



# OXY-SCORE: a new perspective for left ventricular hypertrophy diagnosis

Begoña Quintana-Villamandos , Laia Pazó-Sayós, Irene González del Pozo, Pilar Rodríguez-Rodríguez, Jose María Bellón, Álvaro Pedraz-Prieto, Ángel G Pinto and Maria Carmen González

*Ther Adv Chronic Dis*

2020, Vol. 11: 1–10

DOI: 10.1177/  
2040622320936417

© The Author(s), 2020.  
Article reuse guidelines:  
sagepub.com/journals-  
permissions

## Abstract

**Background:** A recently developed global indicator of oxidative stress (OXY-SCORE), by combining individual plasma biomarkers of oxidative damage and antioxidant capacity, has been validated in several pathologies, but not in left ventricular hypertrophy (LVH). The aim of this study was to design and calculate a plasma oxidative stress global index for patients with LVH.

**Methods:** A total of 70 consecutive adult patients were recruited in our institution and assigned to one of the two study groups (control group/LVH group) by an echocardiography study. We evaluated plasmatic biomarkers of oxidative damage (malondialdehyde and thiolated proteins) and antioxidant defense (total thiols, reduced glutathione, total antioxidant capacity, catalase, and superoxide dismutase activities) by spectrophotometry/fluorimetry in order to calculate a plasma oxidative stress global index (OXY-SCORE) in relation to LVH.

**Results:** The OXY-SCORE exhibited a highly significant difference between the groups ( $p < 0.001$ ). The area under the receiver operating characteristic curve was 0.74 (95% confidence interval (CI), 0.62–0.85;  $p < 0.001$ ). At a cut-off value of  $-1$ , the 68.6% sensitivity and 68.6% specificity values suggest that OXY-SCORE could be used to screen for LVH. A multivariable logistic regression model showed a positive association ( $p = 0.001$ ) between OXY-SCORE and LVH [odds ratio = 0.55 (95% CI, 0.39–0.79)], independent of gender, age, smoking, glucose, systolic and diastolic arterial pressure, dyslipidemia, estimated glomerular filtration rate, body mass index, and valvular/coronary disease.

**Conclusion:** OXY-SCORE could help in the diagnosis of LVH and could be used to monitor treatment response.

**Keywords:** left ventricular hypertrophy, oxidative stress, OXY-SCORE

Received: 5 January 2020; revised manuscript accepted: 22 May 2020.

## Introduction

Left ventricular hypertrophy (LVH) is a common manifestation of cardiovascular disease which has been related to stroke, serious arrhythmias, and sudden cardiac death.<sup>1</sup> Its regression reduces cardiovascular morbidity and mortality;<sup>2</sup> therefore, in clinical settings it is necessary to have an early diagnostic of LVH and to study novel strategies with antiremodeling therapeutic potential.<sup>3,4</sup>

Oxidative stress, which refers to an imbalance between antioxidant defenses and the production of reactive oxygen species, plays a key role in

patients with LVH.<sup>5–7</sup> The complex and multifactorial nature of oxidative stress makes it difficult to assign a prevalent role to a particular marker in cardiovascular disease. Individual biomarkers only partially describe the oxidative status and are associated with a large intra- and inter-subject variability.<sup>8</sup> Thus, no single parameter can yet be recommended as a gold standard for determining individual redox status.

Several authors have previously used calculations based on a global index or score of oxidative stress status, known as OXY-SCORE, in preclinical

Correspondence to:

**Begoña Quintana-Villamandos**  
Department of  
Anesthesiology Hospital  
Gregorio Marañón.  
C/ Doctor Esquerdo  
Nº 46, Madrid, 28007,  
Spain Department of  
Pharmacology and  
Toxicology, Faculty of  
Medicine, Universidad  
Complutense, Madrid,  
Spain  
[begoquinti@gmail.com](mailto:begoquinti@gmail.com)

**Laia Pazó-Sayó**  
**Irene González del Pozo**  
Department of  
Anesthesiology and  
Intensive Care, Gregorio  
Marañón Hospital, Madrid,  
Spain

**Pilar Rodríguez-Rodríguez**  
**Maria Carmen González**  
Department of Physiology,  
Faculty of Medicine,  
Universidad Autónoma,  
Madrid, Spain

**Jose María Bellón**  
Department Statistics,  
Health Research Institute  
of Gregorio Marañón  
Hospital, Madrid, Spain

**Álvaro Pedraz-Prieto**  
**Ángel G Pinto**  
Department of  
Cardiovascular Surgery,  
Gregorio Marañón  
Hospital, Madrid, Spain



and clinical studies. Results are obtained by combining individual plasma biomarkers of oxidative damage and antioxidant capacity to assess the overall oxidative balance in cardiovascular diseases.<sup>9–13</sup> However, the OXY-SCORE has not yet been described in LVH. Biomarkers of oxidative stress play a relevant role in diagnosis, evaluation of disease status, and assessment of the health-enhancing effects of therapies. A global index or score of oxidative stress can be used to help detect anomalies (early stages of chronic venous insufficiency or its progression, early stages of chronic kidney disease, presence and severity of coronary artery disease, and the development of pregnancy complications).<sup>9,12,14,15</sup> Our group recently proposed an OXY-SCORE in a preclinical study with an animal model of primary hypertension and coronary artery disease.<sup>13</sup> In this study, we showed the potential of dronedarone (a multichannel blocker used in routine clinical practice for the treatment of atrial fibrillation) for reducing oxidative stress-related coronary artery remodeling. Dronedarone produced improvement of coronary artery remodeling, an effect that was shown to be associated with improved global oxidative status in plasma as identified by an OXY-SCORE. Therefore, this score could serve as a monitoring tool for the effectiveness of dronedarone in the regression of the coronary artery remodeling.

Recently, we have described a new biomarker for LVH in humans.<sup>16</sup> The plasma protein thiolation index (PTI) is a biomarker of oxidative stress that is defined as the molar ratio of S-thiolated proteins (oxidative damage) to free protein thiols (antioxidant capacity) in plasma.<sup>17</sup> However, the OXY-SCORE exhibits limited variability, and the precision and completeness are expected to increase with the number of parameters included.<sup>18</sup> Thus, this study proposes an OXY-SCORE that takes into account a variety of individual plasmatic biomarkers of oxidative damage and antioxidant defense (biomarkers with a good correlation between levels in the plasma and heart tissue) as an index of oxidative stress status in patients with LVH.

## Methods

### Study design

This is an extension of a previous study carried out in our institution.<sup>16</sup> Seventy consecutive patients were recruited (between December 2015

and March 2016) as they were referred to the cardiac surgery section of our institution and each was assigned to one of the two study groups – control group (group without LVH) and LVH group (group with LVH) – based on an echocardiography study. All patients presented specific pathology (coronary and/or valvular disease), the patients were admitted to the cardiac surgery section for non-urgent cardiac surgery, and no patient had heart failure. When a patient is referred to cardiac surgery section, an echocardiography study is usually performed. The inclusion criteria were age  $\geq 18$  years and written informed consent. The echocardiography was performed using the iE33 system (Philips, CA, USA) equipped with a S5-1 probe (1–5 MHz). To demonstrate a significant increase in the mass of the left ventricle in the LVH group with respect to the control group we calculated left ventricular mass by echocardiography, applying the recommendations of the American Society of Echocardiography (LVH was defined by left ventricular mass indexed to body surface area, LVMI:  $>95 \text{ g/m}^2$  for women, and  $>115 \text{ g/m}^2$  for men).<sup>19</sup>

The patients were considered to have systemic hypertension, dyslipidemia, or diabetes if they had a diagnosis of elevated blood pressure, dyslipidemia, or diabetes requiring long-term treatment, respectively. Using clinical, demographic, and echocardiographic data, and blood samples from all patients (control group  $n=35$  and LVH group  $n=35$ ), we designed an observational study to propose an OXY-SCORE that includes a variety of plasmatic individual biomarkers of oxidative damage and antioxidant defense as an index of oxidative stress status in patients with LVH.

This study was approved by the clinical research ethics committee of the Hospital General Universitario Gregorio Marañón (the number of the protocol is 422/15). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Data measurements (biochemical test)

Blood samples were drawn from the patients to study plasmatic biomarkers of antioxidant defense (thiols, total antioxidant capacity, reduced glutathione, superoxide anion scavenging activity,

and catalase) and biomarkers of oxidative damage (malondialdehyde and thiolated proteins):

Total thiols ( $\mu\text{mol}/\text{mg}$  protein) were assessed using the 5,5-dithiobis (2-nitrobenzoic acid) assay. Absorbance was measured at 412 nm in a Synergy HT multi-mode microplate reader (Synergy HT; Biotek).<sup>20</sup>

Total antioxidant capacity (TAC) (trolox  $\mu\text{M}$ ) was assessed using the CUPRAC-BCS assay. Absorbance at 490 nm was read in a Nanodrop 2000 spectrophotometer (Thermo Scientific, NC, USA). Total antioxidant capacity values were obtained from the standard curve of the antioxidant trolox ( $0\text{--}2\text{ mol L}^{-1}$ ).<sup>21</sup>

Quantification of superoxide anion scavenging activity (SOSA) (mU superoxide dismutase/mg protein) was determined using a luminescence assay with coelenterazine as the detection probe, adapted to a microplate reader. SOSA values were quantified by comparing the inhibition of luminescence for each sample with that observed from the superoxide dismutase (SOD) activity standard curve ( $0\text{--}4\text{ U mL}^{-1}$ ).<sup>22</sup>

Reduced glutathione (GSH) ( $\mu\text{mol}/\text{mg}$  protein) was assessed using a fluorometric micromethod based on the reaction with o-phthalaldehyde. Fluorescence was measured in a Synergy HT multimode microplate reader (Synergy HT; Biotek) at  $360 \pm 40\text{ nm}$  excitation and  $460 \pm 40\text{ nm}$  emission wavelengths.<sup>23,24</sup>

Catalase activity (U catalase/mg protein) was assessed using the Amplex red catalase assay (Catalase Assay Kit Amplex Ultra Red reagent; invitrogen).

Malondialdehyde (MDA) ( $\mu\text{M}$ ) levels as a lipid peroxidation product were assessed using a thio-barbituric acid assay.<sup>25</sup>

S-thiolated proteins ( $\mu\text{mol}/\text{mg}$  protein) were determined by spectrophotometry using a method with a ninhydrin reagent, as previously described.<sup>17</sup>

Protein content was assessed using the Coomassie blue-based microtiter plate assay according to the manufacturer's recommendations (Bio-Rad, Madrid, Spain). Absorbance was measured at 595 nm in a Synergy HT multi-mode microplate

reader (Bio-Tek), and bovine serum albumin was used as the standard.

## Data analysis

### Calculation of OXY-SCORE

The parameters listed previously were used to calculate a global index of oxidative stress related to LVH. We used the statistical methodology previously described to calculate this index.<sup>18</sup> First, we analyzed the normality of the chosen biomarkers using the Kolmogorov–Smirnov test and normalization of the parameters that did not show a normal distribution through a logarithmic transformation; second, we conducted parameter standardization; and finally, we calculated the partial indexes for protein oxidative damage (OXY), antioxidant defense systems (ANTIOX), and OXY-SCORE according to the equation:  $[\text{OXYSCORE} = \text{Mean}(\text{ANTIOX}_{ik} - \text{OXY}_{im})_n]$ , where  $n$  is the experimental group,  $i$  is the individual,  $k$  represents the parameters related to ANTIOX, and  $m$  represents the parameters related to OXY biomarkers.

### Statistical analysis

With a sample size of 35 individuals in each group, a power of 85% was reached to detect an area under the receiver operating characteristic (ROC) curve (AUC) of 0.7 or greater as statistically significant.

Categorical variables were expressed as frequencies and percentages, and the groups were compared using the Pearson chi-square test. Quantitative variables were described as mean  $\pm$  SEM (for continuous, normally distributed variables), and between-group comparison was carried out using an independent  $t$  test. The ability of OXY-SCORE to discriminate between the two clinical groups was assessed by ROC curve analysis. Different cut-off points were chosen for the diagnosis of LVH, and their sensitivity, specificity, predictive values, and likelihood ratios were calculated with their respective confidence intervals. A multivariate logistic regression model was performed to determine the strength of the association between OXY-SCORE and LVH. The independent variables were gender, age, smoking, glucose, systolic arterial pressure, diastolic arterial pressure, dyslipidemia, estimated glomerular

filtration rate, body mass index, and valvular and coronary disease.  $p$  values  $< 0.05$  were considered statistically significant. The analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp, Armonk, NY, USA), and Prism Graph Pad 6.0 (Graph Pad Software, California, USA).

## Results

A total of 70 patients were included in the study. Demographic and clinical characteristics including age, gender, body mass index, cardiovascular risk factors, renal failure, cardiac diseases, systolic dysfunction and pharmacological therapy are shown in Table 1. No patient had heart failure. There were no significant differences between the two study groups (control/LVH) in terms of these variables.

The performances of the OXY-SCORE, a summary index of oxidative stress, and of its individual components (total thiols, TAC, GSH, SOD, catalase, MDA and S-thiolated proteins) were assessed. There were no significant differences between the individual biomarkers of the two study groups (control and LVH), except in the thiolated proteins (Table 2). The ROC analysis of each biomarker shows the lack of capacity of individual biomarkers to discriminate between the two clinical groups:  $AUC_{GSH}$  0.378;  $AUC_{SOD}$  0.430;  $AUC_{thiols}$  0.374;  $AUC_{TAC}$  0.382;  $AUC_{catalase}$  0.508;  $AUC_{MDA}$  0.624, and  $AUC_{S-thiolated\ proteins}$  0.641. The OXY-SCORE was calculated from the normalized and standardized plasma parameters and exhibited a highly significant difference between the groups ( $p < 0.001$ ) (Figure 1). The control group exhibited an OXY-SCORE value of nearly 0, which indicates a balance between antioxidant defense systems and oxidative damage in the individual. However, the LVH group exhibited a negative value, indicating an enhanced oxidative status (predominance of oxidative damage) (Figure 1). To determine whether the OXY-SCORE had diagnostic value for LVH, the ROC curve was plotted to identify a cut-off value that would discriminate between the two clinical groups. The area under the ROC curve was 0.742 [95% confidence interval (CI) 0.626–0.858;  $p < 0.001$ ] (Figure 1), and the optimal cut-off value for OXYSCORE (–1) demonstrated sensitivity of 68.6%, specificity of 68.6%, and positive and negative predictive values of 68.6% and 68.6%, respectively, for the diagnosis of

LVH. The sensitivity and specificity for this cut-off allowed for calculation of the positive likelihood ratio (0.46) and negative likelihood ratio (2.18) (Table 3).

The multivariable logistic regression analysis shows the association between OXY-SCORE and LVH (Table 4). A statistically significant positive association ( $p = 0.001$ ) was observed between OXY-SCORE and LVH [odds ratio = 0.55 (95% CI, 0.39–0.79)], independent of gender, age, smoking, glucose, systolic arterial pressure, diastolic arterial pressure, dyslipidemia, estimated glomerular filtration rate, body mass index, and valvular and coronary disease.

## Discussion

This is, to our knowledge, the first study that shows a global oxidative stress index (OXY-SCORE) for patients with LVH (LVH caused by a variety of pathologies). This score could help in the diagnosis of LVH in the clinical setting. Moreover, we suggest new scores as useful indexes to establish the global oxidative status of patients with hypertension only (since this is the most frequent cause of LVH) for prevention, diagnosis, and treatment of LVH.

An increased understanding of the biology behind diseases and redox biology has led to more specific and sensitive tools for measuring oxidative stress in cardiovascular diseases. Several markers of oxidative stress could represent a viable biomarker opportunity for clinical use, so there is a growing interest in exploring its possible clinical applications.<sup>26</sup> LVH represents an independent risk factor for cardiovascular disease and increases cardiovascular morbidity and mortality.<sup>27,28</sup> Oxidative stress likely plays a role in LVH;<sup>5,6</sup> however, until now, no oxidative stress biomarker has been used routinely in clinical settings for the diagnosis of LVH. There may be several reasons for this: first, a single biomarker may not be representative of LVH; second, a single biomarker might have a large intraindividual and interindividual variability; third, some biomarkers require methodologies too sophisticated or laborious for routine clinical use; and finally, there are high costs involved in using such biomarkers in clinical diagnosis. Therefore, mitigating several parameters (ease of use, speed of measurement, and cost) to provide a representative global

**Table 1.** Participants' baseline characteristics.

	LVH group (n = 35)	Control group (n = 35)
Age (years)	69 ± 1	63 ± 2
Gender, M (%)	23 (65.7)	21 (60)
Weight (kg)	76.16 ± 2.33	75.40 ± 2.50
Body surface area (m <sup>2</sup> )	1.80 ± 0.03	1.83 ± 0.03
Body mass index (kg/m <sup>2</sup> )	30.27 ± 1.04	34.16 ± 6.06
LVMI (g/m <sup>2</sup> )	141.82 ± 8.64	88.78 ± 4.45*
Smokers (%)	4 (11.4)	6 (17.1)
Dyslipidemia (%)	22 (62.8)	17 (48.6)
Glucose (mg/dL)	114.97 ± 6.43	109.80 ± 6.23
Systolic arterial pressure (mmHg)	130.62 ± 2.88	123.65 ± 2.08
Diastolic arterial pressure (mmHg)	65.68 ± 1.78	66.45 ± 1.72
eGFR (ml/min per 1.73 m <sup>2</sup> )	70.20 ± 5.24	77.14 ± 4.86
Coronary disease (%)	1 (2.8)	3 (8.5)
Valvular disease (%)	22 (62.8)	15 (42.8)
Coronary and valvular (%)	12 (34.2)	17 (48.5)
Systolic dysfunction (%)	13 (37.1)	14 (40)
Antihypertensive therapy (%)		
ARBs	7 (20)	3 (8.5)
ACEis	14 (40)	13 (37.1)
β-blockers	12 (34.2)	11 (31.4)
Calcium channel blockers	11 (31.4)	6 (17.1)
Diuretics	15 (42.8)	10 (28.5)
Reproduced with permission from Quintana-Villamandos <i>et al.</i> <sup>16</sup> The data are expressed as the mean ± SEM, frequency (percentage). * <i>p</i> < 0.001. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; M, male		

measurement of oxidative damage, as well as antioxidant defense systems, would be desirable. Taking into account these requirements, a global index of plasma oxidative stress (OXY-SCORE) has been developed and validated for cardiovascular diseases.<sup>9,11–13</sup> In humans, the score could be a tool in the diagnosis of early stages of chronic venous insufficiency<sup>9</sup> and the diagnosis of

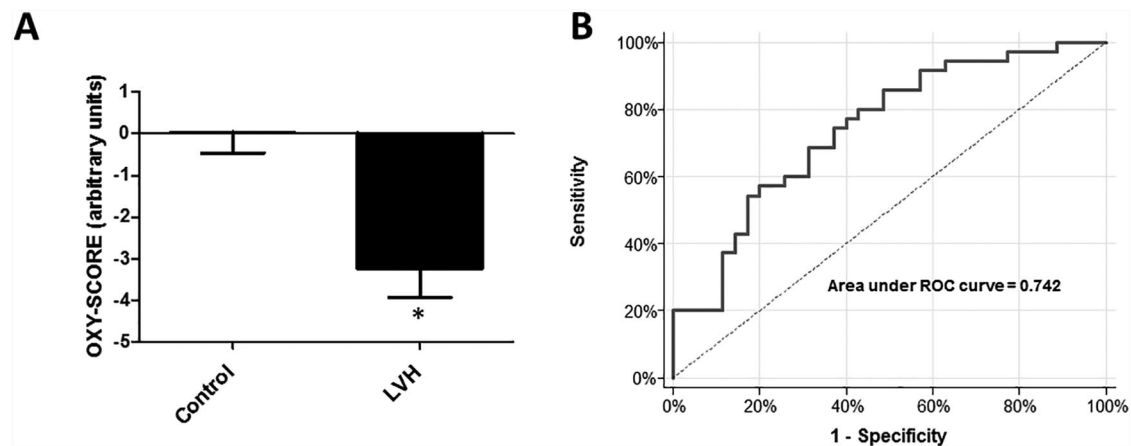
coronary artery disease,<sup>12</sup> and it could accurately depict the time course of oxidative stress induced by coronary revascularization (cardiopulmonary bypass *versus* off-pump procedure).<sup>11</sup> In addition, the global index of plasma oxidative stress was shown to be a therapeutic target in coronary artery remodeling in a model animal with primary hypertension.<sup>13</sup> Therefore, the global index



**Table 2.** Pro- and antioxidant plasmatic biomarkers.

	LVH group (n = 35)	Control group (n = 35)
GSH (μmol/mg protein)	63.14 ± 1.42	67.78 ± 2.19
SOD (mU SOD/mg protein)	18.83 ± 0.46	20.61 ± 0.85
Thiols (μmol/mg protein)	6.97 ± 0.32	7.81 ± 0.34
TAC (Trolox μM)	0.27 ± 0.009	0.30 ± 0.01
Catalase (U catalase/mg protein)	8.32 ± 0.52	8.89 ± 0.81
MDA (μM)	3.54 ± 0.20	2.98 ± 0.19
S-thiolated proteins (μmol/mg protein)	0.10 ± 0.006	0.07 ± 0.005 <sup>#</sup>
OXY-SCORE	-2.4376 ± 0.57	0.0558 ± 0.65 <sup>*</sup>

The data are expressed as the mean ± SEM.  
<sup>#</sup>*p* = 0.01.  
<sup>\*</sup>*p* < 0.001.  
GSH, reduced glutathione; LVH, left ventricular hypertrophy; MDA, malondialdehyde; OXY-SCORE, plasma oxidative stress global index; SOD, superoxide dismutase; TAC, total antioxidant capacity



**Figure 1.** Global oxidative status score (OXY-SCORE) calculated from the plasma biomarkers of oxidative damage and antioxidant capacity (A). The data are expressed as the mean ± SEM, *p* < 0.001. Receiver operator curve (ROC) analysis for OXY-SCORE to diagnose left ventricular hypertrophy (LVH) (B).

of plasma oxidative stress could represent a valuable tool in the prevention, diagnosis and treatment of cardiovascular diseases.

However, the biomarker that should be preferred to assess oxidative stress in human LVH has not been identified. Recently, our group investigated PTI, a biomarker of oxidative stress that combines

oxidative damage (S-thiolated proteins) and antioxidant capacity (thiols) in plasma from patients with LVH.<sup>16</sup> PTI showed an AUC of 0.75, with sensitivity of 70.6% and specificity of 68.8%, thus suggesting that it could be used to screen for LVH.<sup>16</sup> The OXY-SCORE (combining several biomarkers of oxidative damage and antioxidant capacity) shows similar AUC values (0.74) and

**Table 3.** Predictive values of OXY-SCORE for prediction of left ventricular hypertrophy in 70 patients according to the cutoff values.

Cutoff value	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR- (95% CI)
≤-3	40.0	85.7	73.7	58.8	0.36	1.43
>-3	[23.9–57.9]	[69.7–95.2]	[48.8–90.9]	[44.2–72.4]	[0.14–0.89]	[1.06–1.93]
≤-2	54.3	80.0	73.1	63.6	0.37	1.75
>-2	[36.6–71.2]	[63.1–91.6]	[52.2–88.4]	[47.8–77.6]	[0.18–0.76]	[1.18–2.6]
≤-1	68.6	68.6	68.6	68.6	0.46	2.18
>-1	[50.7–83.1]	[50.7–83.1]	[50.7–83.1]	[50.7–83.1]	[0.27–0.79]	[1.27–3.74]
≤0	80.0	51.4	62.2	72.0	0.61	2.57
>0	[63.1–91.6]	[34–68.6]	[46.5–76.2]	[50.6–87.9]	[0.42–0.89]	[1.23–5.37]
≤1	91.4	40.0	60.4	82.4	0.66	4.67
>1	[76.9–98.2]	[23.9–57.9]	[46–73.5]	[56.6–96.2]	[0.49–0.88]	[1.47–14.8]
≤2	94.3	22.9	55.0	80.0	0.82	4.00
>2	[80.8–99.3]	[10.4–40.1]	[41.6–67.9]	[44.4–97.5]	[0.67–1]	[0.91–17.5]
≤3	97.1	14.3	53.1	83.3	0.88	5.00
>3	[85.1–99.9]	[4.81–30.3]	[40.2–65.7]	[35.9–99.6]	[0.76–1.02]	[0.62–40.6]

CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; OXY-SCORE, plasma oxidative stress global index; PPV, positive predictive value

diagnostic validity indexes; however, it exhibits a limited variability, and precision and completeness are expected to increase with the number of parameters included.<sup>18</sup> Two biomarkers of oxidative damage (MDA and thiolated proteins) and five of antioxidant capacity (total thiols, GSH, TAC, catalase, and SOD) have been selected to compute OXY-SCORE. All have been studied by different authors in the field of cardiovascular disease.<sup>9–11,16,29,30</sup> Plasma is simple to obtain from a blood sample and reflects the global oxidative stress status of an individual with cardiovascular disease<sup>9,18</sup> and we have also included biomarkers with a good correlation between plasma concentrations and their levels in tissue.<sup>31</sup> We did not find differences between the individual biomarkers of the two study groups (control and LVH), except in the thiolated proteins. However, the ROC analysis of this biomarker shows the lack of capacity of biomarker to discriminate between the

two clinical groups. Therefore, oxidative stress evaluation in patients with LVH can be improved by simultaneously considering prooxidant and antioxidant defense.

The present study could have great relevance in the clinical setting because it proposes a tool for the diagnosis of patients with LVH. This score could serve as a monitoring tool for the effectiveness of treatments.

We recognize some limitations of this study that should be noted. First, we used a moderate number of biomarkers, which were selected on the basis of previous studies. However, these biomarkers were easy, quickly measurable, and not expensive, in order that they could be considered for use in clinical settings in the future. In addition, a good correlation has been reported between the plasma concentrations of these

**Table 4.** Multivariable logistic regression model: association OXY-SCORE and left ventricular hypertrophy.

	OR (95% CI)	p
OXY-SCORE	0.558 [0.392–0.795]	0.001
Gender	7.382 [0.860–63.366]	0.068
Age	1.057 [0.971–1.152]	0.201
Smokers	2.110 [0.122–36.382]	0.607
Glucose	0.991 [0.960–1.022]	0.554
Systolic arterial pressure	1.131 [1.039–1.230]	0.004
Diastolic arterial pressure	0.910 [0.812–1.020]	0.105
Dyslipidemia	2.385 [0.311–18.294]	0.403
eGFR	0.965 [0.929–1.002]	0.067
Body mass index	1.168 [0.993–1.372]	0.060
Valvular/coronary disease	5.938 [0.809–43.570]	0.080
CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; OXY-SCORE, plasma oxidative stress global index		

biomarkers and their levels in tissue.<sup>31</sup> Second, our data correspond to a population with LVH caused by different pathologies; therefore, it would be interesting to design and calculate a score for patients with hypertension only (since this is the most frequent cause of LVH) to allow for LVH screening in the general population. Finally, the score proposed in the present study could aim to elucidate new disease mechanisms and aid diagnosis,<sup>32</sup> however the results presented here should be replicated in a large population.

In conclusion, we have demonstrated that oxidative stress evaluation in patients with LVH can be improved by simultaneously considering prooxidant and antioxidant defense. We have designed and calculated an OXY-SCORE that, with the appropriate validation in a larger population, could help in the diagnosis of LVH and could be used to monitor treatment response.

#### Conflict of interest statement


The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

#### Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or

publication of this article: this work was supported by a grant from Spanish Health Ministry (number FIS 16/02069) and Fondos Feder.

#### ORCID iD

Begoña Quintana-Villamandos  <https://orcid.org/0000-0002-3685-2841>

#### References

1. Stewart MH, Lavie CJ, Shah S, *et al.* Prognostic implications of left ventricular hypertrophy. *Prog Cardiovasc Dis* 2018; 61: 446–455.
2. Jekell A, Nilsson PM and Kahan T. Treatment of hypertensive left ventricular hypertrophy. *Curr Pharm Des* 2018; 24: 4391–4396.
3. Zanchetti A. Hypertension: cardiac hypertrophy as a target of antihypertensive therapy. *Nat Rev Cardiol* 2010; 7: 66–67.
4. González A, Ravassa S, López B, *et al.* Myocardial remodeling in hypertension. *Hypertension* 2018; 72: 549–558.
5. Sinha N and Dabla PK. Oxidative stress and antioxidants in hypertension—a current review. *Curr Hypertens Rev* 2015; 11: 132–142.
6. Tham YK, Bernardo BC, Ooi JY, *et al.* Pathophysiology of cardiac hypertrophy and heart



- failure: signaling pathways and novel therapeutic targets. *Arch Toxicol* 2015; 89: 1401–1438.
7. Seddon M, Looi YH and Shah AM. Oxidative stress and redox signalling in cardiac hypertrophy and heart failure. *Heart* 2007; 93: 903–907.
  8. Veglia F, Cighetti G, De Franceschi M, *et al.* Age- and gender-related oxidative status determined in healthy subjects by means of OXY-SCORE, a potential new comprehensive index. *Biomarkers* 2006; 11: 562–573.
  9. Condezo-Hoyos L, Rubio M, Arribas SM, *et al.* A plasma oxidative stress global index in early stages of chronic venous insufficiency. *J Vasc Surg* 2013; 57: 205–213.
  10. Rodríguez-Rodríguez P, López de Pablo AL, Condezo-Hoyos L, *et al.* Fetal undernutrition is associated with perinatal sex-dependent alterations in oxidative status. *J Nutr Biochem* 2015; 26: 1650–1659.
  11. Veglia F, Werba JP, Tremoli E, *et al.* Assessment of oxidative stress in coronary artery bypass surgery: comparison between the global index OXY-SCORE and individual biomarkers. *Biomarkers* 2009; 14: 465–472.
  12. Vassalle C, Pratali L, Boni C, *et al.* An oxidative stress score as a combined measure of the pro-oxidant and anti-oxidant counterparts in patients with coronary artery disease. *Clin Biochem* 2008; 41: 1162–1167.
  13. Quintana-Villamandos B, Pazó-Sayós L, Arribas SM, *et al.* Dronedarone induces regression of coronary artery remodeling related to better global antioxidant status. *Hypertens Res* 2019; 42: 1485–1494.
  14. Ruiz-Hurtado G, Condezo-Hoyos L, Pulido-Olmo H, *et al.* Development of albuminuria and enhancement of oxidative stress during chronic renin-angiotensin system suppression. *J Hypertens* 2014; 32: 2082–2091.
  15. Ramiro-Cortijo D, Herrera T, Rodríguez-Rodríguez P, *et al.* Maternal plasma antioxidant status in the first trimester of pregnancy and development of obstetric complications. *Placenta* 2016; 47: 37–45.
  16. Quintana-Villamandos B, González Del Pozo I, Pazó-Sayós L, *et al.* Plasma protein thiolation index (PTI) as a potential biomarker for left ventricular hypertrophy in humans. *PLoS One* 2019; 14: e0216359.
  17. Giustarini D, Dalle-Donne I, Lorenzini S, *et al.* Protein thiolation index (PTI) as a biomarker of oxidative stress. *Free Radic Biol Med* 2012; 53: 907–915.
  18. Veglia F, Cavalca V and Tremoli E. OXY-SCORE: a global index to improve evaluation of oxidative stress by combining pro- and antioxidant markers. *Methods Mol Biol* 2010; 594: 197–213.
  19. Lang RM, Badano LP, Mor-Avi V, *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. *J Am Soc Echocardiogr* 2015; 28: 1–39.
  20. Hawkins CL, Morgan PE and Davies MJ. Quantification of protein modification by oxidants. *Free Radic Biol Med* 2009; 46: 965–988.
  21. Campos C, Guzman R, Lopez-Fernandez E, *et al.* Evaluation of the copper (II) reduction assay using bathocuproinedisulfonic acid disodium salt for the total antioxidant capacity assessment: the CUPRAC-BCS assay. *Anal Biochem* 2009; 392: 37–44.
  22. Saleh L and Plieth C. A coelenterazine-based luminescence assay to quantify high-molecular-weight superoxide anion scavenger activities. *Nat Protoc* 2010; 5: 1635–1641.
  23. Hissin PJ and Hilf R. A fluorometric method for determination of oxidized and reduced glutathione in tissues. *Anal Biochem* 1976; 74: 214–226.
  24. Jia Z, Saha S, Zhu H, *et al.* Spectrofluorometric measurement of reduced glutathione levels in human neuronal cells. In: Dap DK (ed.) *Methods redox signal*. New York: Mary Ann Liebert, 2010, pp.235–237.
  25. Esterbauer H and Cheeseman KH. Determination of aldehydic lipid peroxidation products: malonaldehyde and 4-hydroxynonenal. *Methods Enzymol* 1990; 186: 407–421.
  26. Frijhoff J, Winyard PG, Zarkovic N, *et al.* Clinical relevance of biomarkers of oxidative stress. *Antioxid Redox Signal* 2015; 23: 1144–1170.
  27. Cacciapuoti F. Molecular mechanisms of left ventricular hypertrophy (LVH) in systemic hypertension (SH)-possible therapeutic perspectives. *J Am Soc Hypertens* 2011; 5: 449–455.
  28. Kühl JT, Nielsen JB, Stisen ZR, *et al.* Left ventricular hypertrophy identified by cardiac computed tomography and ECG in hypertensive individuals: a population-based study. *J Hypertens* 2019; 37: 739–746.
  29. Quintana-Villamandos B, Goukassian DA, Sasi SP, *et al.* Short-term treatment with esmolol

Visit SAGE journals online  
[journals.sagepub.com/  
home/taj](http://journals.sagepub.com/home/taj)

 SAGE journals

- reverses left ventricular hypertrophy in adult spontaneously hypertensive rats via inhibition of Akt/NF- $\kappa$ B and NFATc4. *Biomed Res Int* 2018; 2018: 2691014.
30. Arnalich-Montiel A, González MC, Delgado-Baeza E, *et al.* Short-term esmolol improves coronary artery remodeling in spontaneously hypertensive rats through increased nitric oxide bioavailability and superoxide dismutase activity. *Biomed Res Int* 2014; 2014: 531087.
31. Veskoukis AS, Nikolaidis MG, Kyparos A, *et al.* Blood reflects tissue oxidative stress depending on biomarker and tissue studied. *Free Radic Biol Med* 2009; 47: 1371–1374.
32. Turakhia MP and Sabatine MS. How we evaluate biomarker studies. *JAMA Cardiol* 2017; 2: 524.