Prevalence, Predictors, and Prognostic Value of Renal Dysfunction in Adults With Congenital Heart Disease

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Background—Renal insufficiency in patients with ischemic heart disease and acquired heart failure is associated with higher mortality and morbidity. We studied the prevalence of renal dysfunction in adult patients with congenital heart disease (ACHD) and its relation to outcome.

Methods and Results—A total of 1102 adult patients with congenital heart disease (age 36.0±14.2 years) attending our institution between 1999 and 2006 had creatinine concentration measured. Glomerular filtration rate (GFR) was calculated with the Modification of Diet in Renal Disease equation. Patients were divided into groups of normal GFR (≥90 mL·min⁻¹·1.73 m⁻²), mildly impaired GFR (60 to 89 mL·min⁻¹·1.73 m⁻²), and moderately/severely impaired GFR (<60 mL·min⁻¹·1.73 m⁻²). Survival was compared between GFR groups by Cox regression. Median follow-up was 4.1 years, during which 103 patients died. Renal dysfunction was mild in 41% of patients and moderate or severe in 9%. A decrease in GFR was more common among patients with Eisenmenger physiology, of whom 72% had reduced GFR (<90 mL·min⁻¹·1.73 m⁻², P<0.0001 compared with the remainder), and in 18%, this was moderate or severe (P=0.007). Renal dysfunction had a substantial impact on mortality (propensity score–weighted hazard ratio 3.25, 95% CI 1.54 to 6.86, P=0.002 for moderately or severely impaired versus normal GFR).

Conclusions—Deregulated physiology in adult patients with congenital heart disease is not limited to the heart but also affects the kidney. Mortality is 3-fold higher than normal in the 1 in 11 patients who have moderate or severe GFR reduction. (Circulation. 2008;117:2320-2328.)

Key Words: heart defects, congenital kidney renal function prognosis

As the number of patients with congenital heart disease reaching adulthood (ACHD) continues to increase, it is becoming clear that pathophysiological derangement occurs not only in the heart but in other organs as well. Renal dysfunction has been reported in ACHD patients, but its prevalence and relation to outcome in this population remain unknown. In acquired heart disease, renal dysfunction is an ominous sign. We sought to assess the prevalence of renal dysfunction across the spectrum of ACHD and its predictors and impact on survival.

Editorial p 2311
Clinical Perspective p 2328

Methods

All ACHD patients attending our institution from 1999 to June 2006 and in whom serum creatinine concentration was measured were entered into the study. Only the first measurement was used if there were several. For each subject, an estimated glomerular filtration rate (GFR) was calculated from serum creatinine levels by the Modification of Diet in Renal Disease equation, which adjusts for age, gender, and race. Patients were categorized into groups according to the cutoff values suggested by the National Kidney Foundation practice guidelines: GFR >90 mL·min⁻¹·1.73 m⁻² was considered normal, 60 to 89 mL·min⁻¹·1.73 m⁻² was considered mildly decreased, and <60 mL·min⁻¹·1.73 m⁻² was considered moderately or severely decreased. Patients were classified according to the principal underlying anatomic defect (Table 1). Systemic ventricular function from transthoracic echocardiograms within a year of blood sampling was recorded as a 3-level categorical variable: normal, mildly impaired, and moderately/severely impaired. Previous operations were divided into (1) major reparative surgery that required median sternotomy and/or cardiopulmonary bypass and (2) palliative operations. Survival status was assessed through the National Health Service computer system, which is linked to a national database of patient survival held by the United Kingdom’s Office for National Statistics. Approval by the local research ethics committee was obtained.
Table 1. Demographic and Clinical Characteristics of Patients With ACHD According to Underlying Diagnosis

<table>
<thead>
<tr>
<th>Atrial septal defect</th>
<th>Ventricular septal defect</th>
<th>Atrioventricular septal defect</th>
<th>Valve/outflow tract disease</th>
<th>Coarctation</th>
<th>Tetralogy of Fallot</th>
<th>Mustard</th>
<th>Congenitally corrected TGA</th>
<th>Ebstein anomaly</th>
<th>Fontan</th>
<th>Complex†</th>
<th>Eisenmenger physiology</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>152 (13.8)</td>
<td>47 (4.3)</td>
<td>56 (5.1)</td>
<td>153 (13.9)</td>
<td>113 (10.3)</td>
<td>131 (11.9)</td>
<td>46 (4.2)</td>
<td>27 (2.5)</td>
<td>58 (5.3)</td>
<td>93 (8.4)</td>
<td>102 (9.3)</td>
<td>97 (8.8)</td>
<td>1102 (100.0)</td>
</tr>
<tr>
<td>Age, y</td>
<td>44.6±17.5</td>
<td>31.9±11.7</td>
<td>36.0±13.4</td>
<td>36.7±15.0</td>
<td>33.8±13.7</td>
<td>36.8±13.2</td>
<td>29.7±7.0</td>
<td>43.1±13.0</td>
<td>26.9±9.2</td>
<td>30.7±9.7</td>
<td>36.0±11.8</td>
<td>35.9±14.8</td>
<td>36.0±14.2</td>
</tr>
<tr>
<td>Male, %</td>
<td>36.8</td>
<td>44.7</td>
<td>44.6</td>
<td>60.1</td>
<td>55.8</td>
<td>57.3</td>
<td>52.2</td>
<td>40.7</td>
<td>48.3</td>
<td>52.7</td>
<td>32.4</td>
<td>45.4</td>
<td>48.5</td>
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<tr>
<td>Cyanosis,* %</td>
<td>1.3</td>
<td>2.1</td>
<td>5.4</td>
<td>1.3</td>
<td>0.0</td>
<td>3.8</td>
<td>2.2</td>
<td>14.8</td>
<td>32.8</td>
<td>61.3</td>
<td>83.3</td>
<td>4.1</td>
<td>17.0</td>
</tr>
<tr>
<td>Functional NYHA Class</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>71.6</td>
<td>78.7</td>
<td>71.4</td>
<td>73.7</td>
<td>85.7</td>
<td>64.2</td>
<td>66.7</td>
<td>50.0</td>
<td>40.8</td>
<td>29.3</td>
<td>7.1</td>
<td>73.9</td>
<td>61.1</td>
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<tr>
<td>Class II</td>
<td>19.1</td>
<td>12.8</td>
<td>26.5</td>
<td>20.4</td>
<td>8.9</td>
<td>22.5</td>
<td>28.2</td>
<td>30.0</td>
<td>44.9</td>
<td>30.2</td>
<td>42.4</td>
<td>18.5</td>
<td>24.7</td>
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<tr>
<td>Class III</td>
<td>9.2</td>
<td>8.5</td>
<td>2.0</td>
<td>5.8</td>
<td>5.4</td>
<td>12.5</td>
<td>5.1</td>
<td>20.0</td>
<td>8.2</td>
<td>30.5</td>
<td>45.9</td>
<td>7.7</td>
<td>6.1</td>
</tr>
<tr>
<td>Class IV</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.8</td>
<td>0.0</td>
<td>0.0</td>
<td>6.1</td>
<td>0.0</td>
<td>4.7</td>
<td>1.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Single ≥ 2</td>
<td>41.4</td>
<td>51.1</td>
<td>57.1</td>
<td>37.9</td>
<td>40.7</td>
<td>45.0</td>
<td>65.2</td>
<td>33.3</td>
<td>67.2</td>
<td>24.7</td>
<td>9.8</td>
<td>32.0</td>
<td>38.9</td>
</tr>
<tr>
<td>Single ≥ 2</td>
<td>2.0</td>
<td>19.1</td>
<td>28.6</td>
<td>45.1</td>
<td>0.0</td>
<td>55.0</td>
<td>34.8</td>
<td>0.0</td>
<td>32.8</td>
<td>15.1</td>
<td>2.9</td>
<td>31.0</td>
<td>22.2</td>
</tr>
</tbody>
</table>

TGA indicates transposition of the great arteries.
* Cyanotic patients were those with resting oxygen saturations <90% on room air.
† Patients with “complex anatomy” were those with unprepared double-outlet and double-inlet ventricle or complex pulmonary atresia.

Statistical Analysis
Analyses were performed by 2 of the authors (KD and NB) using R version 2.6.0.13 To assess the relation between GFR as a continuous variable and clinical and demographic parameters, univariable and multivariable linear regression analysis was used.

Cox regression analysis was used to assess the relation between GFR and death. Propensity scores were used as a means of accounting for differences observed among patients classified into the 3 GFR groups. Pairwise comparison of mortality in the 3 GFR groups was performed. Propensity scores were estimated by means of generalized boosted regression (R version 2.6.0, package “twang”), a flexible method that can model the effects of numerous covariates without greatly reducing estimate precision.14 The following parameters were included in the construction of the propensity scores: age; sex; presence of resting cyanosis; New York Heart Association (NYHA) functional class; previous palliative surgery (none, 1, or >1); previous reparative surgery (none, 1, or >1); treatment with diuretics, β-blockers, ACE inhibitors/angiotensin receptor blockers, or digoxin; and systemic ventricular dysfunction (none, mild, or moderate-severe). The generalized boosted regression algorithm iteratively forms a collection of simple regression tree models added together to estimate the propensity score (to find the maximum likelihood estimate of the log-odds of treatment assignment). A large number of iterations were performed, with selection of different random subsamples of the data at each iteration to decrease bias and variance in the resulting model fit. Stopping rules were applied (minimization of average effect size difference) to choose the number of iterations that maximized predictive performance. Analysis of outcomes was performed by Cox analysis, accounting for the calculated propensity score weights. Hazard ratios (HRs) with 95% CIs are reported. Balance was assessed by means of plots comparing the quintiles of the probability values of comparison tests on the baseline covariates before and after weighting to the uniform distribution of probability values. Probability values to test group mean differences in a true experiment would, in fact, follow a uniform distribution on the interval 0 to 1 and would thus follow the 45° line on the Q-Q plot. The substantial reduction in standardized differences of single covariates before and after weighting was also presented graphically. Analysis of outcome (mortality) was performed by Cox proportional hazards regression with propensity weights. As a sensitivity analysis and for the construction of adjusted survival curves, unweighted multivariable Cox analysis was performed with renal function, age, and a limited (due to the relatively low number of events) number of clinically relevant dichotomized parameters. The proportional hazards assumption, a key assumption of the Cox model, was verified for each variable by testing for zero correlation between the scaled Schoenfeld residuals and survival time. Evidence of violation of the proportional hazards assumption was present for diuretic use. Stratification, which is an effective strategy to account for nonproportionality, was used. The parameter that violated the proportional hazards assumption was incorporated in the multivariable model as a stratification factor (stratum) rather than a regressor, which removed the problem of nonproportionality. Unadjusted Kaplan–Meier and adjusted cumulative mortality curves for a typical noncyanotic and cyanotic ACHD patient were plotted. Two adjusted survival curves graphs per case are presented for each of the diuretic strata. All probability values were 2-sided, and a probability value of <0.05 was considered statistically significant.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results
Prevalence and Predictors of Renal Dysfunction
Background congenital heart diagnoses are shown in Table 1, whereas both clinical and surgical characteristics of the 1102 ACHD patients are given in Table 2. Mean age was 36.0±14.2 years, and 48.5% of patients were male. Mean GFR was 91.3±26.1 mL · min⁻¹ · 1.73 m⁻², with half of the patients having reduced GFR. In 9.3% of these, GFR was moderately or severely reduced (Table 2; Figure 1A). There were significant differences between diagnostic groups in both mean GFR and GFR category (Figure 1B). Patients with Eisenmenger physiology had the lowest GFR (78.3±24.2 mL · min⁻¹ · 1.73 m⁻², P<0.0001 compared with the remainder) and the highest prevalence (18%) of moderately or severely reduced GFR (P=0.007).
GFR was 9 mL·min⁻¹·1.73 m² lower among cyanotic patients (83.9±26.2 versus 92.9±25.9 mL·min⁻¹·1.73 m² in noncyanotic patients, P<0.0001). The prevalence of moderate or severe GFR impairment was, in fact, 16.0% in cyanotic patients versus 7.9% in noncyanotic patients (P=0.0017); 65.7% of cyanotic patients had a GFR <90 mL·min⁻¹·1.73 m².

Patients in NYHA class II, III, and IV, respectively, had on average 6, 12, and 19 mL·min⁻¹·1.73 m² lower GFRs than patients in NYHA class I (P<0.001). Patients with moderate or severe ventricular dysfunction had 7 mL·min⁻¹·1.73 m² lower GFRs than those with normal systemic ventricular function. Patients with previous reparative surgery had 7 mL·min⁻¹·1.73 m² lower GFRs than patients without such a history (P=0.0001).

<table>
<thead>
<tr>
<th>GFR</th>
<th>Overall (≥90 mL·min⁻¹·1.73 m²)</th>
<th>Moderate to Severe Reduction (&lt;60 mL·min⁻¹·1.73 m²)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>1102 (100)</td>
<td>549 (49.8)</td>
<td>102 (9.3)</td>
</tr>
<tr>
<td>Age, y</td>
<td>36.0±14.2</td>
<td>30.1±11.5</td>
<td>50.4±16.1</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>48.6</td>
<td>51.2</td>
<td>40.2</td>
</tr>
<tr>
<td>Cyanosis, %</td>
<td>17</td>
<td>11.7</td>
<td>29.4</td>
</tr>
<tr>
<td>NYHA class I/II/III/IV, %</td>
<td>61/25/13/1</td>
<td>69/21/9/1</td>
<td>56/28/16/1</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>27.3</td>
<td>19</td>
<td>58.8</td>
</tr>
<tr>
<td>ACEI/ARB, %</td>
<td>28.1</td>
<td>25</td>
<td>39.2</td>
</tr>
<tr>
<td>β-Blockers, %</td>
<td>23.2</td>
<td>19</td>
<td>27.4</td>
</tr>
<tr>
<td>Digoxin, %</td>
<td>12.3</td>
<td>7.5</td>
<td>29.4</td>
</tr>
<tr>
<td>Warfarin, %</td>
<td>26.1</td>
<td>20.6</td>
<td>43.1</td>
</tr>
<tr>
<td>Aspirin, %</td>
<td>15.7</td>
<td>12.8</td>
<td>26.5</td>
</tr>
<tr>
<td>Repair or previous sternotomy: single/≥2, %</td>
<td>38.9/25.8</td>
<td>40.6/27.3</td>
<td>39.7/25.5</td>
</tr>
<tr>
<td>Palliative surgery: single/≥2, %</td>
<td>11.7/5.6</td>
<td>13.3/5.8</td>
<td>10.6/6.0</td>
</tr>
</tbody>
</table>

ACEI/ARB indicates ACE inhibitor/angiotensin receptor blocker.

Figure 1. Renal dysfunction in patients with ACHD. A, Distribution of GFR values across the spectrum of ACHD. B, Distribution of mild and moderate to severe GFR reduction according to underlying cardiac diagnosis. Bar width reflects population size in each group. GA indicates great arteries.
higher GFRs than palliated patients or those in the unoperated group. Multivariable linear regression identified cyanosis, age, and use of diuretics as predictors of GFR levels, with the adjusted estimated reduction (95% CI) in GFR being 10.6 mL·min⁻¹·1.73 m⁻² (6.6 to 14.7 mL·min⁻¹·1.73 m⁻²) for cyanotic patients versus noncyanotic patients; 8.3 mL·min⁻¹·1.73 m⁻² (7.3 to 9.4 mL·min⁻¹·1.73 m⁻²) per 10-year increase in age; and 4.5 mL·min⁻¹·1.73 m⁻² (1.2 to 7.9 mL·min⁻¹·1.73 m⁻²) for patients using diuretics.

Impact of Renal Dysfunction on Mortality
During a median follow-up period of 4.1 years, 103 patients died (mortality rate of 22.6/1000 patients per year, 95% CI 18.5 to 27.5). Mean age at death was 41 ± 15 (range 17 to 79) years. Most deaths were observed in the Eisenmenger physiology (n=18/100), complex physiology (n=18/96), Fontan (n=13/54), and valvar disease (n=12/138) groups.

ACHD patients with moderate or severe GFR reduction had a 6-year mortality rate that was ~5-fold higher than for those with normal GFR and 3-fold higher than for those with mildly impaired GFR (Figure 2; log-rank test P<0.0001). In addition, patients with mildly impaired GFR had a 2-fold increase in 6-year mortality compared with patients with normal GFR (log-rank test P=0.03). Divergence between the moderately to severely impaired and normal GFR groups was obvious after just 1 year of follow-up (11% versus 2% mortality; Figure 2).

The use of propensity scores was effective in reducing differences between groups (Figure 3). Moderate to severe impairment of GFR was a strong predictor of death on propensity-weighted Cox analysis (adjusted HR 3.25, 95% CI 1.54 to 6.86, P=0.002; Table 3). A strong trend toward higher mortality was also seen in patients with moderate or severe impairment of GFR compared with those with mild GFR impairment (P=0.06). The significant relation between moderate to severe impairment of GFR and mortality risk was confirmed by multivariable analysis in which functional (NYHA) class and systemic ventricular dysfunction were included (Table 3).

Discussion
The present study shows that despite relatively young age, half of all patients with ACHD have significantly impaired renal function, with impairment being moderate or severe in 1 in 5. This is particularly common in cyanotic patients and affects two thirds of patients with Eisenmenger syndrome. The death rate was 3-fold higher among patients with moderate to severe renal impairment than among patients with normal renal function even after adjustment for other clinical parameters.

Prevalence of Renal Dysfunction in ACHD
The prevalence of significant renal dysfunction in the present ACHD population is far beyond that of the general population. The prevalence of significant renal impairment (GFR < 60 mL·min⁻¹·1.73 m⁻²) in the latter, for individuals 35 to 44 years of age, is on the order of 0.6% in men and 0.3% in women.23 In contrast, the prevalence of significant renal impairment in the present study (8.0%) was 18-fold higher in noncyanotic ACHD patients than in the general population and 35-fold higher in cyanotic ACHD patients (15.8%). Furthermore, there was a trend toward more renal dysfunction in patients with more complex anatomy. Nevertheless, renal dysfunction was even present in patients with “simple” defects (Figure 1B).

Mechanisms of Renal Dysfunction in ACHD
Renal dysfunction is a common complication of acquired heart failure. Low cardiac output secondary to left ventricular dysfunction results in decreased perfusion of vital organs, including the kidneys. Unloading of baroreceptors in the heart and arteries results in activation of the sympathetic nervous system, which leads to arterial vasoconstriction and activation of the renin-angiotensin-aldosterone system.21,22 The renin-angiotensin-aldosterone system is also activated by the kid-
neys in an attempt to preserve renal perfusion and GFR. Even in the early stages of heart failure, renal vasoconstriction and reduced renal perfusion, together with stimulation of the adrenergic system and the renin-angiotensin-aldosterone system, result in increased sodium and water retention and promote left ventricular remodeling and deterioration of cardiac function. Progressive renal dysfunction occurs as a result of the progressive drop in cardiac output and renal perfusion and the increase in renal vasoconstriction mediated by the neurohormonal and autonomic activation.

Congenital heart disease appears to have similar systemic manifestations to acquired heart failure. Elevated levels of atrial natriuretic peptide, renin, aldosterone, and norepinephrine have been reported in ACHD patients, even when asymptomatic, many years after surgical repair of cardiac defects. Deranged cardiac autonomic nervous activity has been described in various ACHD cohorts, including those with tetralogy of Fallot and in patients after Fontan-type operations. It is likely that chronic renal hypoperfusion and significant neurohormonal activation contribute to the deterioration of renal function seen in ACHD.

**Renal Dysfunction and Cyanosis**

More than 65% of cyanotic patients had renal dysfunction in the present study population, and in 16%, this was at least moderate. Even though there is no doubt that cyanotic heart
Disease impairs renal function, the underlying mechanism remains a matter of debate. Cyanosis was a strong multivariable predictor of GFR, together with functional class and the use of diuretics, which suggests an additional effect of cyanosis over that of disease severity. Chronic hypoxia could affect renal function, both directly and through secondary erythrocytosis and increased blood viscosity. Hyperviscosity could lead to an increase in efferent glomerular arteriolar resistance, hydraulic pressure across the glomerulus, and filtration fraction, which would result in an increase in oncocytic pressure in the postglomerular vessels that perfuse the proximal tubules and promote fluid and solute reabsorption and fluid retention.

Renal Dysfunction and Systemic Ventricular Function

Renal dysfunction was related to systemic ventricular dysfunction in the present study. The latter is common in ACHD and reflects either intrinsic abnormalities, such as a single ventricle or a systemic right ventricle, or a residual and progressive hemodynamic abnormality, which inevitably leads to reduced cardiac output and may in turn contribute to organ damage and failure, including the kidneys.

Renal Dysfunction and Outcome

The prognostic power of GFR could derive from its relation to the severity of the underlying cardiac disease and the degree of compensation. Nevertheless, the present data show a clear additional effect of renal impairment over that of functional class and systemic ventricular function (Table 3; Figure 4). It is conceivable that NYHA classification underestimates the true extent of functional impairment in ACHD patients. The degree of renal impairment could also reflect the extent of neurohormonal activation, which is known to be associated with an adverse outcome in patients with acquired cardiac disease. Moreover, renal dysfunction could be associated with other risk factors of atherosclerosis, endothelial dysfunction, and death, such as hypertension, inflammation, oxidative stress, prothrombotic state, and hyperhomocysteinemia. Renal dysfunction itself can promote cardiac remodeling and progression of cardiac dysfunction through loss of sodium balance and volume overload. It may also lead to deterioration of cardiac function by aggravating hypertension and anemia. Finally, patients with renal dysfunction may be less likely to receive aggressive medical treatment and are less likely to be offered cardiac surgery or other intervention because renal impairment significantly increases the perioperative risk for both.

Clinical Implications

The presence of renal dysfunction, even mild, appears to be related to adverse outcome among ACHD patients. These data call for routine, periodic screening of renal function in all ACHD patients to obtain prognostic information and identify patients who may benefit from earlier intervention, whether surgical or other.

Study Limitations

There was no formal measurement of GFR (ie, with 24-hour creatinine clearance) in this retrospective study. However, the Modification of Diet in Renal Disease equation provides a well-validated estimation of GFR and requires only simple data universally available in clinical practice.

The study population was clearly heterogeneous, with the inclusion of patients with various types of congenital heart disease. Nevertheless, this is a population representative of ACHD patients attending a tertiary care center. Furthermore, despite the vast spectrum of underlying cardiac anatomy, many types of ACHD share important features regarding pathophysiology, symptoms, and natural history, with each other and with those of acquired heart failure. The sample size of certain diagnostic subgroups (eg, Ebstein’s anomaly of the tricuspid valve and congenitally corrected transposition of great arteries) was relatively small, but again, this merely reflects the prevalence of these subgroups in the overall

| Table 3. HRs for Death Among Patients With ACHD: Propensity Score–Weighted and Multivariable Models |
|---------------------------------------------------|----------|----------|
| Propensity score weight-adjusted models            | HR       | 95% CI    |
| Moderate/severe impairment vs normal GFR           | 3.25     | (1.54–6.86) |
| Moderate/severe impairment vs mild GFR impairment  | 1.72     | (0.97–3.05) |
| Mild GFR impairment vs normal GFR                  | 1.25     | (0.69–2.27) |
| Multivariate models of death with diuretic as stratum |
| Moderate/severe GFR impairment                     | 2.31     | (1.17–4.56) |
| Mild GFR impairment                                | 1.22     | (0.70–2.10) |
| NYHA class >2                                      | 2.50     | (1.52–4.10) |
| Any systemic ventricular dysfunction               | 2.66     | (1.62–4.38) |
| Previous reparative surgery/ sternotomy            | 0.69     | (0.41–1.14) |
| Previous palliative surgery                        | 2.42     | (1.45–4.03) |
| Age, y                                            | 1.09     | (0.92–1.29) |
| Cyanosis                                           | 1.16     | (0.65–2.09) |

*For 10-year increase.
ACHD population of patients followed up in a tertiary care center.

Recently decompensated patients may have a transient rise in creatinine at the time of renal screening that could be a potential bias in a study such as ours. Our center, however, is a tertiary referral center with a national referral base and without an accident and emergency department. Acutely decompensated patients would therefore usually be admitted in local hospitals and not in our center and may be referred to us once clinical stabilization has taken place. We thus submit that the ACHD cohort reported here does not include acutely decompensated patients.

We elected not to present data on ventricular ejection fraction because of the inherent difficulties and the limitations of such a measure in patients with a variety of systemic ventricles. Regardless, in acquired heart disease, simple measurement of renal function has prognostic implications over those of systemic ventricular function.42

Even though multivariable analysis did confirm the major finding of the propensity-weighted analysis, ie, that moderate to severe GFR reduction is strongly associated with mortality, the estimated HR was somewhat lower (Table 3). Furthermore, the strong trend for higher mortality in patients with moderately or severely impaired GFR compared to those with mildly impaired GFR observed in the propensity analysis was not confirmed by the multivariable analysis. This discrepancy is likely due to the fact a limited number of variables could be included in the multivariable analysis because of the relatively low number of events. Propensity score analysis, which overcomes such limitations and accounts for all available variables, is more likely to provide an accurate estimate of the HR.

Potential confounders in the analysis of the relation between renal dysfunction and mortality are the presence of secondary erythrocytosis and iron-deficiency anemia, common in cyanotic ACHD patients.35 Even though anemia, as conventionally defined, is rare among cyanotic patients, relative anemia is often present secondary to iron depletion, with adverse effects on oxygen-carrying capacity, exercise tolerance, and possibly prognosis. However, a clear definition of relative anemia in this group is not yet available, and therefore, use of empirical cutoff values based on other blood parameters may lead to inaccurate conclusions and may not be applicable to the remainder of ACHD patients without cyanosis.

Conclusions

Congenital heart disease is a systemic disease, with consequences reaching far beyond the heart. Nine percent of
ACHD patients have moderate or severely impaired renal function and as a result have an additional adjusted 3-fold increased mortality risk. A simple calculation of GFR from readily available clinical variables and the application of the 60-mL·min⁻¹·1.73 m²⁻¹ threshold can identify patients at increased risk of death at 3 years of follow-up.

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

The prognosis of adults with congenital heart disease is importantly influenced by noncardiac comorbidities. In this study on 1102 adult patients with congenital heart disease from a single specialist center, renal dysfunction was found to be a common complication of congenital heart disease, with 41% of patients having mild and 9% having moderate or severe reduction in glomerular filtration rate. Renal dysfunction was also found to be a strong predictor of survival, with a 3-fold adjusted increase in mortality in patients with moderately or severely impaired renal function. These data support routine, periodic screening of renal function in all adult patients with congenital heart disease to obtain broader prognostic information.
Prevalence, Predictors, and Prognostic Value of Renal Dysfunction in Adults With Congenital Heart Disease


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