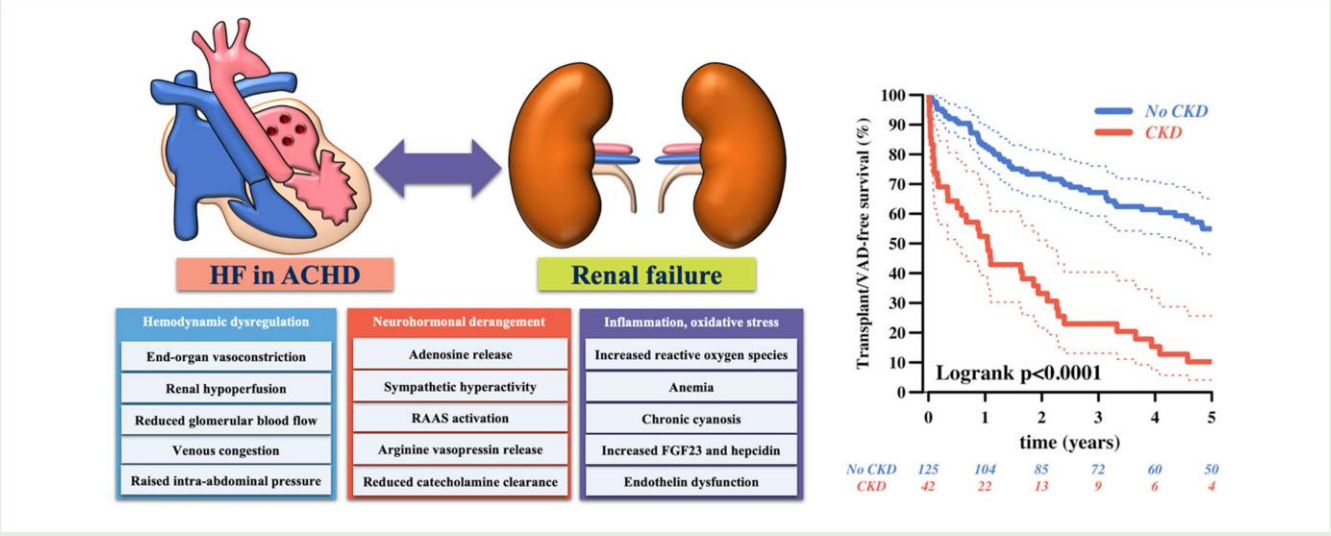

Figure 1 The complex interplay between the heart and the kidney in adults with congenital heart disease and heart failure, and the impact of chronic kidney disease on outcome. ACHD, adult congenital heart disease; CKD, chronic kidney disease; FGF23, fibroblast growth factor-23; HF, heart failure; RAAS, renin–angiotensin–aldosterone system.

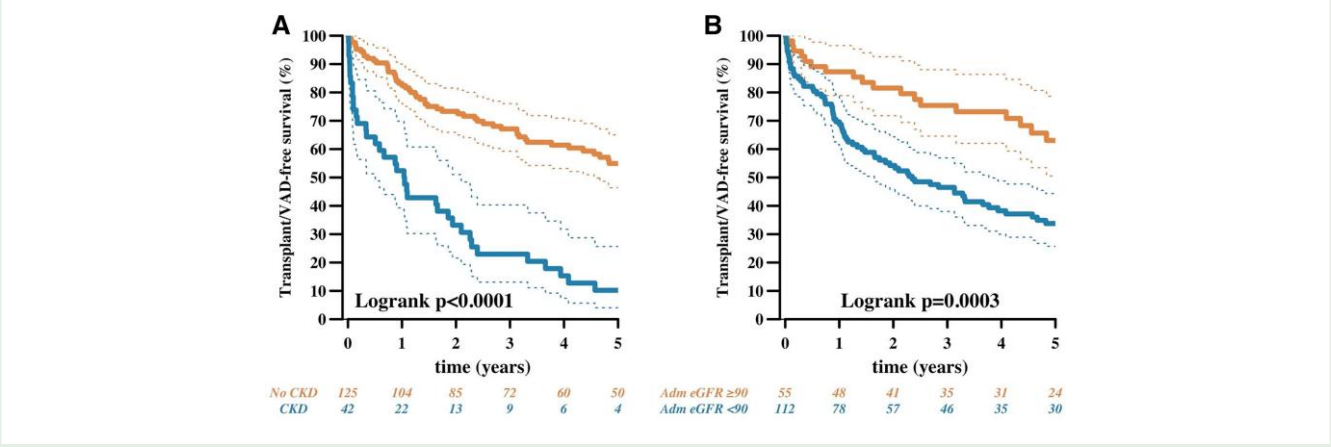

Figure 2 Survival in adult congenital heart disease after heart failure hospitalization by (*A*) presence of chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2 for >3 months pre-admission), and (*B*) renal dysfunction on admission (admission estimated glomerular filtration rate <90 mL/min/1.73 m^2).

CKD and evidence of renal dysfunction on admission were common and influenced the diuretic requirements and the length of hospital stay. CKD was the strongest independent predictor of death or transplantation/VAD post-discharge. Therefore, renal function should be regularly assessed in patients with CHD of great complexity and those with signs of heart failure to identify individuals with kidney disease early, optimize therapy, and exclude or treat reversible causes. Patients who are admitted with impaired renal function, require a multidisciplinary approach to their care, with optimization of their management to improve outcomes.

People with CHD have greatly benefitted from surgical and medical advances over the last several decades, with a striking increase in survival to adulthood for all forms of CHD. Adults now outnumber children with CHD in most high-income countries. Although most adult survivors have simple forms of CHD, such as ventricular septal defects, the proportion of adults with CHD of moderate or great complexity has increased, the latter making up over 10% of the adult CHD population.[9] Over one half of patients presenting to our service with acute decompensated heart failure had greatly complex CHD, including Eisenmenger syndrome, systemic right ventricle or univentricular circulations with or without a Fontan-type operation. These patients often have residual anatomic and haemodynamic lesions, including shunts and valvular disease, ventricular dysfunction, systemic and pulmonary hypertension, cyanosis, ischaemia, and arrhythmia. This substrate has led to progressively higher numbers of patients at risk of acute and chronic heart failure, especially as patients become older. Heart failure has become the leading cause of death in adults with CHD, accounting for one quarter of deaths in large registries.[10–12]

Extracardiac disease is commonly encountered in adults with CHD, especially in those with complex disease, and can adversely impact the prognosis. Renal impairment is prevalent in adults with CHD and is more common in the presence of older age, cyanosis, ventricular

dysfunction, and the absence of definitive repair.[3] The cause of renal dysfunction in adults with CHD is multifactorial and varies according to the cardiac anatomy, previous interventions, and the effects of chronic heart failure, which are well described in the acquired heart failure population.[4] One common pathway stems from renal hypoperfusion secondary to a reduced cardiac output, which activates the—initially compensatory—renin–angiotensin–aldosterone system and the adrenergic system. Neurohormonal activation is well described in CHD and is likely to contribute to cardiac remodelling and renal dysfunction in these patients.[13–15] Venous congestion can also reduce glomerular blood flow and the gradient between the afferent and efferent arterioles. Most therapies used in patients with acquired heart failure modulate neurohormonal activation and, despite the lack of strong evidence from randomized controlled trials, there is a theoretical benefit for their use in CHD, with potential benefits to the heart and kidneys.

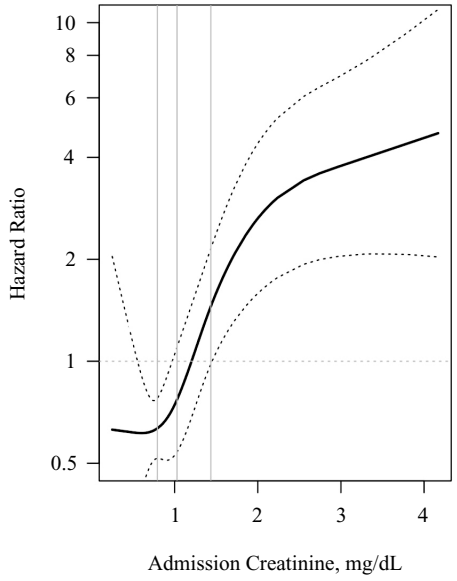

Figure 3 Unadjusted relationship between plasma creatinine concentration on index heart failure admission and the hazard of death or transplantation/ventricular assist device, and 95% confidence intervals using smoothing splines.

The association between chronic cyanosis and renal dysfunction is well described. In our population, over a third of patients had resting cyanosis, which is typically associated with secondary erythrocytosis, a compensatory mechanism aimed at increasing the oxygen-carrying capacity of the blood. The associated increase in blood viscosity and glomerular hypertension may cause proteinuria and interstitial fibrosis.[15,16] Moreover, patients with cyanotic CHD often have chronically low cardiac output and/or raised systemic venous pressures. The combination of the above makes patients with cyanotic CHD an extremely high-risk group for both heart failure and renal dysfunction, who require close monitoring and care to avoid acute kidney injury through nephrotoxic agents.

Renal dysfunction can be triggered or worsened by decompensated heart failure.[17,18] This study focused on high-risk patients with CHD with difficult-to-manage heart failure who required a prolonged hospital stay and were resistant to oral diuretics, hence required intravenous diuresis. In this setting, two-thirds of patients had renal dysfunction on admission and one-quarter required a high daily diuretic dose (>160 mg furosemide equivalents). In addition, 15% of patients required inotropic support, indicating a population with advanced disease and fluid overload. Indeed, in our cohort, the presence of renal dysfunction complicated the management of heart failure, with a requirement for longer intravenous diuretic therapy, more frequent inotropic support, and a longer hospital stay.

After discharge from the hospital following a heart failure hospitalization, adults with CHD are at high risk of an adverse outcome, with

Variables	HR(95%CI)	P value
Age (/10years)	1.37 (1.18-1.59)	<0.0001
Complex CHD	1.70 (1.14-2.53)	0.009
History of arrhythmia	2.01 (1.29-3.13)	0.002
CKD	3.64 (2.41-5.48)	<0.0001
Systemic ventricular dysfunction	1.77 (1.11-2.80)	0.02
Subpulmonary ventricular dilatation	1.78 (1.13-2.80)	0.01
RA area (10cm2)	1.22 (1.09-1.37)	0.0007
TAPSE (cm)	0.55 (0.32-0.93)	0.03
Preadmission HF therapies (n)	1.32 (1.09-1.60)	0.004
Preadmission loop diuretics	3.42 (1.96-5.94)	<0.0001
Preadmission diuretic dose (40mg)	1.23 (1.13-1.35)	<0.0001
Renal dysfunction on admission	2.33 (1.45-3.74)	0.0005
Admission BNP (log ng/L)	1.58 (1.24-2.01)	0.0002
Inpatient diuretic duration (/7days)	1.26 (1.06-1.48)	0.007
Max. inpatient diuretic dose (log mg)	2.04 (1.39-3.00)	0.0003
Requirement of inotropes	2.72 (1.58-4.71)	0.0003
Peak creatinine (mg/dL)	1.52 (1.27-1.83)	<0.0001

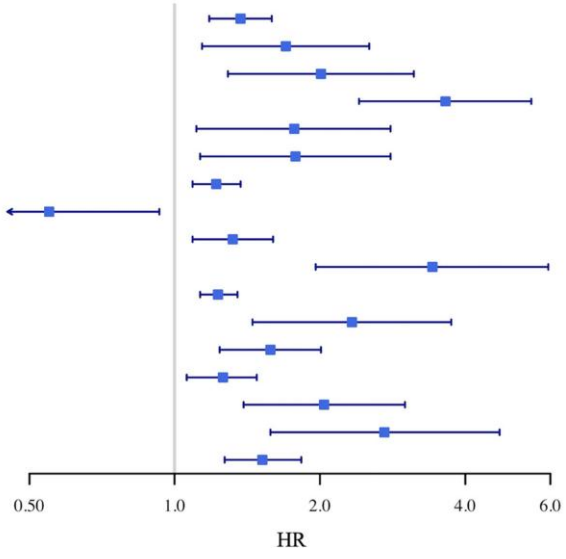

Figure 4 Results of univariable Cox proportional hazards regression analysis for mortality or heart/heart–lung transplantation. BNP, b-type natriuretic peptide; CHD, congenital heart disease; CKD, chronic kidney disease; RA, right atrial; TAPSE, tricuspid annular plane systolic excursion.

Table 3 Survival analysis of imputed data: Cox regression for predictors of death or transplantation

Variable	Univariable			Multivariable			Model selection[a]		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	PEP
Pre-admission									
Age (/10 years)	1.37	1.18–1.59	**<0.001**	1.15	0.95–1.39	0.16	—	—	0.28
CKD	3.64	2.41–5.48	**<0.001**	2.49	1.54–4.01	**<0.001**	2.80	1.82–4.31	1
Complex CHD	1.70	1.14–2.53	**0.01**	1.76	1.11–2.80	**0.02**	1.27	0.64–2.49	0.55
History of arrhythmia	2.01	1.29–3.13	**0.003**	1.42	0.87–2.33	0.17	—	—	0.35
Number of heart failure therapies	1.32	1.09–1.60	**0.005**	0.96	0.76–1.21	0.7	—	—	0
Any loop diuretics	3.42	1.96–5.94	**<0.001**	1.92	1.00–3.70	0.052	2.40	1.29–4.47	0.81
Systemic ventricular dysfunction	1.77	1.11–2.80	**0.02**	1.28	0.77–2.12	0.3	—	—	0.23
Subpulmonary ventricular dilatation	1.78	1.13–2.80	**0.01**	1.09	0.66–1.81	0.7	—	—	0.14
Right atrial area (/10 cm^2)	1.22	1.09–1.37	**0.001**	1.14	0.94–1.38	0.2	1.12	0.86–1.46	0.49
Inpatient									
Maximum daily diuretic dose[b]	1.74	1.23–2.48	**0.003**	0.93	0.56–1.54	0.8	—	—	0.11
Requirement of inotropes	2.72	1.57–4.71	**<0.001**	2.60	1.43–4.73	**0.002**	2.67	1.53–4.66	0.91

Bold font is representative of statistical significance ($P < 0.05$). Posterior effect probability (PEP) after Bayesian model averaging: This is the posterior probability that the Hazard in the Cox regression model for a variable is not 1, taking model selection uncertainty into account. CKD had the highest PEP and hence the least uncertainty regarding inclusion in the multivariable model.

[a]Using BIC and model averaging.

[b]Log_e transformation of variable following multiple imputation.

CHD, congenital heart disease; CKD, chronic kidney disease.

22.2% dying or requiring heart/heart–lung transplantation within 1 year. Moreover, almost one half of patients met the combined endpoint of death, transplantation/VAD or heart failure hospitalization, and 1 in 10 patients also required renal replacement therapy, which can be difficult in many patients with CHD, especially those who cannot tolerate frequent haemodynamic shifts and are more prone to complications from indwelling catheters, including infective endocarditis and paradoxical embolism in the setting of right-left shunts. Therefore, discharge planning in this group should include a plan for close monitoring after discharge.

Chronic kidney disease was the strongest predictor of adverse outcomes in our cohort of patients with CHD admitted with decompensated heart failure. The relationship of renal dysfunction to mortality has been documented in a previous unselected cohort of adults with CHD,[3] and our study confirms this very strong association in a contemporary group of adults with CHD admitted with decompensated heart failure and substantially higher event rates. The presence and severity of renal dysfunction should feed into decisions on the frequency and intensity of follow-up, and timing of referral for transplant assessment. Indeed, there is a paucity of evidence surrounding the management of decompensated heart failure in adults with CHD, which is reflected in current practice guidelines.[5,19] As the population of adults with CHD continues to expand, specialist centres are faced with an epidemic of heart failure and other long-term complications that are often difficult to manage and adversely affect outcomes.[20] Regular risk stratification of all adult patients with CHD is essential, especially for those with complex disease or presenting with heart failure, to optimize outcomes and improve resource allocation. Renal dysfunction is not only a marker of adverse outcomes, but also a contributor to morbidity and mortality. Patients can benefit from a multidisciplinary approach with renal specialist input when renal dysfunction is detected, and ideally before an admission with heart failure, to exclude primary kidney disease, improve risk stratification, and make appropriate management choices in terms of medication, initiation of dialysis, and listing for renal transplantation.

Limitations

This is a single-centre retrospective study with a population representative of adults with moderate-to-greatly complex CHD admitted with decompensated heart failure in tertiary centres. Even though adults with CHD are a heterogenous population in terms of anatomy, pathophysiology, and surgical history, they all share a predisposition towards heart and multi-organ failure. We identified all patients with CHD who were admitted with congestive heart failure requiring intravenous diuretics. Indeed, the management of acute decompensated heart failure does not differ significantly between different types of CHD. Renal dysfunction is also prevalent and appears to be an important prognostic tool for ACHD physicians managing this high-risk population.

We focused our analysis on markers of renal dysfunction routinely measured in the majority of our patients. Future studies should include additional markers of renal disease, including assessments of proteinuria or tubular dysfunction on urinalysis.[21] Moreover, direct measurement of the glomerular filtration rate was not undertaken in this study, e.g. by 24 h creatinine clearance. Alternative plasma biomarkers such as Cystatin C may provide a better estimate of eGFR, especially in certain CHD subgroups, such as Fontan patients, but this was not measured as part of routine clinical practice in our centre.[22] Finally, small numbers of patients received a transplant or VAD, limiting our ability to perform meaningful statistical comparisons between these groups. Nevertheless, our study is the first to focus on renal dysfunction in adults with CHD presenting with acute decompensated heart failure, a vastly growing population and a clinical conundrum.

Conclusions

Adults with CHD admitted with heart failure are a high-risk population, with a long hospitalization length and an increased risk of death, transplantation/VAD or rehospitalization post-discharge. The presence of renal dysfunction, prior to and on admission, can complicate in-hospital management and is a strong independent predictor of outcome post-

discharge. Close monitoring and a multidisciplinary approach are strongly recommended.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contributions

K.K., K.D., and A.C. contributed to the conception and design of the work. K.K. and A.C. were responsible for data acquisition. A.C. and K.D. contributed to the analysis and interpretation of the work. All authors reviewed and revised the manuscript and gave final approval and agree to be accountable for all aspects of work, ensuring integrity and accuracy.

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Data availability

To minimize the possibility of unintentionally sharing information that can be used to reidentify private information, in line with the conditions of the ethical approval, patient-level data are not available for use outside of this study.

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