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ORIGINAL RESEARCH

Prevalence and Prognostic Association of a Clinical Diagnosis of Depression in Adult Congenital Heart Disease: Results of the Boston Adult Congenital Heart Disease Biobank

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BACKGROUND: In adults with acquired heart disease, depression is common and associated with adverse outcomes. Depression may also be important in adults with congenital heart disease (CHD).

METHODS AND RESULTS: We conducted a cohort study of outpatients with CHD, aged ≥18 years, enrolled in a prospective biobank between 2012 and 2017. Clinical data were extracted from medical records. Survival analysis assessed the relationship between depression, defined by a history of clinical diagnosis of major depression, with all-cause mortality and a composite outcome of death or nonelective cardiovascular hospitalization. A total of 1146 patients were enrolled (age, 38.5±13.8 years; 49.6% women). Depression had been diagnosed in 219 (prevalence=19.1%), and these patients were more likely to have severely complex CHD (41.3% versus 33.7%; *P*=0.028), cyanosis (12.1% versus 5.7%; *P*=0.003), and worse functional class (≥II; 33.3% versus 20.4%; *P*<0.0001), and to be taking antidepressant medication at time of enrollment (68.5% versus 5.7%; *P*<0.0001). Depression was associated with biomarkers indicative of inflammation (hsCRP [high-sensitivity C-reactive protein], 1.71 [25th–75th percentile, 0.82–4.47] versus 1.10 [0.45–2.40]; *P*<0.0001) and heart failure (NT-proBNP [N-terminal pro-B-type natriuretic peptide], 190 [92–501] versus 111 [45–264]; *P*<0.0001). During follow-up of 605±547 days, 137 participants (12.0%) experienced the composite outcome, including 33 deaths (2.9%). Depression was associated with increased risk for both all-cause mortality (multivariable hazard ratio, 3.0; 95% CI, 1.4–6.4; *P*=0.005) and the composite outcome (multivariable hazard ratio, 1.6; 95% CI, 1.1–2.5; *P*=0.025), adjusting for age, sex, history of atrial arrhythmia, systolic ventricular function, CHD complexity, and corrected QT interval.

CONCLUSIONS: In adults with CHD, major depression is associated with impaired functional status, heart failure, systemic inflammation, and increased risk for adverse outcomes.

Key Words: adult congenital heart disease ■ adverse effects ■ biomarkers ■ depression ■ prognosis ■ survival

There is growing awareness that depression and other psychiatric diagnoses are common among adolescents and adults with congenital heart disease (ACHD).[1–6] Among patients with acquired forms of heart disease, a diagnosis of depression is associated with adverse outcomes, including

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CLINICAL PERSPECTIVE

What Is New?

- Depression is common among adults living with congenital heart disease: almost 1 in 5 carry a diagnosis of major depression.
- Those who have major depression are more likely to have worse functional status, biomarker profiles indicative of systemic inflammation and heart failure, and higher risk for death or cardiovascular events.

What Are the Clinical Implications?

- Screening for depression may be appropriate to both facilitate appropriate treatment and identify a subgroup of patients at higher risk for adverse outcomes.

Nonstandard Abbreviations and Acronyms

ACHD	Adults with congenital heart disease / adult congenital heart disease
CKD-EPI	Chronic Kidney Disease Epidemiology collaboration
eGFR	Estimated glomerular filtration rate
hsCRP	High sensitivity C-reactive protein
NYHA	New York Heart Association
NT-proBNP	N-terminal pro B-type natriuretic peptide
QTc	Corrected QT interval

cardiovascular mortality, independent of other known risk factors.[7] Depression and cardiovascular disease are both associated with neurohormonal and autonomic nervous system abnormalities, as well as chronic low-grade systemic inflammation.[8–10] Use of antidepressant drugs (antidepressants) to treat depression has also become increasingly common in developed nations over the past several decades.[11] Antidepressant use is generally safe and effective in patients with cardiovascular disease, and may attenuate the association between depression and adverse cardiovascular events. Some antidepressants, however, may have countervailing effects, including an increase in blood pressure, prolonged QT interval, and other proarrhythmic effects.[12–14]

Depression appears to be more common in ACHD compared with the general population. The prevalence of depression over a given 2-week period is estimated at 8.1% in adults aged >20 years in the United States,[15] but reported rates in ACHD are 2- to 4-fold higher, between 17% and 33%.[2–4,15,16] Direct comparison across studies is limited, however, because of variable ascertainment (eg, self-report, clinical assessment, administrative codes, and medication use) and definitions (eg, 2-week prevalence and lifetime prevalence). In this study, we examined social, clinical, and biological correlates of a history of diagnosis of major depression in ACHD, as well as the association between depression and both all-cause mortality and a composite outcome of death or nonelective cardiovascular hospitalization. We hypothesized that in ACHD: (1) the prevalence of major depression would be higher than reported in the general population, (2) a history of major depression would be associated with biomarkers indicative of increased inflammation and heart failure, and (3) a history of major depression would be associated with an increased risk for adverse health outcomes.

METHODS

Description of the Cohort

The data that support the findings of this study are available from the corresponding author on reasonable request. We enrolled outpatients with CHD, aged ≥18 years, between 2012 and 2017 seen at Boston Children's or Brigham and Women's Hospitals in the Boston ACHD Biobank; a detailed description of the protocol has been published elsewhere.[17] The current study was approved by Boston Children's Hospital's Institutional Review Board, and there was a formal reliance agreement with the Partners HealthCare/Brigham and Women's Hospital Institutional Review Board. Informed consent was obtained from each participant.

Data Collection and Definitions

Demographic and clinical data, including physical comorbidities and clinically documented psychiatric diagnoses, were collected from medical records via detailed review of problem lists, medication lists, and all available clinical notes. Data were collected around the time of enrollment, typically on the date of baseline biospecimen collection, with follow-up limited to time of enrollment to time of data collection in 2017. In the absence of a relevant cardiovascular intervention (eg, valve replacement), we also included data obtained within 2 years of sample collection. Clinical data extracted from the medical record included New York Heart Association (NYHA) functional class (I versus ≥II), presence of cyanosis (defined as resting arterial oxygen saturation <92%), diagnosis complexity classified per the 32nd Bethesda conference guidelines,[18] presence of a single ventricle versus biventricular circulation, and clinical diagnosis of major depression or other psychiatric diagnoses. Depression and other

psychiatric diagnoses were defined on the basis of review of the complete electronic medical record at the time of enrollment. This included cardiology clinic documentation from the time of enrollment, as well as all available cardiology, primary care, and any other documentation. Major depression was defined as any historical (lifetime to date) documentation of this diagnosis, without distinction between current active depression and history. No distinction between current active depression and history was made. The corrected QT (QTc) interval was calculated using Bazett's formula on the basis of data from ECG reports.

Laboratory Testing

Blood was collected in a serum separator tube and allowed to clot for 30 to 60 minutes at room temperature, followed by centrifugation at 1300*g* for 10 minutes at 4°C.[17] hsCRP (high-sensitivity C-reactive protein) was measured from these fresh serum samples with a Cobas 8000 analyzer using a latex particle-enhanced immunoturbidimetric assay (Roche Diagnostics, Indianapolis, IN) by a Clinical Laboratory Improvement Amendments–approved laboratory (LabCorp, Laboratory Corporation of America, Burlington, NC) with a lower limit of detection of 0.1 mg/L and between-run coefficients of variation of 3.1% and 2.3% at mean values of 1.5 and 11.4 mg/L, respectively. A subset of the blood was collected in an EDTA tube and processed to plasma by centrifugation at 1300*g* for 10 minutes at 4°C, and then aliquoted and frozen at −80°C. All measurements were performed on specimens with no prior freeze-thaw cycles. Estimated glomerular filtration rate was calculated using published equations based on cystatin C (Tina-quant Cystatin C Gen. 2; Roche Diagnostics).[19] NT-proBNP (N-terminal pro-B-type natriuretic peptide) was measured using an electrochemiluminescence immunoassay (Roche Diagnostics) on a Cobas Elecsys e601 analyzer. The NT-proBNP assay lower limit of detection is 5 pg/mL (0.6 pmol/L), with intermediate precision of 3.1%, 2.7%, and 1.7% at mean values of 46, 125, and 32 930 pg/mL, respectively.

Outcomes

The primary outcomes of interest were: (1) all-cause mortality and (2) a combined outcome of either all-cause mortality or nonelective cardiovascular hospitalization. Nonelective cardiovascular hospitalization was defined as overnight admission for heart failure, arrhythmia, or symptoms of arrhythmia, thromboembolism, cerebral hemorrhage, or cardiovascular disease–related events (eg, protein-losing enteropathy).

Statistical Analysis

The primary analysis focused on describing differences in the clinical characteristics of patients with and without a recorded diagnosis of major depression at any point, with a secondary analysis comparing groups on the basis of current antidepressant medication use at the time of enrollment. Normally distributed continuous variables are presented as mean±SD, and median [25th–75th percentile] values are given for nonnormally distributed variables. The Wilcoxon rank sum test was used to compare continuous variables between 2 groups. The χ^2 or Fisher's exact test was used to analyze categorical variables between groups. The log-rank test and Cox regression were used to perform univariate and multivariable survival analysis, respectively. Time to event was defined from a time origin of the date of biospecimen collection until the date of the first clinical event, with censoring of event-free individuals at the most recent clinical follow-up date when event status was known. Multivariable models adjusted for age, sex, history of atrial arrhythmia, systolic ventricular function, CHD diagnosis complexity, and QTc interval. Because of the limited number of deaths, models with all-cause mortality as the dependent variable were repeated, adjusting for only atrial arrhythmia and ventricular function. The C-statistic was calculated using Harrell's method.[20] The assumption of proportional hazards was assessed for each model, and there was no apparent violation. We calculated E-values for the adjusted hazard ratios (HRs). The E-value represents the minimum magnitude of association on the risk ratio scale for an unmeasured confounder or set of confounders to have with both the exposure (ie, depression) and outcome (ie, mortality and the composite outcome), conditional on the measured covariates and in addition to the covariates we adjusted for, to explain away the entire association between depression and the outcome.

Analyses were performed using SAS 9.4 (SAS Institute, Inc, Cary, NC), R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria), and GraphPad Prism (GraphPad Software, Inc, La Jolla, CA). A 2-sided $P<0.05$ was considered statistically significant.

RESULTS

Description of the Cohort

A total of 1146 patients enrolled in the biobank between 2012 and 2017. The average age at time of enrollment was 38.5±13.8 years, and 49.6% were women. Most patients had moderately or severely complex CHD (Table 1). The most common underlying diagnoses were left-sided obstructive lesions (n=251 [21.9%]),

Table 1. Demographic and Clinical Characteristics of ACHD, by Depression Status

Variable	Overall	Depression		*P* Value
		Absent	Present	
N	1146	927 (80.9)	219 (19.1)	…
Age, y	38.5±13.8	38.0±13.7	40.6±13.7	0.0061
Sex (men)	577 (50.4)	492 (53.1)	85 (38.9)	0.0002
Race (white)	840 (73.3)	672 (72.5)	168 (76.7)	0.2344
BMI, kg/m^2	27.0±5.7	26.7±5.5	28.4±6.3	0.0003
BMI >30 kg/m^2	289 (25.5)	217 (23.7)	72 (33.3)	0.0042
Hypertension	171 (14.9)	141 (15.2)	30 (13.7)	0.6731
Diabetes mellitus	45 (3.9)	33 (3.6)	12 (5.5)	0.1804
Stroke	51 (4.4)	38 (4.1)	13 (5.9)	0.2723
Cirrhosis	26 (2.3)	16 (1.7)	10 (4.6)	0.0198
Atrial fibrillation or flutter	243 (21.2)	187 (20.2)	56 (25.6)	0.0814
Pulmonary hypertension	44 (3.8)	33 (3.6)	11 (5.0)	0.3276
Cyanosis	73 (6.9)	49 (5.7)	24 (12.1)	0.0029
Pacemaker	164 (14.3)	121 (13.0)	43 (19.6)	0.0178
ICD	71 (6.2)	53 (5.7)	18 (8.2)	0.1635
Peak VO_2, mL/kg per min	23.7±8.0	24.9±7.8	20.1±7.2	<0.0001
Peak VO_2, % predicted	72.3±19.7	74.3±18.9	68.1±18.7	<0.0001
NYHA functional class				
I	884 (77.1)	738 (79.6)	146 (66.7)	<0.0001
≥II	262 (22.9)	189 (20.4)	73 (33.3)	
Systemic ventricular systolic function				0.1796
Normal	834 (76.2)	682 (76.9)	152 (70.2)	
Mildly reduced	186 (17.0)	151 (17.0)	35 (16.9)	
Moderately or severely reduced	74 (6.8)	54 (6.1)	20 (9.7)	
Disease complexity				0.0281
Simple	254 (22.2)	202 (21.8)	52 (23.8)	
Moderate	489 (42.7)	413 (44.5)	76 (34.9)	
Severe	402 (35.1)	312 (33.7)	90 (41.3)	
Medications				
ACEI/ARB	318 (27.7)	253 (27.3)	65 (29.7)	0.5022
β Blocker	347 (30.3)	264 (28.5)	83 (37.9)	0.0070
Aspirin/antiplatelet	360 (31.4)	277 (29.9)	83 (37.9)	0.0235
Anticoagulant	241 (21.0)	196 (21.1)	45 (20.6)	0.9266
Loop diuretic	180 (15.7)	132 (14.2)	48 (21.9)	0.0070
Any psychiatric medication*	288 (25.1)	121 (13.0)	167 (76.3)	<0.0001
Antidepressant medication*	203 (17.7)	53 (5.7)	150 (68.5)	<0.0001

Data are given as number (percentage), unless otherwise indicated. Age, BMI, peak VO_2, and peak VO_2 predicted are presented as mean±SD. Univariate *P* values reflect comparison using the Wilcoxon rank sum test or Chi-squared test, for continuous and categorical variables, respectively. Data were unavailable or missing for: BMI (n=14), CHD complexity (n=1), and cardiopulmonary exercise testing data (n=378). Anticoagulant use included vitamin K antagonists and direct oral anticoagulants. ACEI indicates angiotensin-converting enzyme inhibitor; ACHD, adults with congenital heart disease; ARB, angiotensin II receptor blocker; BMI, body mass index; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; and VO_2, oxygen consumption during cardiopulmonary exercise testing.

*Psychiatric medication and antidepressant medication refer to medications that are frequently used for psychiatric purposes or to treat depression, respectively. Many of these medications are also used for other indications, and these figures refer to overall use, irrespective of indication.

tetralogy of Fallot (n=216 [18.8%]), single-ventricle physiological features with a Fontan palliation (n=158 [13.7%]), transposition of the great arteries with a systemic right ventricle (n=158 [13.7%]), and simple shunt lesions (eg, isolated atrial or ventricular septal defect) without clinical sequelae (n=155 [13.5%]) (Table 2).

Cross-Sectional Analysis

A clinical diagnosis of major depression was included in the medical record for 219 patients (19.1%). Women were more likely to have had a prior diagnosis of depression than were men (61.1% versus 46.9%; *P*=0.0002), and depression was also associated with

Table 2. Comparison of CHD Diagnoses Between Patients With and Without Depression

Diagnosis	Depression	
	Absent	Present
Simple shunt without clinical sequelae	119 (76.8)	36 (23.2)
Eisenmenger or complex cyanotic heart disease	19 (82.6)	4 (17.4)
Simple shunt with clinical sequelae	27 (81.8)	6 (18.2)
AVSD	27 (93.1)	2 (6.9)
Left-sided obstructive lesions	220 (87.6)	31 (12.4)
D-TGA/ccTGA with systemic right ventricle	76 (72.4)	29 (27.6)
D-TGA after ASO	30 (78.9)	8 (21.1)
ToF/DORV/PA	171 (79.2)	45 (20.8)
SV-Fontan	127 (80.4)	31 (19.6)
Ebstein/Uhl anomaly	24 (80)	6 (20)
Miscellaneous	87 (80.6)	21 (19.4)

Data are given as number (percentage). Simple shunt lesions are defined as atrial septal defect, ventricular septal defect, partial anomalous pulmonary venous return, or patent ductus arteriosus (repaired or unrepaired) without clinical sequelae, including pulmonary hypertension, congestive heart failure, and arrhythmia. ASO indicates arterial switch operation; AVSD, atrioventricular septal defect, including isolated primum atrial septal defect or inlet ventricular septal defect; ccTGA, congenitally corrected or l-loop transposition of the great arteries; CHD, congenital heart disease; DORV, double-outlet right ventricle; D-TGA, d-loop transposition of the great arteries; PA, pulmonary atresia; SV, single-ventricle spectrum; and ToF, tetralogy of Fallot.

more complex CHD, cyanosis, and higher body mass index (Table 1 and Figure 1). Patients with a history of major depression were more functionally limited, with worse NYHA functional class and lower peak oxygen consumption during cardiopulmonary exercise testing. Only a small subset of patients had a known genetic syndrome associated with psychiatric effects. For most syndromes, there was no statistically significant difference in the proportion of patients with depression compared with the prevalence of depression among patients without that genetic syndrome; this included Down syndrome (3 of 12 patients with Down syndrome had a clinical diagnosis of depression, 25.0% versus 19.0% among those without Down syndrome; P=0.60), heterotaxy syndrome (6 of 20, 30.0% versus 18.9% among those without heterotaxy syndrome; P=0.21), or Noonan syndrome (1 of 5, 20.0% versus 19.1% among those without Noonan syndrome; P=0.96). However, patients with 22q11 deletion syndrome had a substantially higher prevalence of depression compared with those without 22q11 deletion (6 of 11, 54.5% versus 18.8% of those without 22q11 deletion; P=0.003). There were <5 patients each with Williams, Holt-Oram, Turner, Goldenhar, or other identified genetic syndromes.

There was no statistically significant relationship between underlying CHD diagnostic group and the prevalence of depression (χ^2 P=0.065; logistic regression adjusted for age, sex, and NYHA functional class P=0.10). Those with left-sided obstructive lesions tended to be less likely to have depression (12.4% of 251 patients; P=0.03; adjusted P=0.22), as did those with atrioventricular septal defects, but the number of patients was small (6.9% of 29 patients; P=0.11; adjusted P=0.11); conversely, depression was more common among patients with transposition of the great arteries and a systemic right ventricle (27.6% of 105 patients; P=0.02; adjusted P=0.004). For all other diagnostic groups, the prevalence of depression was between 17% and 23%. For example, depression was present in 19.6% of the 158 patients with a single ventricle Fontan circulation; furthermore, there was no statistically significant difference between the various single-ventricle CHD diagnoses in terms of the prevalence of depression (P=0.49; adjusted P=0.47).

Depression was associated with lower educational attainment and lower probability of full-time employment or being a full-time student (59.5% versus 74.0%), with a higher proportion unemployed or collecting disability benefits (Table 3). Fewer patients with a diagnosis of depression were married. Depression was also associated with less frequent moderately strenuous exercise. The observed associations of depression with educational attainment, employment, exercise habits, and marital status were not accounted for by differences in age, sex, CHD diagnosis complexity, or NYHA functional class between those with and without a diagnosis of depression (Table 3).

Those with depression had higher hsCRP, higher NT-proBNP, and lower estimated glomerular filtration rate, as calculated using the Chronic Kidney Disease Epidemiology Collaboration cystatin C equation (Table 4). Mean hemoglobin was also lower in patients with a history of depression than those without, although this appeared to be an artifact of the higher prevalence of depression among women (because mean hemoglobin concentration is normally lower in women than men).

ECG data were available for 1052 patients (91.8%), of whom 73 were ventricular paced, 21 had left bundle branch block, and 296 had right bundle branch block. Patients with depression were about twice as likely to be ventricular paced (12.1% versus 5.7%; P=0.002), but there was no notable difference in the frequency of left or right bundle branch block. Overall, 641 participants (60.9%) were not ventricular paced and had QRS duration <120 milliseconds. Among this subset, heart rate averaged 71.0±13.7 beats per minute, QRS duration averaged 96.9±11.8 milliseconds, and QTc interval averaged 429.7±30.8 milliseconds. Those

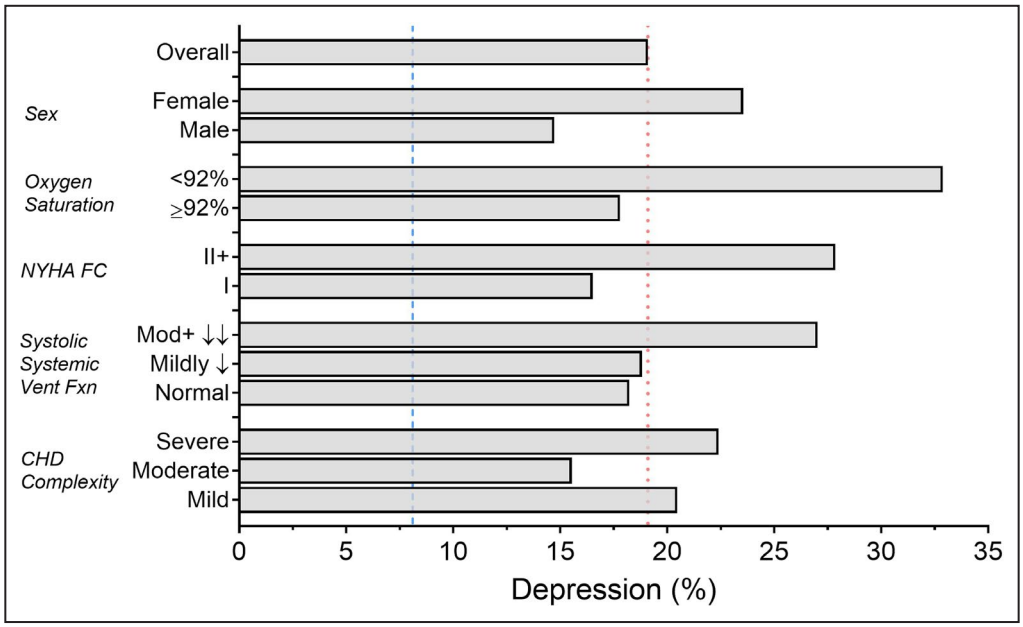

Figure 1. Percentage of patients with a history of major depression in 1146 adults with congenital heart disease, by clinical characteristics.
History of major depression as a diagnosis documented in the medical record among a cohort of 1146 adults with congenital heart disease. Blue dashed line presents an estimate of the 2-week prevalence of major depression in the general US population, whereas the orange dotted line represents the overall prevalence of major depression in this cohort. CHD Complexity indicates congenital heart disease complexity, as defined by the 32nd Bethesda conference guidelines; Fxn, function; II+, NYHA FCs II to IV; Mildly ↓, mildly depressed systemic ventricular systolic function; Mod+ ↓↓, moderate to severely depressed systemic ventricular systolic function; and NYHA FC, New York Heart Association functional class.

with depression had higher average resting heart rate (74.4±14.6 versus 70.2±13.6 beats per minute; *P*=0.002) but equivalent QRS duration (95.9±12.2 versus 97.2±11.7 milliseconds; *P*=0.31). QTc interval was longer in those with depression (437.7±30.9 versus 427.9±30.6 milliseconds; *P*<0.0001; Figure 2); however, there was no appreciable independent association between depression and QTc interval after adjustment for age, sex, CHD complexity, and antidepressant use (4.3±3.8 milliseconds; *P*=0.27).

Other Psychiatric Diagnoses and Events

Other psychiatric diagnoses tended to be more common in those with depression, including: anxiety (42.3% versus 14.1%; *P*<0.0001), attention-deficit hyperactivity disorder (7.3% versus 3.3%; *P*=0.01), posttraumatic stress disorder (3.2% versus 0.7%; *P*=0.005), bipolar disorder (2.7% versus 0.8%; *P*=0.02), any personality disorder (0.9% versus 0%; *P*=0.04), and substance use disorder other than tobacco (9.1% versus 1.7%; *P*<0.0001). Tobacco abuse and abstinence from alcohol were also more common in patients with depression (Table 3). There were no patients with a diagnosis of schizophrenia or dementia. There was no significant difference in the prevalence of autism spectrum disorder, cognitive impairment, or obsessive-compulsive disorder between those with and without depression. Twenty-four patients (11.0%) with a history of depression had a prior hospitalization for any psychiatric reason compared with 8 patients (0.9%) without depression. One patient with depression had received electroconvulsive therapy.

More than two thirds of patients with a history of a depression diagnosis were using an antidepressant medication at the time of enrollment (n=150/219 [68.5%]). A much smaller proportion of patients without depression were taking an antidepressant (5.7%). Of the 53 patients on antidepressants who did not have a diagnosis of depression, 43 had an anxiety disorder, and other indications included migraine headaches, obsessive-compulsive disorder, neuropathy, bipolar disorder, attention-deficit disorder, and fibromyalgia. Most patients with a diagnosis of depression had been prescribed antidepressants chronically (for ≥3 months in 81.3%). Only 2% of participants had been prescribed antidepressants within the past 3 months; the duration of antidepressant use was undefined in 16.7%. Selective serotonin reuptake inhibitors were the most common type of antidepressant prescribed, followed by selective norepinephrine reuptake inhibitors and serotonin modulators; a small number of patients were on a tricyclic antidepressant (Table 5). Sertraline was the most commonly

Table 3. Comparison of Socioeconomic Characteristics and Health-Related Behavior at Time of Enrollment, by Depression Diagnosis Status

Variable	Depression		*P* Value	Adjusted *P* Value
	Absent	Present		
Marital status				
Married	404 (43.6)	84 (38.4)	0.009	0.0185
Widowed	3 (0.3)	4 (1.8)		
Divorced	26 (2.8)	7 (3.2)		
Separated	6 (0.7)	5 (2.3)		
Never married	332 (35.8)	71 (32.4)		
Never married, living with partner	72 (7.8)	26 (11.9)		
Employment status				
Full-time work	581 (63.4)	115 (53.0)	<0.0001	0.0025
Part-time work	39 (4.3)	19 (8.8)		
Part-time work/student	26 (2.8)	2 (0.9)		
Full-time student	97 (10.6)	14 (6.5)		
Cares for own children in home	24 (2.6)	3 (1.4)		
Unemployed, looking for work	10 (1.1)	9 (4.2)		
Unemployed, not looking for work, not disabled	45 (4.9)	16 (7.4)		
Long-term disability (with benefits)	29 (3.2)	17 (7.8)		
Retired	25 (2.7)	6 (2.8)		
Educational attainment				
Less than high school	9 (1.2)	5 (2.8)	0.0026	0.006
High school	119 (16.1)	45 (25.6)		
Some college	111 (15.0)	34 (19.3)		
College	311 (42.1)	57 (32.4)		
More than college	188 (25.5)	35 (19.9)		
Exercise (moderately strenuous)				
Low/infrequent	255 (27.5)	85 (38.8)	<0.0001	0.0004
Occasional (<2 times/wk)	88 (9.5)	22 (10.1)		
Frequent (>2 times/wk)	322 (34.7)	39 (17.8)		
Intensive (>5 times/wk, >45 min)	37 (4.0)	2 (0.9)		
Substance use				
Substance use disorder (other than tobacco/alcohol)	16 (1.7)	20 (9.1)	<0.0001	<0.0001
Current tobacco use	33 (3.6)	17 (7.8)	0.006	0.003
Alcohol use			0.005	0.049
None (<1 time/y)	239 (25.8)	84 (38.4)		
1–3 drinks/mo	250 (27.0)	51 (23.3)		
At least weekly	324 (35.0)	61 (27.8)		
≥ 5 drinks in a given day at least weekly	8 (0.9)	3 (1.4)		

Data are given as number (percentage). *P* values reflect comparison using the χ^2 test for univariate comparisons and logistic regression for multivariable analysis, adjusting for age, sex, diagnosis severity, and New York Heart Association functional class. Data missing for marital status (n=106), employment status (n=69), education status (n=176), exercise (n=296), and alcohol (n=126); percents presented are for the proportion of patients with available data. Data for education are presented only for patients aged >21 years.

prescribed antidepressant to patients with depression (21.9%), followed by fluoxetine and venlafaxine (each 7.8%) (Table 6).

Patients with depression were also more likely to be taking another class of psychiatric medication, including mood stabilizers (11.0% versus 2.2%; *P*<0.0001), benzodiazepines (23.3% versus 5.7%; *P*<0.0001), stimulants (5.5% versus 1.3%; *P*=0.0001), and antipsychotics (5.9% versus 0.4%; *P*<0.0001).

Survival Analysis

Over a follow-up period of 605±547 days (median, 458 [25th–75h percentile: 116–995] days), there were

Table 4. Comparison of Laboratory Testing Between Patients With and Without Depression

Variable	Depression		*P* Value	*P* Value, Adjusted*
	Absent	Present		
hsCRP, mg/L	1.10 [0.45–2.40]	1.71 [0.82–4.47]	<0.0001	<0.0001
NT-proBNP, pg/mL	111 [45–264]	190 [92–501]	<0.0001	0.005
CKD-EPI$_{CysC}$ eGFR, mL per 1.73 m^2 per min	101±23	100±23	0.0003	0.25
Hemoglobin, g/dL	14.4±1.7	13.9±1.8	0.0001	0.13

NT-proBNP and hsCRP were natural log transformed for multivariable linear regression analysis but presented as median (interquartile range) of the untransformed values. The other variables are presented as mean±SD. *P* values reflect comparison using the Wilcoxon rank sum test for all unadjusted comparisons. Data were available for those without/with depression in n=869/216 for hsCRP, n=704/173 for NT-proBNP, n=704/173 for cystatin C, and n=857/211 for hemoglobin. CKD-EPI$_{CysC}$ eGFR indicates Chronic Kidney Disease Epidemiology Collaboration cystatin C equation for estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Linear regression adjusted for age, sex, and New York Heart Association functional class.

33 deaths and 137 combined outcomes. Patients with a history of depression were at increased risk for all-cause mortality (univariate HR, 3.44; 95% CI, 1.74–6.83; *P*=0.0004; full multivariable HR, 2.99; 95% CI, 1.40–6.41; *P*=0.005; adjusting only for atrial arrhythmia and ventricular function HR, 3.20; 95% CI, 1.40–7.29; *P*=0.005) (Figure 3). A diagnosis of depression was also associated with the occurrence of the combined outcome (HR, 1.78; 95% CI, 1.23–2.59; *P*=0.002; multivariable HR, 1.63; 95% CI, 1.06–2.50; *P*=0.025). Omitting QTc interval from the multivariable model did not affect the regression coefficients for depression in either the all-cause mortality or combined outcome model, although longer QTc interval itself was independently associated with an increased risk for both outcomes.

There was no evidence of effect modification by patient sex (depression*sex interaction term *P*=0.86); the HR was 1.88 for women (95% CI, 1.13–3.14) and 1.76 for men (95% CI, 1.01–3.07).

The E-value for the relationship between depression and mortality was 5.5. That is, to explain away the observed the HR=3.0 for mortality among patients with depression, an unmeasured confounder or set of counfounders would have to be associated with depression and mortality with a relative risk and HR (for depression and mortality, respectively) of at least 5.5; and the E-value for the lower bound of the 95% CI was 2.2. Therefore, substantial unmeasured confounding would be required to account for the association we observed between depression and mortality. For the composite outcome, the E-values for the HR point estimate and lower 95% CI bound were 2.6 and 1.4, respectively.

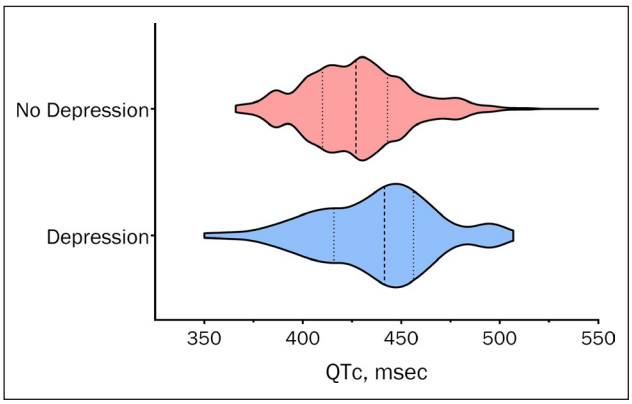

Figure 2. Corrected QT (QTc) interval distribution for patients with and without depression.
Violin plot of the distribution of QTc interval for patients without and with depression (above/red, below/blue). Median is designated by the thick dashed line, and 25th/75th percentiles by the dotted lines. The Bazett formula was used to calculate QTc on the basis of data from ECG heart rate and QT interval.

DISCUSSION

Results of this observational follow-up study of a prospectively enrolled cohort suggest that among ACHD, clinical depression is (1) common, especially in women and those with lower functional status, (2) associated with increased systemic inflammation and heart failure, and (3) associated with an increased risk for adverse outcomes, including all-cause mortality.

Psychiatric disorders, including major depression, are more commonly diagnosed among people with ACHD compared with the general population, and depression is associated with decreased quality of life.[21,22] CHD-related risk factors for these diagnoses

Table 5. Antidepressant Drug Use, by Class

Variable	Depression		*P* Value
	Absent	Present	
SSRI	33 (3.6)	101 (46.1)	<0.0001
SNRI	7 (0.8)	30 (13.7)	<0.0001
Serotonin modulator	7 (0.8)	18 (8.2)	<0.0001
Tricyclic antidepressant	6 (0.6)	7 (3.2)	0.0051

Data are given as number (percentage). *P* values reflect comparison using the χ^2 test. No patient was taking atypical depressants or monoamine oxidase inhibitors during the study period. SNRI indicates selective norepinephrine reuptake inhibitor; and SSRI, selective serotonin reuptake inhibitor.

Table 6. Specific Antidepressant Drug Use

Variable	Depression		*P* Value
	Absent	Present	
Selective serotonin reuptake inhibitors			
Sertraline	12 (1.3)	48 (21.9)	<0.0001
Fluoxetine	3 (0.3)	17 (7.8)	<0.0001
Citalopram	12 (1.3)	14 (6.4)	<0.0001
Escitalopram	3 (0.3)	13 (5.9)	<0.0001
Paroxetine	2 (0.2)	9 (4.1)	<0.0001
Fluvoxamine	1 (0.1)	0 (0.0)	1.0
Selective norepinephrine reuptake inhibitors			
Desvenlafaxine	0 (0.0)	1 (0.5)	0.1911
Duloxetine	5 (0.5)	12 (5.5)	<0.0001
Venlafaxine	2 (0.2)	17 (7.8)	<0.0001
Serotonin modulators			
Nefazodone	0 (0.0)	2 (0.9)	0.0364
Trazodone	6 (0.6)	16 (7.3)	<0.0001
Vilazodone	1 (0.1)	0 (0.0)	1.0000
Vortioxetine	0 (0.0)	2 (0.9)	0.0364
Tricyclic antidepressants			
Amitriptyline	5 (0.5)	6 (2.7)	0.0089
Doxepin	1 (0.1)	0 (0.0)	1.0
Nortriptyline	0 (0.0)	1 (0.5)	0.1911
Atypical antidepressants			
Bupropion	3 (0.3)	16 (7.3)	<0.0001
Mirtazapine	0 (0.0)	5 (2.3)	0.0002

P values reflect comparison in the proportion of patients with and without depression taking a specific antidepressant medication, using the Chi-squared test for all variables. Data are presented as number (percentage) of patients in the column taking the specific medication.

may include exposure to early medical adversity; repeated episodes involving emotional distress, pain, and anesthetic administration; cardiac surgery with or without cardiopulmonary bypass; and other developmental insults.[23] Shared genetic predisposition could contribute, as may be the case for neurodevelopmental issues.[24] Ecobiodevelopmental factors may also influence mental health.[25] Emotional stressors and traumatic experiences may account for some of the increased burden of depression, although individual responses to such events are variable.

To date, only 2 large retrospective studies have assessed the relationship between depression and clinical outcomes in ACHD. The first used antidepressant medication prescription as a surrogate for a diagnosis of depression without further assessment. That study, from the United Kingdom where rates of antidepressant use are much lower than the United States, suggested that antidepressant use was associated with adverse outcomes in men but not women with CHD.[26] The second study, from Israel, used administrative codes to identify patients with depression and reported increased resource use and higher mortality in this subset of patients.[16]

Depression may also be associated with other medical diagnoses and is particularly common among those with multiple comorbidities. Compared with the general population, higher rates of major depression are reported in patients with diabetes mellitus, chronic pulmonary disease, and rheumatologic disease, among others.[27] Both genetic and environmental factors may confer an increased risk of depression in those with greater functional limitations from physical disorders, creating a cyclic decrement of health in those vulnerable populations.[28–30]

Previous studies have reported an association between depression and increased cardiovascular mortality among adults with acquired heart disease.[31–33] Possible explanations include dysregulation of inflammatory and neurohormonal processes, effects of medications used in the treatment of both cardiovascular conditions and depression, a consequence of worsening somatic disorder(s), and more limited access to care, especially in the context of significant comorbidities. Behavioral mechanisms likely also contribute to worse outcomes among patients with depression; examples include an increased burden of medication and dietary nonadherence and substance use disorders as well as less frequent physical activity. The current analysis suggests that ACHD diagnosed with major depression are less likely to be married, have lower educational attainment, are less physically active in terms of frequency of moderately strenuous exercise, and are more likely to have a substance use disorder. There is significant overlap in dysfunction of neurohormonal cascades between patients with heart failure from acquired heart disease and those with CHD as noted by elevated biomarkers, such as B-type natriuretic peptide, and abnormal cardiac autonomic nervous system activity.[34–36] ACHD tend to be substantially younger than adults with acquired forms of heart disease, as seen in the current study, and this complicates direct comparisons. Nevertheless, ACHD often manifest similar symptoms as their non-ACHD heart failure counterparts, especially with regard to acute decompensation. Although evidence remains sparse, ACHD are also often treated with standard heart failure medications, including β blockers, renin-angiotensin-aldosterone system modulators, and diuretics.[37,38] In addition, biomarkers of inflammation, such as tumor necrosis factor-α and interleukin-6, are elevated in specific ACHD populations.[39] Given the overlap between both abnormal neurohormonal activation and elevated markers of inflammation in both acquired heart failure and ACHD, it is plausible that the underlying pathophysiologic mechanisms relating depression and adverse cardiovascular effects may be similar for heart failure and ACHD.

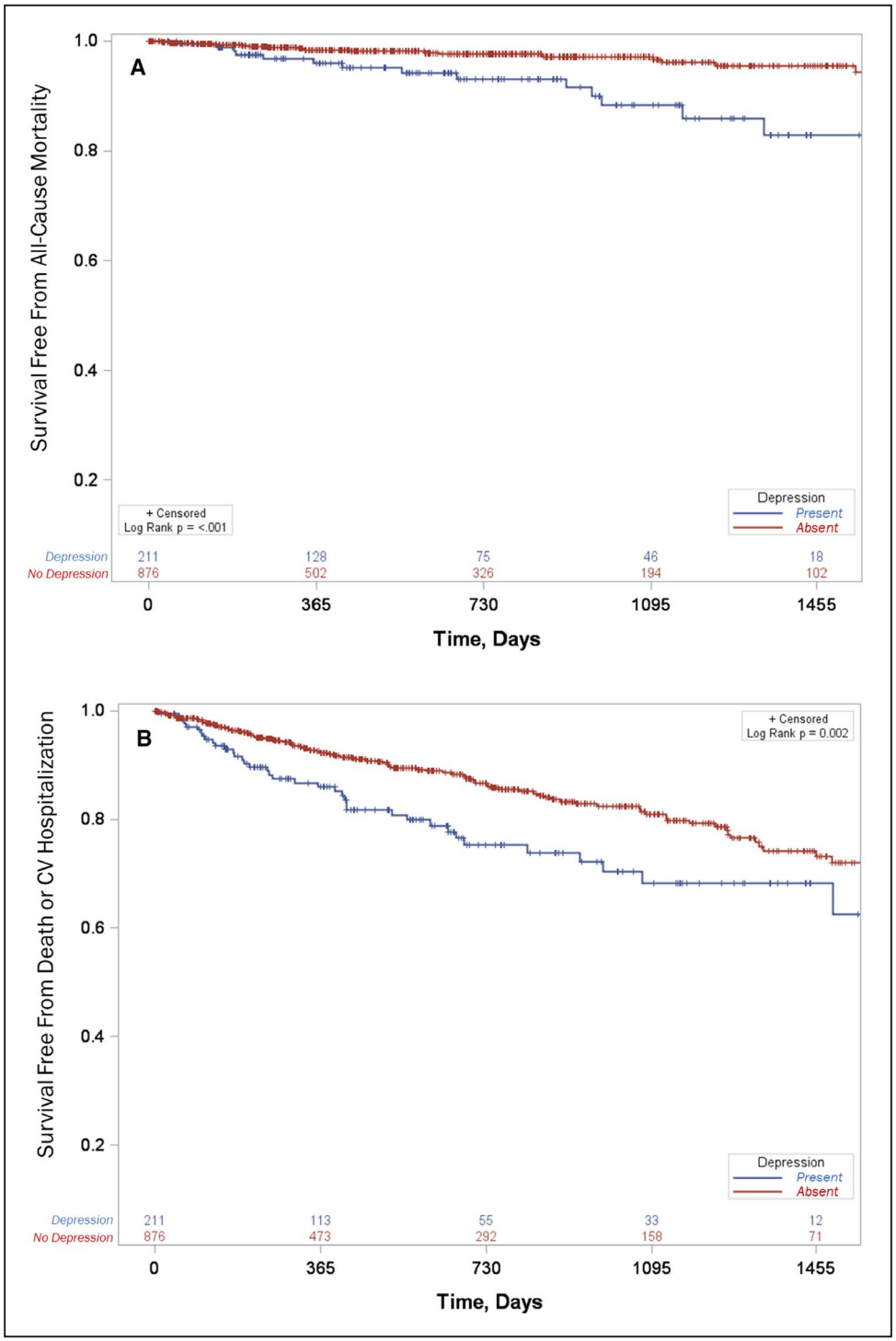

Figure 3. Kaplan-Meier plots illustrating survival from all-cause mortality (A) and cardiovascular hospitalization or all-cause mortality (B) for adults with congenital heart disease with and without depression.

Kaplan-Meier plots of survival from all-cause mortality (**A**) and a composite outcome of cardiovascular hospitalization or all-cause mortality (**B**) for patients with and without depression. Log-rank *P* values are presented, and the number of patients at risk at specific time points is plotted just above the *x* axes. CV indicates cardiovascular.

The link between depression and inflammation observed in our analysis is notable given the association of elevated CRP with adverse outcomes in ACHD.[40,41] In the general population, depression is associated with increased inflammatory markers, including CRP, interleukin-1, and interleukin-6.[31–33,40,41]

Endothelial dysfunction and increased platelet reactivity are also associated with cardiac disease and depression, and treatment of depression with a selective serotonin reuptake inhibitor may reverse some of these abnormalities.[8]

The prevalence of major depression reported in this cohort, 19.1%, is similar to reports in acquired heart failure. One meta-analysis of 27 studies reported a prevalence of 21.5% for depression among adults with acquired heart failure.[42] Almost 18% of patients in the current ACHD cohort were prescribed antidepressants, compared with an estimated 13% of all adults in the United States in 2011 to 2012.[11] Interpretation of this comparison is complicated by the higher use of these medications in older age groups and regional differences in prescription patterns.[11,43] Although the magnitude of difference is not readily quantified, there appears to be a meaningfully higher prevalence of depression and antidepressant use in ACHD compared with similarly aged people in the general population.

Depression has been linked to decreased long-term survival in patients with acquired heart failure, especially in the setting of more severe disease, as indicated by advanced NYHA functional class, prior hospitalization for heart failure, and lower left ventricular ejection fraction.[44] Use of antidepressants is generally accepted as effective in treating symptoms of depression in adults with acquired heart failure, and these medications have not been associated with worse long-term mortality[12–14]; however, antidepressant therapy does not demonstrably improve survival in patients after recent myocardial infarction or with NYHA class II to IV heart failure symptoms and decreased left ventricular ejection fraction.[45,46] Care must be taken when prescribing antidepressants in patients with symptomatic heart failure, as the pharmacokinetics may be affected, such as decreased oral absorption or distribution volume.[47]

Cardiac medications, such as β blockers, can cause fatigue, sexual dysfunction, and depressive mood, but do not appear to be associated with increased risk for major depression per se.[48] Cardiac adverse effect profiles for antidepressants can vary greatly between drugs and include orthostatic hypotension, hypertension, tachycardia, bradycardia, and conduction abnormalities.[49] Tricyclic antidepressants and typical antipsychotics may prolong the QT interval, but other classes of antidepressants have a more modest and variable effect on QT duration.[50] Although we observed that patients with depression had longer QTc interval before factor adjustment, the category of risk for torsade de pointes associated with prolonged QTc interval is variable regardless of antidepressant use. Most patients within our cohort were on selective serotonin reuptake inhibitor or selective norepinephrine reuptake inhibitor therapies, which usually do not have a relevant effect on the QT interval, with the exception of citalopram at higher doses.[51] For patients without a history of arrhythmias, further monitoring beyond a baseline ECG before initiation of selective serotonin reuptake inhibitor therapy (other than citalopram) is not generally indicated.[51]

LIMITATIONS

The findings of this analysis must be interpreted in the context of the observational study design. Depression was defined by clinical diagnosis listed in the available medical record. The accuracy of this approach is presumably lower than with systematic clinical assessment. Patients with undiagnosed depression likely differ from those who receive a diagnosis. Of course, undiagnosed symptoms cannot be appropriately treated, making this an especially important group to understand to have a maximal impact on improving outcomes for ACHD and those with depression. Symptoms of depression may have a somatic or cardiac cause that might merit further evaluation before mental health diagnosis and treatment. We included patients with a diagnosis of depression irrespective of severity or the frequency and timing of prior episodes; however, inclusion of patients in long-term remission with a historical diagnosis is likely to bias our results to the null. Recent diagnosis of depression may be more strongly associated with adverse outcomes over 5 to 10 years of follow-up compared with a distant depression diagnosis.[16] However, we were unable to test this hypothesis without data on timing of depression diagnosis. The mechanisms underlying the association between depression and adverse outcomes remain opaque, and our study design precludes a substantive understanding of the potential for antidepressant medications to ameliorate the attributable cardiovascular risk associated with depression in ACHD. Although examination of the relationship between depression and adherence to recommended medical care and medications, as well as the psychological and social determinants of mental health, were beyond the scope of this study, these are important factors for future investigation. The observational study design also constrained our ability to better define the association between depression, antidepressants, and QTc interval. The relatively small effect size and limited number of patients with depression not taking antidepressants preclude a clear understanding of the mechanism of longer QTc interval. Ideally, one would measure QTc interval before and after starting antidepressant medication. Whatever the mechanism(s), however, adjustment for QTc interval did not affect the relationship between depression and adverse outcomes, arguing against QTc interval being a causal mechanism behind this association in ACHD.

CONCLUSIONS

Our findings suggest that among ACHD, a diagnosis of depression is associated with worse functional status, heart failure, and systemic inflammation. Patients with depression have a higher risk for adverse outcomes, including mortality. Further studies using standardized, prospective mental health assessment and controlled trials are needed in ACHD to understand better the potential benefits of identifying and treating symptomatic depression.

ARTICLE INFORMATION

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Disclosures

None.

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