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Gamma-glutamyl transferase and cardiovascular events in patients with congenital heart disease

Efrén Martínez-Quintana[1,2] | Javier Pardo-Maiza[2] | Beatriz Déniz-Alvarado[2] | Marta Riaño-Ruiz[3] | Jesús María González-Martín[4] | Fayna Rodríguez-González[5]

[1]Cardiology Department, Complejo Hospitalario Universitario Insular-Materno Infantil, Las Palmas de Gran Canaria, Spain

[2]Medical and Surgical Sciences Department, Facultad de Ciencias de la Salud, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain

[3]Department of Biochemistry and Clinical Analyses, Complejo Hospitalario Universitario Insular-Materno Infantil, Las Palmas de Gran Canaria, Spain

[4]Research Unit, Complejo Hospitalario Universitario Insular-Materno Infantil, Las Palmas de Gran Canaria, Spain

[5]Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain

Correspondence
Efrén Martínez-Quintana, Servicio de Cardiología, Complejo Hospitalario Universitario Insular-Materno Infantil, Avd. Marítima del Sur s/n, Las Palmas de Gran Canaria 35016, Spain.
Email: efrencardio@gmail.com

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None.

Abstract

Introduction: Serum gamma-glutamyl transferase activity (GGT) seems to predict cardiovascular events in different populations. However, no data exist on patients with congenital heart disease (CHD).

Methods: Observational, analytic, prospective cohort study design involving CHD patients and a control population to determine the effect of GGT levels on survival.

Results: A total of 589 CHD patients (58% males, 29 ± 14 years old) and 2745 matched control patients were followed up. A total of 69 (12%) CHD patients had a major acute cardiovascular event (MACE) during the follow-up time (6.1 [0.7–10.4] years). Patients with CHD and a GGT >60 U/L were significantly older, more hypertensive and dyslipidemic, had a worse NYHA functional class and a greater anatomical complexity than CHD patients with a GGT ≤60 U/L. The binary logistic regression analysis showed that age, a great CHD anatomical complexity, and having atrial fibrillation/flutter were the predictive factors of higher GGT levels (>60 U/L). The Kaplan–Meier analysis showed that patients with CHD and a GGT concentration above 60 UL showed the lowest probability of survival compared to that of CHD with GGT ≤60 U/L and controls irrespective of their GGT concentrations ($p < .001$). Similarly, the multivariable Cox regression analysis found an independent association between higher GGT levels (>60 U/L) and a worse prognosis (HR 2.44 [1.34–4.44], $p = .003$) among patients with CHD.

Conclusion: Patients with CHD showed significant higher GGT levels than patients in the control group having those with higher GGT concentrations (>60 U/L) the worst survival.

KEYWORDS
cardiovascular outcome, congenital heart disease, oxidative stress, survival

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1 | INTRODUCTION

Oxidative stress is defined as a dysregulation between the production of reactive oxygen species and the endogenous antioxidant defence mechanisms, resulting in excessive and highly reactive chemicals formed from O_2, which are linked to multiple pathophysiological pathways in the heart.

Ample evidence suggests that elevated gamma-glutamyl transferase (GGT), an enzyme that is not only expressed in the liver but also in the kidney, pancreas and bile ducts, is associated with an increased risk of cardiovascular disease. It hydrolyses glutathione into glutamate and a cysteinyl glycine dipeptide, and inside the cell, the amino acids are subsequently reused, producing additional reduced glutathione.[1] As glutathione is an antioxidant product that reduces cell damage-elevated serum GGT concentrations are often considered an indirect measure of increased oxidative stress.[2]

Although, initially, elevated concentrations of this enzyme were associated with liver disease, especially cholestasis, and alcohol consumption in several studies, systematic reviews and metanalysis have shown that elevated serum GGT levels are related not only to liver disease but also to an increased risk of heart failure,[3] atherosclerosis,[4] cardiovascular events[5] and all-cause mortality.[6] However, no studies have shown an association between high GGT levels and a worse outcome in patients with congenital heart disease (CHD).

The purpose of this study is to compare the GGT levels in patients with CHD and a control group as well as determining its influence on survival and to establish if there are clinical or blood test variables that predispose to higher serum GGT concentrations among patients with CHD.

2 | METHODS

Observational, analytic, prospective cohort study design. Cases included clinically stable CHD patients, older than 14 years with a structural CHD verified with imaging tests, recruited consecutively from a single adolescent and adult CHD outpatient unit between January 2007 and December 2018. Controls were drawn from patients older than 14 years attending the primary health care centres of a same geographical area between July 2017 and December 2018 due to preventive activities or minor illnesses such as anxiety, palpitations or muscle aches. Controls were matched for age, sex, systemic arterial hypertension, diabetes mellitus and dyslipidemia to patients with CHD. Patients excluded from the study were those who did not meet the inclusion criteria or did not give written informed consent to participate. The study was approved by the hospital Research Ethics Committee, and reporting of the study conforms to broad EQUATOR guidelines.[7]

2.1 | Clinical data

Cardiovascular imaging established the diagnosis of CHD, and patients were classified into diagnostic groups, according to their anatomical complexity, in simple, moderate, or great cardiac defects.[8] Cardiovascular risk factors (arterial hypertension, diabetes mellitus, dyslipidemia and smoking habit) were categorized as previously reported.[9] Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres. Having atrial fibrillation or flutter and being a carrier of a mechanical valve prosthesis was determined by electrocardiogram or medical history. Medical treatment, obtained from their medical records, included antiplatelet therapy, oral anticoagulation, beta-blockers, angiotensin-converting enzyme inhibitor (ACE inhibitor), angiotensin II receptor blockers (ARBs), calcium channel blockers, loop diuretics, statins and iron supplements. Glomerular filtration rate (GFR) was calculated according to the Modification of Diet in Renal Disease Study equation.[10] In patients with CHD, systemic ventricular dysfunction was defined, by echocardiogram, as a left ventricular ejection fraction <40% or a tricuspid annular plane systolic excursion (TAPSE) of the right ventricle <17 mm.[11] The optimal cutoff point of the NT-pro-BNP level, to rule out heart failure, was 125 pg/ml.[12]

2.2 | Blood test

After giving written informed consent, blood samples were collected after an overnight fast of at least 10 h. The tested analytes were obtained by spectrophotometry using an Olympus AU 2700 equipment (Olympus Diagnostic), and the NT-pro-brain natriuretic peptide (NT-pro-BNP) levels were measured by immunoassay with the Siemens Stratus CS Acute Care Diagnostic System (Siemens Healthcare Diagnostics, Inc). The same blood test equipments and the same references values were used for all CHD and control patients. In our laboratory, GGT levels in the range of 0–55 U/L were considered normal. We used 60 U/L as a GGT cutoff value for CHD patients and the 95th percentile of the GGT value in the control group.

2.3 | Follow-up

Major adverse cardiac event (MACE) was defined as cardiovascular and noncardiovascular death, arterial thrombotic events (myocardial infarction, stroke or peripheral vascular disease),[13] pulmonary embolism, heart failure, arrhythmia or major haemorrhagic events requiring hospital admission. Patients were censored at the first occurring component of the composite endpoint. The follow-up process was undertaken by reviewing the

International Classification of Diseases (ICD) diagnostic coding system of the medicoadministrative data from our hospital, the clinical history or telephone calls.

A medium-term prospective comparison of CHD and control patients was carried during the first 4 years, depending on whether they had GGT concentrations above or below 60 U/L, and subsequently, we did a long-term prospective comparison of only CHD patients as their recruitment process started earlier.

2.4 | Statistical analysis

Numerical data were evaluated for a normal distribution using the Kolmogorov-Smirnov test; parametric data are presented as mean and standard deviation (±), and nonparametric data are presented as median and 5–95 percentiles. Categorical values were compared by using the chi-squared test. Statistical comparisons of parametric data were made with the Student's *t*-test for two-group comparisons, and nonparametric data were compared with the use of the Mann-Whitney rank-sum test.

Logistic regression analysis was used to predict the variables associated with high GGT concentrations in patients with CHD. It was performed with GGT concentration classified in a binary manner (above or below 60 U/L) as the dependent variable, and the variables that showed significant association in the univariate analysis ($p < .05$) as covariates. Covariates were entered into the regression analysis with the enter method selection in which all variables in a block are entered in a single step. Previously, the chi-squared test and Pearson's correlation coefficient were the statistics tests used to measure the statistical relationship, or association, between two categorical or continuous variables respectively. Effect estimates were reported along with odds ratio (OR) value, 95% confidence intervals (CI) and *p*-value. Crude OR was obtained after considering the effect of only one predictor variable, and the adjusted OR was determined after including all variables that showed significance in the crude odds ratio analysis.

The Kaplan–Meier test was used to compute the survival over time in patients with CHD and the control population depending on whether their GGT levels were above or below 60 U/L. Event-free survival was defined as the time from inclusion to any MACE, and the log-rank test was used to test whether the difference between survival times was statistically different or not. Also, the survival probability, the proportion of patients that survive beyond a specified time, was determined in the medium term in both cohorts and in the long term among CHD patients. On the other hand, Cox regression analysis was the method used to test the effect of independent variables on survival times. Cox regression generated hazard ratios (HR), which were interpreted with 95% CI. Risk prediction model was obtained using the receiver-operating characteristic (ROC) curve. To check the goodness of fit in the logistic regression model, the area under the ROC curve was calculated. A *p*-value ≤.05 was statistically significant. Statistical analysis was performed using the R program (R Development Core Team 2021), version 4.1.0.

3 | RESULTS

3.1 | Study population

A total of 589 out of 712 (83%) CHD patients followed up in our outpatient CHD unit signed the informed consent and had blood samples drawn. Control population consisted of 2745 patients. According to the CHD complexity, patients were classified in simple (309 [52%] patients), moderate (174 [30%] patients) and great (106 [18%] patients) defects as shown in Table 1.

3.2 | Clinical and blood test data in patients with CHD and the control population

From a clinical point of view, patients with CHD took significantly more antiplatelet therapy, oral anticoagulants, beta-blockers, ACE inhibitors, ARBs, calcium channel blockers, loop diuretics and spironolactone than patients in the control group. On the contrary, no significance was found in oral iron or statins treatment. In relation to the blood test, as can be seen in Table 2, no significant differences were seen in serum glucose and liver enzymes concentrations (ALT, alanine aminotransferase and AST, aspartate aminotransferase) between patients with CHD and the control group. By contrast, CHD patients had significantly lower GFR and higher creatinine, haemoglobin, alkaline phosphatase (AP), lactate dehydrogenase (LDH) and GGT concentrations than patients in the control population (GGT, 20 [11–105] vs 18 [10–60] U/L respectively [$p < .001$]). Likewise, 142 (5%) patients in the control group and 63 (11%) patients with CHD had a GGT concentration >60 U/L ($p < .001$).

3.3 | Clinical and blood test data in the control population according to their GGT levels

Control patients with GGT concentrations above 60 U/L were more frequently males, older, more hypertensive, diabetic and dyslipidemic than controls with GGT levels below 60 U/L ($p < .001$). Similarly, controls with higher GGT concentrations (>60 U/L) showed higher ALT (49

TABLE 1 Congenital cardiac classification according to complexity

Types of CHD according to complexity	Number of patients
Simple complexity	309
Aortic valve disease	45
Pulmonary valve disease	54
Atrial septal defect	63
Ventricular septal defect	99
Ductus	12
Other simple defects	36
Moderate complexity	174
Subvalvular or supravalvular aortic stenosis	22
Coarctation of the aorta	52
Subvalvular or supravalvular pulmonary stenosis	9
Tetralogy of Fallot	49
Ebstein	6
Atrioventricular septal defects	34
Sinus venosus septal defect	2
Great complexity	106
Dextro transposition of the great arteries	27
Levo transposition of the great arteries	9
Pulmonary atresia	5
Single ventricle	10
Double outlet right ventricle	13
Tricuspid atresia	4
Trucus arteriosus	2
CHD with pulmonary arterial hypertension	36
Total of CHD	589

Abbreviation: CHD, congenital heart disease.

[18–156] vs 17 [9–49], $p < .001$), AST (32 [19–115] vs 21 [14–38], $p < .001$), AP (81 [50–197] vs 72 [46–137], $p = .001$) and LDH (188 [144–321] vs 176 [136–236], $p < .001$) concentrations than controls with GGT levels below 60 U/L.

3.4 | Clinical and blood test data in CHD patients according to their GGT levels

Patients with CHD and a GGT concentration >60 U/L were significantly older, more hypertensive and dyslipidemic, had a worse NYHA functional class and showed a greater CHD complexity than CHD patients with a GGT ≤60 U/L. On the contrary, no significant differences were seen, neither in systemic ventricular dysfunction nor in patients carrying a mechanical valve between both groups. On the other hand, CHD patients with higher GGT concentrations showed, significantly, higher serum creatinine, red cell distribution width (RDW), bilirubin, ALT, AST, AP, LDH and NT-pro-BNP levels than patients with lower levels (GGT ≤60 U/L; Table 3). Meanwhile, Pearson's correlation test showed a significant positive correlation between GGT levels and serum creatinine, RDW, ALT, AST, AP, LDH and NT-pro-BNP concentrations ($p < .001$). Likewise, patients with a great CHD complexity had, significantly, a worse NYHA functional class and used more frequently oral anticoagulation, beta-blockers, ACE inhibitors/ARBs, loop diuretics and iron treatment.

3.5 | Predictors of high GGT levels among patients with CHD

After modelling the relationship between variables in patients with CHD, the binary logistic regression analyses showed that age, the great anatomical complexity and having atrial fibrillation/flutter were the predictive factors of high GGT levels (>60 U/L) (Table 4). Meanwhile, the area under the ROC curve was 0.774 ([CI (95%) 0.681–0.814], $p < .001$].

3.6 | MACE outcome

Patients with CHD and controls were followed up during a median time of 6.1 (0.7–10.4) and 3.9 (2.9–4.2) years, respectively. The number of patients in the different groups (CHD and control patients with GGT levels above and below 60 U/L), the number of MACE and the probability of survival in the medium-term (cases and controls) and long-term (only cases) follow-up are shown in Table 5. As derived from it, in the medium-term follow-up, 29 (1%) controls (12 noncardiovascular deaths, six strokes, five myocardial infarctions, five arrhythmias requiring hospitalization and one pulmonary embolism) and 50 (8.5%) patients with CHD had a MACE. However, if we look at the long-term follow-up, we may observe that the number of MACE among patients with CHD increased to 69 (12%; 21 cardiovascular deaths, 18 strokes, seven noncardiovascular deaths, nine heart failure, four arrhythmias and four major bleeding requiring hospitalization, two myocardial infarctions, two peripheral vascular events and two pulmonary embolisms).

As can be seen in Figure 1 (first 4 years of follow-up), patients with CHD and a GGT concentration above 60 U/L showed a worse survival than controls, irrespective of their GGT concentrations, and CHD patients with GGT ≤60 U/L ($p < .001$). Furthermore, survival tends to decline in the long-term follow-up among CHD patients

TABLE 2 Demographic, clinical and analytical data in CHD patients and the control population

	Control	CHD	p^a
CHD patients, n	2745	589	
Age, years	29 ± 12	29 ± 14	.122
Sex (male), n	1554 (57)	341 (58)	.568
Arterial hypertension, n	296 (11)	78 (13)	.086
Diabetes mellitus, n	123 (4)	28 (5)	.773
Dyslipidemia, n	564 (20)	019 (18)	.263
Smoking, n	344 (12)	29 (5)	<.001
Laboratory results			
Glucose, mg/dl	93 (80–118)	93 (79–115)	.431
Creatinine, mg/dl	0.8 ± 0.2	0.9 ± 0.2	<.001
GFR, ml/min/1.73 m^2	116 (84–167)	92 (60–159)	<.001
Haemoglobin, mg/dl	14 ± 2	15 ± 2	<.001
Total bilirubin, mg/dl	0.6 (0.3–1.5)	0.7 (0.3–2.1)	<.001
AP, UL	73 (46–140)	75 (46–214)	<.001
LDH, UL	178 (137–241)	187 (134–325)	<.001
GGT, UL	18 (10–60)	20 (11–105)	<.001
ALT, IU/L	18 (9–58)	18 (9–51)	.317
AST, IU/L	21 (14–43)	22 (14–43)	.101
Medical treatment			
Antiplatelet, n	30 (1)	63 (11)	<.001
Oral anticoagulation, n	9 (0.3)	75 (13)	<.001
Beta-blockers, n	55 (2)	86 (15)	<.001
ACE inhibitors/ARBs, n	219 (8)	89 (15)	<.001
Calcium channel blockers, n	44 (2)	19 (3)	.009
Loop diuretics, n	79 (3)	83 (14)	<.001
Spironolactone, n	5 (0.2)	50 (8)	<.001
Oral iron, n	129 (5)	28 (5)	.955
Statins, n	166 (6)	48 (8)	.202

Note: The data are expressed as mean ± standard deviation; median and (5–95) percentiles and as number and percentage.

Abbreviations: ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; AP, alkaline phosphatase; ARBs, angiotensin receptor blockers; AST, aspartate aminotransferase; CHD, congenital heart disease; GFR, glomerular filtration rate; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; n, number of patients.

[a]Categorical variables are evaluated by Pearson's chi-squared test; continuous data with normal distribution are compared by Student´s t-test and continuous data without normal distribution by the Mann-Whitney test.

with higher GGT concentrations (>60 U/L; Figure 2). Similarly, controls with higher GGT levels (>60 U/L) showed a worse survival than controls with lower GGT concentrations (GGT ≤60 U/L; $p < .001$; Figure 1).

On the other hand, the multivariable Cox regression analysis carried out among patients with CHD, including clinical and blood test variables, found an independent association between age (HR 1.03 [1.01–1.04], $p = .002$), great CHD complexity (HR 3.38 [1.95–5.87], $p < .001$), NT-pro-BNP concentration (>125 pg/ml; HR 3.80 [1.73–8.32], $p = .001$) and high GGT levels (>60 U/L; HR 2.44 [1.34–4.44], $p = .003$) and a worse outcome in the long-term follow-up (Table 6).

4 | DISCUSSION

Gamma-glutamyl transferase is a liver enzyme, which is located on the plasma membranes of most cells and organ tissues, but more commonly in hepatocytes, being routinely used in clinical practice to help indicate liver injury and as a marker of excessive alcohol consumption.[14]

TABLE 3 Demographic, clinical and blood test data in CHD patients according to the GGT levels

	CHD patients		
	GGT ≤60 U/L	GGT >60 U/L	p^a
CHD patients, n	526	63	
Age, years	27 ± 14	38 ± 17	<.001
Sex (male), n	228 (43)	43 (68)	.078
BMI, kg/m^2	23 (17–34)	24 (14–38)	.279
Great CHD complexity, n	88 (17)	18 (29)	.021
NYHA functional class (≥2), n	20 (4)	7 (11)	.009
Arterial hypertension, n	64 (12)	14 (22)	.026
Diabetes mellitus, n	22 (4)	6 (9)	.060
Dyslipidemia, n	89 (17)	20 (31)	.004
Smoker, n	26 (5)	3 (5)	.498
Laboratory results			
Glucose, mg/dl	93 (80–112)	94 (73–124)	.932
Creatinine, mg/dl	0.9 ± 0.2	0.9 ± 0.3	.001
GFR, ml/min/1.73 m^2	93 (63–160)	87 (48–148)	.007
Haemoglobin, mg/dl	14.6 ± 1.7	14.7 ± 2.7	.923
RDW, %	13.3 (12.2–16.8)	14.6 (12.6–19.0)	<.001
Total bilirubin, mg/dl	0.7 (0.3–2.0)	0.9 (0.3–2.9)	<.001
AP, U/L	74 (45–180)	95 (47–234)	<.001
LDH, U/L	183 (133–304)	211 (134–483)	<.001
GGT, U/L	18.9 (10.6–47.7)	96.9 (63.2–297)	<.001
ALT, IU/L	17 (9–44)	30 (12–152)	<.001
AST, IU/L	21 (14–38)	29 (21–106)	<.001
NT-pro-BNP, pg/ml	63 (0–949)	416 (12–4417)	<.001
Iron, μg/dl	81 (26–144)	76 (19–179)	.392
Ferritin, ng/ml	37 (7–184)	51 (4–414)	.265
Treatment			
Antiplatelet, n	54 (10)	9 (14)	.329
Oral anticoagulation, n	56 (11)	28 (44)	<.001
Beta-blockers, n	61 (11)	25 (40)	<.001
ACE inhibitors/ARBs, n	71 (13)	18 (29)	.002
Calcium channel blockers, n	17 (3)	2 (3)	.981
Loop diuretics, n	59 (11)	24 (38)	<.001
Statins, n	35 (7)	13 (20)	<.001
Oral iron, n	21 (4)	7 (11)	.012
Mechanical valve prosthesis, n	20 (4)	3 (5)	.710
Systemic ventricular dysfunction, n	88 (17)	12 (19)	.690
Atrial fibrillation/flutter, n	12 (21)	11 (17)	<.001
Clinical outcome (MACE), n	45 (9)	24 (38)	<.001

Note: The data are expressed as mean ± standard deviation, median and (5–95) percentiles and as number and percentage.

Abbreviations: ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; AP, alkaline phosphatase; ARBs, angiotensin receptor blockers; AST, aspartate aminotransferase; BMI, body mass index; CHD, congenital heart disease; GFR, glomerular filtration rate; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; MACE, major adverse cardiovascular events; n, number of patients; NT-pro-BNP, NT-pro-brain natriuretic peptide; NYHA, New York Heart Association; RDW, red cell distribution width.

[a]Categorical variables are evaluated by Pearson's chi-squared test; continuous data with normal distribution are compared by Student´s t-test and continuous data without normal distribution by the Mann-Whitney test.

TABLE 4 Binary logistic regression analyses in CHD patients to predict a GGT above 60 UL

	OR (crude) (95% CI)	*p*	OR (adjusted) (95%CI)	*p*
Age, years	1.04 (1.03–1.06)	<.001	1.03 (1.01–1.05)	.001
CHD complexity, great	1.99 (1.10–3.60)	.023	2.03 (1.08–3.82)	.027
AHT, yes	1.99 (1.16–3.42)	.012	1.05 (0.48–2.29)	.901
Atrial/flutter fibrillation	9.06 (3.81–21.55)	<.001	4.05 (1.51–10.84)	.005
Bilirrubin, mg/dl	0.99 (0.94–1.05)	.864		

Abbreviations: AHT, arterial hypertension; CHD, congenital heart disease; CI, confidence interval; OR, odds ratio.

TABLE 5 Probability of survival in the medium- and long-term follow-up

Medium-term prospective follow-up

			Probability of survival						
Groups	**n**	**MACE**	**1 year**	**2 years**	**3 years**	**4 years**	**HR**	**CI (95%)**	***P***
CHD & GGT >60 UL	63	19	0.841	0.807	0.692	0.669	1 (ref)	–	–
CHD & GGT ≤60 UL	526	31	0.971	0.965	0.955	0.936	0.16	0.09–0.29	<.001
Control & GGT >60 UL	142	7	0.979	0.965	0.958	0.949	0.13	0.05–0.31	<0.001
Control & GGT ≤60 UL	2603	22	0.997	0.996	0.993	0.991	0.02	0.01–0.04	<0.001

Long-term prospective follow-up

			Probability of survival						
Groups	**n**	**MACE**	**2 years**	**4 years**	**6 years**	**8 years**	**HR**	**CI (95%)**	***p***
CHD & GGT >60 UL	63	24	0.807	0.669	0.618	0.523	1 (ref)	–	–
CHD & GGT ≤60 UL	526	45	0.965	0.963	0.916	0.902	0.18	0.11–0.29	<.001

Abbreviations: CHD, congenital heart disease; CI, confidence interval; GGT, gamma-glutamyl transferase; HR, hazard ratio; MACE, major acute cardiovascular events; n, number of patients.

However, the multifunctional role of the liver in metabolism and inflammation suggests that complex relationships are likely to exist between the liver markers and several biochemical, metabolic, lipid or inflammatory factors, which would in part explain why increased GGT activity is a marker of antioxidant inadequacy that leads to oxidative stress and therefore to cardiovascular risk factors, metabolic syndrome, insulin resistance and systemic inflammation.[15]

Previous meta-analysis of cohort studies have found an association of increased risk of cardiovascular disease, stroke, heart failure and coronary artery heart disease in later life among patients with CHD.[16] However, it is not known whether this association is related to a worse cardiovascular risk profile or whether CHD is an independent risk factor by itself influenced by oxidative stress. In this context, old age[17] and a variety of cardiovascular diseases, such as heart failure,[18] atrial fibrillation,[19] arterial hypertension[20] and atherosclerosis,[21] have been shown to be associated, at least partially, with an excess production of reactive oxygen species.[22] In fact, in our series, being older, having a complex CHD and being affected by atrial fibrillation/flutter were predictors of higher GGT levels among our CHD patients, which may translate into increased person's risk of oxidative stress.[23]

Also, GGT has been regarded as a promising biomarker for cardiovascular outcome, since its serum levels may reflect not only the oxidative stress response, but also its production and accumulation. Moreover, some authors have reported that serum GGT activity within the reference interval is positively associated with an increased risk of cardiovascular mortality in a dose-response manner in otherwise healthy individuals.[24] In fact, at normal values, serum GGT catalyzes LDL oxidation, which is believed to participate in other processes such as cell proliferation and development of atheroma within the vascular endothelial wall, which provides support for the strong predictive power of GGT for cardiovascular disease.[6] In this regard, some authors have found that patients between 40–59 years old and high GGT levels had

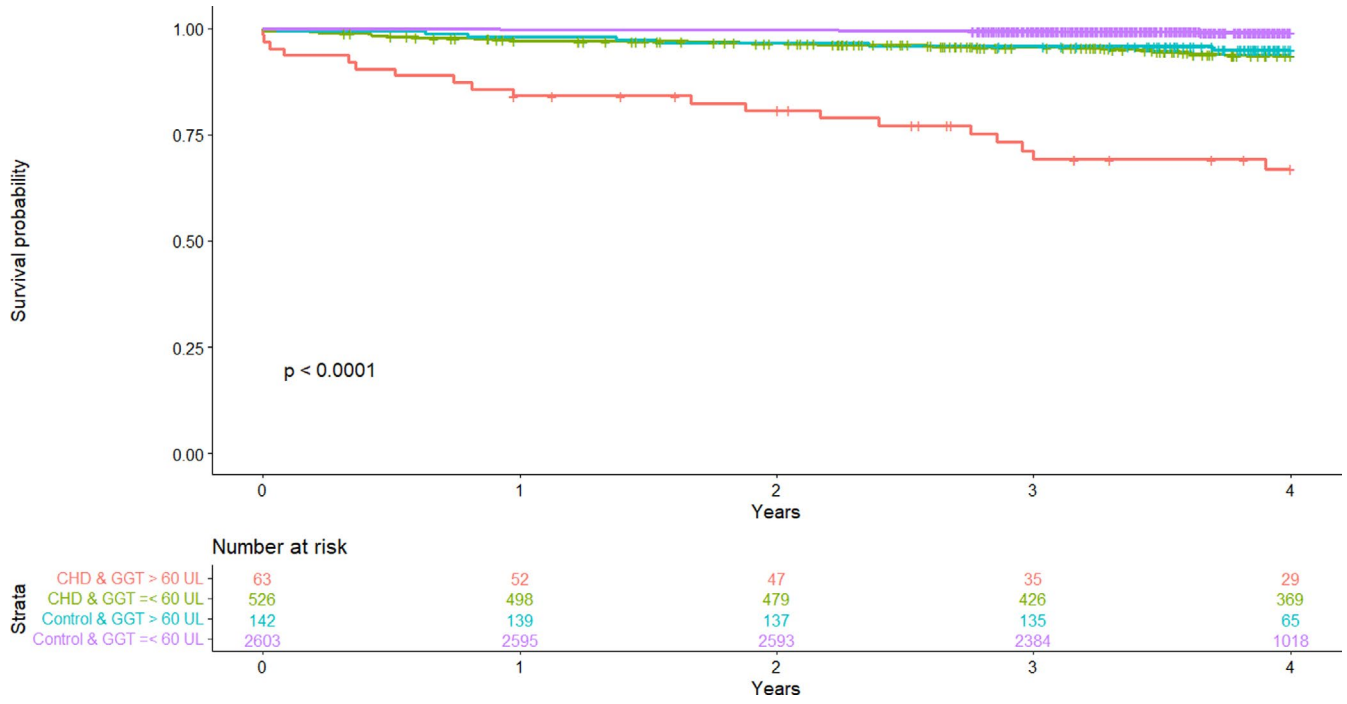

FIGURE 1 Kaplan–Meier curve showing major adverse cardiovascular events in congenital heart disease (CHD) patients and the control population according to their gamma-glutamyl transferase (GGT) levels (above or below 60 U/L) in the medium-term follow-up ($p < .0001$)

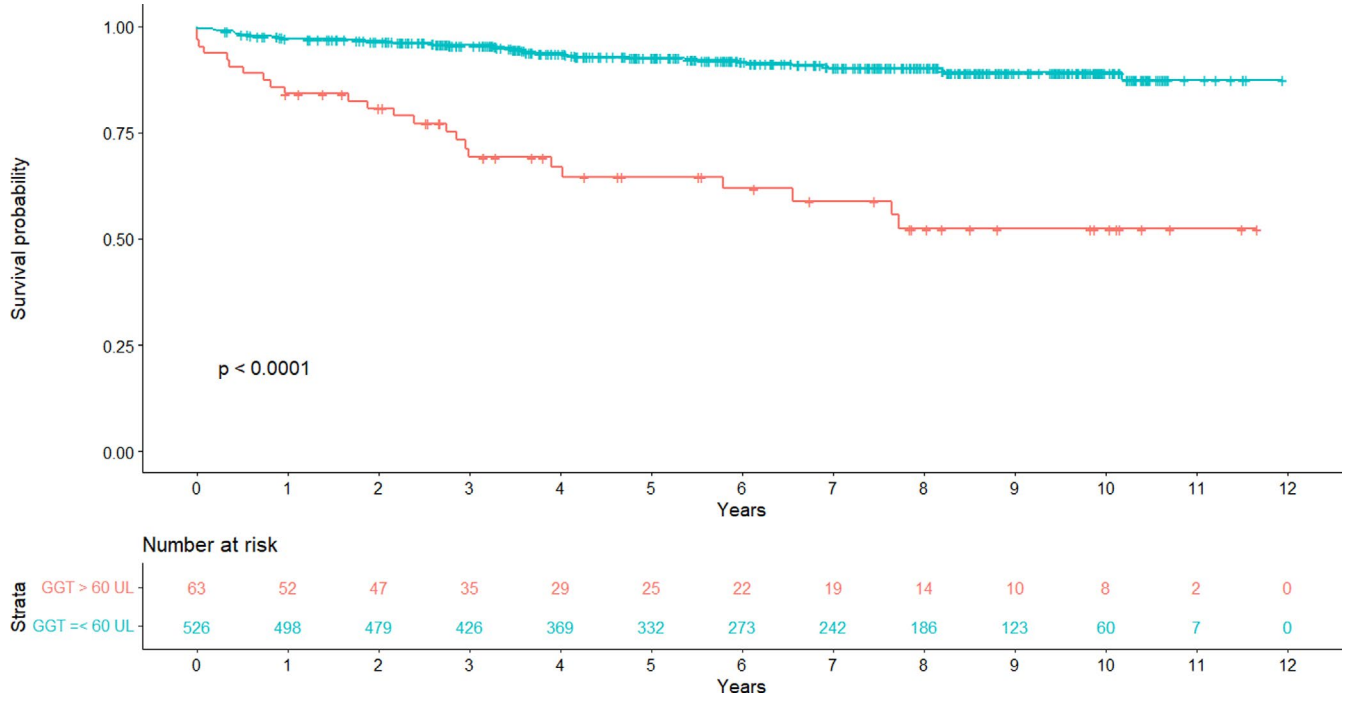

FIGURE 2 Kaplan–Meier curve showing major adverse cardiovascular events in congenital heart disease (CHD) patients according to their gamma-glutamyl transferase (GGT) levels (above or below 60 U/L) in the long-term follow-up ($p < .0001$)

an increased risk of acute coronary events, stroke and overall cardiovascular mortality after adjustment for traditional cardiovascular risk factors.[25] Similarly, other authors reached the conclusion that GGT could represent an early marker of subclinical inflammation and oxidative stress in healthy patients.[26] Likewise, other studies strongly support an association of GGT with the risk for heart failure even suggesting a direct participation of GGT

TABLE 6 Univariate and multivariate Cox regression analysis of variables associated with major adverse cardiovascular events in CHD patients

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95%CI)	*p*
Age, years	1.05 (1.03–1.06)	<.001	1.03 (1.01–1.04)	.002
CHD complexity, great	4.87 (2.92–8.18)	<.001	3.38 (1.95–5.87)	<.001
Cardiovascular risk factors[a]	1.66 (0.98–2.81)	.060		
Atrial fibrillation/flutter	4.01 (1.82–8.86)	.001	1.06 (0.43–2.64)	.895
NT-pro-BNP, >125 pg/ml	7.41 (3.51–15.62)	<.001	3.80 (1.73–8.32)	.001
RDW, >15%	3.71 (2.18–6.26)	<.001	1.40 (0.79–2.49)	.249
GGT, >60 UL	5.17 (2.99–8.94)	<.001	2.44 (1.34–4.44)	.003

Abbreviations: CHD, congenital heart disease; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; NT-pro-BNP, NT-pro-brain natriuretic peptide; RDW, red distribution width.

[a]Cardiovascular risk factors include patients with arterial hypertension and diabetes mellitus.

in the pathophysiology of it.[27,28] Similarly, in our series, patients with higher GGT levels, irrespective if they belong to the CHD or control group, showed a worse outcome than those with lower GGT concentrations.

There are, however, limitations in our study that may impact our findings. Firstly, the low number of patients with a GGT >60 U/L and the low number of MACE observed during the follow-up time, typical of young populations. Nonetheless, we think that the sample size is large enough to draw a link between GGT and MACE in our CHD patients. Secondly, the lack of determination of alcoholic habit or the absence of abdominal ultrasound among our patients with CHD. Despite of this, in our series no significance was seen in AST and ALT concentrations between cases and controls. As both liver enzymes have been usually used to determine liver injury in clinical practice, we could exclude, at least initially, liver disease as the mainly cause of higher GGT levels among CHD patients. Thirdly, we did not determine oxidative stress. However, its measurement in biological systems is a complex task given the short half-life and high reactivity.[29] On the other hand, "footprints" of oxidative stress, such as GGT, are extremely stable and may provide a more reliable approach to evaluate oxidative stress in clinical samples. Finally, patients with CHD represent a heterogeneous population, so it may be difficult to draw final conclusions in the overall prognosis.

In conclusion, patients with higher GGT levels (>60 U/L), in both the CHD and the control groups, showed a worse survival than those with lower concentrations (GGT ≤60 U/L). However, CHD patients with GGT levels above 60 U/L showed a much worse outcome than the rest of groups existing an independent association between high GGT levels (>60 U/L) and a worse prognosis in the long-term follow-up among patients with CHD.

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CONFLICT OF INTEREST

None.

ORCID

Efrén Martínez-Quintana https://orcid.org/0000-0002-1289-7279

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