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Modified Haller index validation and correlation with left ventricular strain in a cohort of subjects with obesity and without overt heart disease

Andrea Sonaglioni[1] · Gian Luigi Nicolosi[2] · Roberta Trevisan[3] · Alberto Granato[4] · Maurizio Zompatori[3] · Michele Lombardo[1]

Abstract

The present study was primarily designed to validate the modified Haller index (MHI), the ratio of chest transverse diameter over the distance between sternum and spine, measured by a ruler and transthoracic echocardiography (TTE), respectively, in a cohort of subjects with obesity, but otherwise healthy, by comparing the results to the conventional Haller index (HI) measured on chest X-ray (CXR). 100 consecutive subjects with body mass index (BMI) ≥ 30 kg/m^2 and 60 matched controls with BMI < 30 kg/m^2, who underwent a two-plane CXR for any clinical indication, were prospectively examined over a 6-month period. All participants underwent MHI assessment, TTE and speckle-tracking analysis of left ventricular (LV) global longitudinal strain (GLS). Bland–Altman analysis was used to compare the radiological and nonradiological techniques. Second, independent predictors of subclinical myocardial dysfunction, defined as LV-GLS less negative than − 20%, were evaluated. Bland–Altman analysis revealed a bias of − 4.91 cm for latero-lateral thoracic diameter, of − 0.74 cm for antero-posterior (A–P) thoracic diameter and of − 0.22 for HI assessment, suggesting a systematic overestimation of the nonradiological methodology in comparison to that radiological. Despite normal LV systolic function on TTE, LV-GLS resulted impaired in 76% of subjects with obesity. Waist circumference (OR 1.13, 95%CI 1.04–1.22) and nonradiological A–P thoracic diameter (OR 0.51, 95%CI 0.28–0.93) were the main independent predictors of subclinical myocardial dysfunction in subjects with obesity. The impairment in LV myocardial strain detected in subjects with obesity appears to be primarily related to extrinsic abdominal and thoracic compressive phenomena, rather than intrinsic myocardial dysfunction.

Keywords Obesity · Modified Haller index · Chest X-ray · Bland–Altman analysis · Left ventricular strain

Abbreviations

2D	Two-dimensional
A–P	Antero-posterior
AUC	Area under curve
BMI	Body mass index
CI	Confidence interval
CO	Cardiac output
CXR	Chest X-ray
eGFR	Estimated glomerular filtration rate
GLS	Global longitudinal strain
HI	Haller index
ICC	Intraclass correlation coefficient
LAVi	Left atrial volume index
LDL	Low-density lipoprotein
L–L: latero-lateral; LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVMi	Left ventricular mass index
LVOT	Left ventricular outflow tract
MAPSE	Mitral annular plane systolic excursion
MHI	Modified Haller index
OR	Odds ratio

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OSAS	Obstructive sleep apnea syndrome
P–A	Postero-anterior
ROC	Receiver operating characteristics
RV	Right ventricular
RWT	Relative wall thickness
SPAP	Systolic pulmonary artery pressure
STE	Speckle-tracking echocardiography
Svi	Stroke volume index
TAPSE	Tricuspid annular plane systolic excursion
TTE	Transthoracic echocardiography

Introduction

Over the last two decades, obesity has become a major public health problem globally due to its increasing prevalence worldwide [1, 2]. For this reason, subjects with obesity are more frequently encountered in the clinical practice.

It is known that obesity is an independent predictor of left ventricular (LV) hypertrophy, diastolic dysfunction, and heart failure [3–8].

Although LV systolic function measured by left ventricular ejection fraction (LVEF) is usually preserved in the early stages of obesity, subjects with obesity may be found with subclinical LV systolic dysfunction, assessed by two-dimensional (2D) speckle-tracking echocardiography (STE), a more sensitive echocardiographic modality, with incremental diagnostic and prognostic value compared to conventional 2D transthoracic echocardiography (TTE) [9–12].

A number of 2D-STE studies [13–19] have demonstrated impaired myocardial strain indices in asymptomatic subjects with obesity. All these studies attributed the reduction in myocardial strain deformation to a metabolic cardiomyopathy/intrinsic myocardial dysfunction.

We have previously demonstrated that chest wall conformation, as noninvasively assessed by modified Haller index (MHI) [20], may affect myocardial strain parameters in both adults [21] and infants [22] with pectus excavatum, in subjects with mitral valve prolapse [23] and finally in healthy pregnant women [24]. Notably, the subjects with anterior chest wall deformity and/or concave-shaped chest wall, defined by MHI > 2.5 [25, 26], showed the greater impairment in myocardial strain indices, due to extrinsic thoracic compression, in absence of any intrinsic myocardial dysfunction.

As far as we know, no previous study compared the conventional radiological measurements of thoracic diameters and Haller index (HI) to those obtained by a noninvasive modality without the use of any ionizing radiation, such as the MHI, in subjects with obesity. Moreover, the validation study did not include subjects with obesity [20]. In addition, the potential impact of chest shape on myocardial deformation indices in subjects with obesity has never been previously investigated.

We hypothesized that myocardial strain indices might be impaired by mechanical factors and/or compressive phenomena not only in subjects with pectus excavatum but also in subjects with a more circular axial thoracic shape, such as those with obesity.

Accordingly, the present study was primarily designed to test the MHI methodology in subjects with obesity, by comparing the nonradiological measurements of thoracic diameters and HI to those derived from chest X-ray (CXR) obtained in a consecutive series subjects with obesity and without overt heart disease versus a control group of subjects without obesity. Second, we aimed at investigating the influence of chest wall conformation on LV global longitudinal strain (GLS) in subjects with obesity.

Methods

This prospective case–control study was conducted on 100 consecutive subjects with obesity, but otherwise healthy, and 60 subjects without obesity matched by age, sex and cardiovascular risk factors [27] as controls, who underwent both a two-plane CXR for any clinical reason/indication at the Radiology Department of the San Giuseppe MultiMedica hospital (Milano, Italy) and a conventional 2D-TTE at the Outpatient Cardiology Division of the same hospital, between September 2021 and February 2022.

Obesity was defined by a body mass index (BMI) ≥ 30 kg/m^2, according to the World Health Organization (WHO) definition [28]. Class 1 obesity included subjects with a BMI of 30 to 34.9 kg/m^2, class 2 included those with BMI of 35 to 39.9 kg/m^2 and finally class 3 included those with a BMI of ≥ 40 kg/m^2.

Exclusion criteria were the following: totally or partially dependent patients who were unable to maintain the standing position (to perform a two-plane CXR); atrial fibrillation; left bundle branch block; history of coronary artery disease (previous myocardial infarction, previous percutaneous coronary intervention or previous coronary artery bypass graft); moderate-to-severe mitral and/or aortic valve disease; hypertrophic, infiltrative and/or dilated cardiomyopathy; history of congenital heart disease; LVEF < 50%; acute coronary syndrome, acute congestive heart failure, acute respiratory failure, acute renal failure; hemodynamic instability; poor echocardiographic acoustic windows (not adequate for appropriate visualization and definition of endocardial border of the left ventricle); lack of consent.

Following demographic, anthropometric, clinical and biochemical parameters were collected: anagraphic age; body surface area; BMI; waist circumference; prevalence of relevant cardiovascular risk factors (hypertension, smoking, type 2 diabetes mellitus, dyslipidemia) and concomitant obstructive sleep apnea syndrome (OSAS); heart rate; blood tests comprehensive of serum levels of creatinine and estimated glomerular filtration rate (eGFR) [29], serum levels of glycosylated hemoglobin, low-density lipoprotein (LDL) cholesterol and triglycerides; finally, the current medical treatment.

During the same day, all participants underwent blood tests, blood pressure measurement, CXR, MHI assessment [20] and a conventional 2D-TTE implemented with 2D-STE analysis of left ventricular myocardial deformation. Both CXRs and echocardiographic examinations were performed by the same radiologist (R.T.) and by the same cardiologist (A.S.), respectively, in blinded manner.

All procedures were performed according to the ethical standards of the Institutional Research Committee and to the Declaration of Helsinki (1964) and its subsequent amendments or equivalent ethical standards. A written and informed consent was obtained from each participant and the study protocol was authorized the local Ethics Committee (Committee's reference number CE 99.2019).

Conventional radiological Haller index

The radiologist measured chest diameters at the end of inspiration on the two-plane postero-anterior (P–A) and latero-lateral (L–L) CXR. The L–L thoracic diameter was measured on a P–A view, at the level of the distal third of the sternum and/or of the eighth thoracic vertebra, without including the soft tissues, according to the conventional criteria (Fig. 1, Panel A). The antero-posterior (A–P) thoracic diameter was measured on a L–L view, at the level of the maximum sternal depression, from the internal anterior chest wall to the anterior surface of the eighth thoracic vertebral body (Fig. 1, Panel B). The conventional radiological HI was obtained by dividing the L–L thoracic diameter by the A–P thoracic diameter.

Modified Haller index

The nonradiological Haller index was assessed by the cardiologist. The L–L thoracic diameter was measured with the subject in the standing position and with open arms, using a rigid ruler in centimeters coupled to a level (the measuring device), placed at the distal third of the sternum, at the point of maximal depression of the sternum, at the end of inspiration (Fig. 1, Panel C). The A–P thoracic diameter was measured from a parasternal long-axis view during conventional 2D-TTE: it was tracked the distance from the true apex of the sector to the anterior surface of the vertebral body. The vertebral body was identified using, as reference point, the posterior wall of the descending thoracic aorta, visualized behind the left atrium (Fig. 1, Panel D). The MHI without radiological exposure was then calculated by dividing the L–L thoracic diameter by the A–P thoracic diameter.

Conventional echoDoppler examination

All echocardiographic examinations were performed using a Philips Sparq ultrasound machine (Philips, Andover, Massachusetts, USA) with a 2.5 MHz transducer. All parameters were measured according to the Recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [30, 31].

Following M-mode and 2D echocardiographic parameters were recorded: (1) relative wall thickness (RWT); (2) left ventricular mass index (LVMi) calculated by the Deveraux formula; (3) left ventricular end-diastolic volume index, left ventricular end-systolic volume index and LVEF estimated with the biplane modified Simpson's method [30]; (4) mitral annular plane systolic excursion (MAPSE); (5) left atrial volume index (LAVi); (6) right ventricular inflow tract and tricuspid annular plane systolic excursion (TAPSE).

Doppler measurements included: (1) E/A ratio and average E/e' ratio, as indices of left ventricular diastolic function [31]; (2) stroke volume (SV), measured from the product of the left ventricular outflow tract (LVOT) area and LVOT time velocity integral, using pulsed Doppler echocardiography; (3) cardiac output, calculated by multiplying the SV by the heart rate; (4) systolic pulmonary artery pressure (SPAP), derived by the modified Bernoulli equation, where $SPAP = 4 \times (\text{tricuspid regurgitation velocity})^2 + \text{right atrial pressure}$ [32]. The latter was estimated from inferior vena cava diameter and collapsibility.

Degree of valvulopathy was assessed according to the AHA/ACC recommendations for the management of patients with valvular heart disease [33].

Speckle□tracking echocardiography

2D speckle-tracking strain analyses were performed offline, immediately after conventional 2D-TTE, using the Philips QLAB 10.3.1 ultrasound software (Philips Healthcare, Andover, Massachusetts, USA).

Analysis of left ventricular longitudinal strain was performed on 2D images acquired during conventional 2D-TTE, using apical four-chamber, two-chamber and three-chamber views.

According to Philips QLAB software, LV wall was automatically divided into seven segments for each apical view. After manual adjustment to ensure the best quality of tracking, left ventricular peak systolic strain was calculated as the

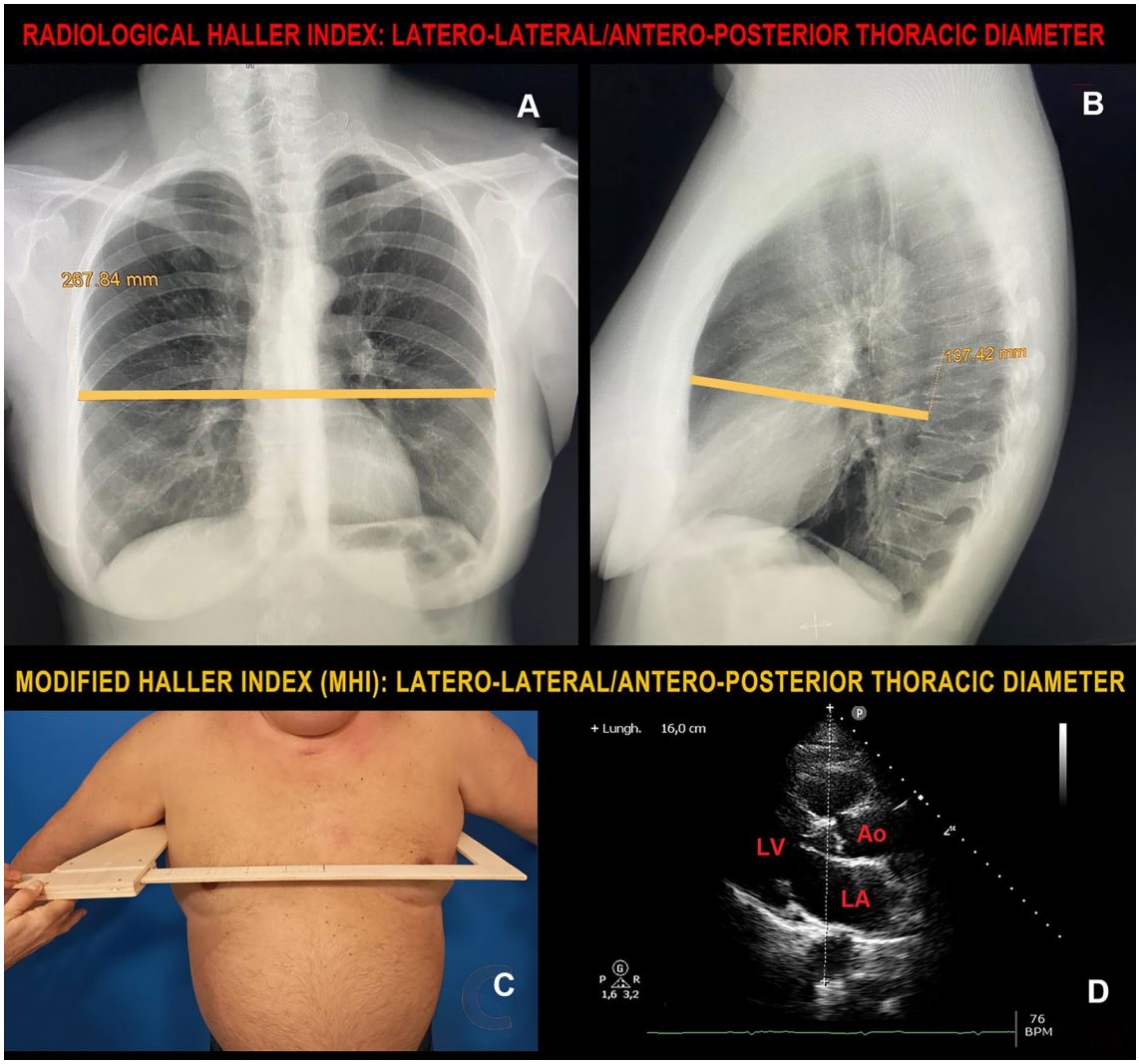


Fig. 1 Radiological Haller index (Panels A and B). **Panel A** The L–L thoracic diameter, measured on a P–A view, at the level of the distal third of the sternum and/or of the eighth thoracic vertebra, without including the soft tissues (yellow line). *L–L* latero-lateral, *P–A* postero-anterior. **Panel B**. The A–P thoracic diameter measured on a L–L view, at the level of the maximum sternal depression, from the internal anterior chest wall to the anterior surface of the eighth thoracic vertebral (yellow line). *A–P* antero-posterior, *L–L* latero-lateral. Modified Haller index (Panels C and D). **Panel C**. The L–L thoracic diameter, measured with the subject in the standing position and with open arms, using a rigid ruler in centimeters coupled to a level (the measuring device), placed at the distal third of the sternum, in the point of maximum depression of the sternum. *L–L* latero-lateral. **Panel D**. The A–P thoracic diameter, obtained with the subject in left lateral decubitus position, using the transthoracic echocardiography, by placing a 2.5 mHz transducer near the sternum in the left third or fourth intercostal space, to obtain a parasternal long-axis view, and measuring the distance between the true apex of the sector (the point of entry of ultrasound) and the anterior surface of the vertebral body. The vertebral body was identified using, as reference point, the posterior wall of the descending thoracic aorta, visualized behind the left atrium. *Ao* aorta, *A–P* antero-posterior, *LA* left atrium, *LV* left ventricle

systolic shortening percentage of the myocardium in each segment. Global longitudinal strain was calculated as the average value of the peak systolic strain of 17 left ventricular myocardial segments (5 apical segments, 6 basal segments and 6 mid-ventricular segments) and was displayed as a single bull's-eye summary. Early peak diastolic strain rate was derived from longitudinal measurements. Absolute values more negative than −20% for LV-GLS were considered normal, according to the recommendations of the the European Association of Cardiovascular Imaging [34].

Statistical analysis

In the present study, two groups of subjects were prospectively analyzed: 100 subjects with BMI ≥ 30 kg/m^2 and 60 subjects with BMI < 30 kg/m^2 as controls. For each group of

subjects, continuous data were summarized as mean ± standard deviation, whereas categorical data were presented as number (percentage). Each continuous variable was checked through the Shapiro–Wilk test and all data were determined to be normally distributed. An independent two-tailed *t* test was used to estimate the difference between the means of the continuous variables, while categorical variables were compared using the chi-square test or the Fisher's exact test.

Bland–Altman analysis [35] was used to assess the accuracy and precision of nonradiological measurements of thoracic diameters and Haller index compared with conventional radiological measurements, obtained in subjects with obesity. The accuracy of the nonradiological technique was assessed by estimating the mean difference between invasive and noninvasive measures of L–L thoracic diameter, A–P thoracic diameter and Haller index and their 95% confidence interval (CI). Precision was assessed by calculating the lower and upper limit of agreement [mean difference ± 1.96*(SD of the differences)] between radiological and nonradiological measures of chest diameters and Haller index.

Correlations between radiological and nonradiological measurements of each single thoracic diameter and Haller index were determined using the Pearson's correlation coefficient.

Univariate logistic regression analysis was performed to evaluate the effect of the main demographic, anthropometric, clinical, biochemical and conventional echoDoppler variables on the prediction of an impaired LV-GLS (defined as an absolute value less negative than − 20%) [34], in subjects with obesity. For each variable investigated, correspondent odds ratios (OR) with 95% confidence intervals (CIs) were calculated. Variables with a p value < 0.05 were then entered into a multivariate model.

The receiver operating characteristics (ROC) curve analysis was performed to establish the sensitivity and the specificity of the main statistically significant continuous variables, associated with LV-GLS less negative than – 20% in our study population. Area under curve (AUC) was estimated.

Multiple linear regression analysis was used to estimate the relationship between LV-GLS (dependent variable) and extrinsic mechanical factors. For this purpose, two models of multiple linear regression were built: the first one included radiological thoracic measurements (L–L diameter, A–P diameter and HI) and waist circumference as independent variables, whereas the second one evaluated the relationship of LV-GLS with nonradiological thoracic measurements (L–L diameter, A–P diameter and MHI) and waist circumference.

Statistical power analysis was conducted for this study. A sample size of 100 subjects with obesity and 60 controls reached 90% of statistical power to detect a 2 points difference in both the investigated traditional echoDoppler parameters and LV-GLS between the 2 groups, with a SD of 3.5 for each parameter, using a two-sided equal-variance t test with a level of significance (α) of 5%.

To evaluate intra- and inter-observer variability in the assessment of main conventional and functional echocardiographic parameters, the key echocardiographic variables were finally remeasured in a sized subgroup of 15 randomly selected subjects with obesity by the same cardiologist and by a second one (M.R.). The analyses were performed in a blinded manner on the same day of the echocardiographic examinations. The intraclass correlation coefficient (ICC) with its 95% CI was used as a statistical method for assessing intra- and inter-observer measurement variability. An ICC of 0.70 or more was considered to indicate acceptable reliability.

Statistical analysis was performed with SPSS version 26 (SPSS Inc., Chicago, Illinois, USA), with p values below 0.05 deemed statistically significant.

Results

All demographics, anthropometrics, biochemical and clinical parameters detected in subjects with obesity (BMI ≥ 30 kg/m^2) and controls (BMI < 30 kg/m^2) at basal evaluation are reported in Table 1.

The prevalence of females was slightly increased in both groups of participants, without statistically significant difference between the two groups.

Majority of subjects with obesity (52% of total) had class I obesity, 28% had class II obesity and the remaining 20% had class III obesity.

Considering the age-related normal ranges for HI [36, 37], the average value of both radiological and nonradiological HI was normal in both groups of subjects. No subject with pectus excavatum (Haller index > 2.5) [25, 26] was found in our study population. Concerning the components of Haller index in the two groups of subjects, similar results were obtained using the invasive methodology and the noninvasive one. Notably, subjects with obesity were found with significantly greater A–P thoracic diameter than controls, whereas the L–L thoracic diameter was similar in the two groups of subjects, indicating a more circular transversal thoracic shape in subjects with obesity. The resultant Haller index was significantly lower in subjects with obesity than controls. However, both A–P and L–L nonradiological thoracic diameters, especially the L–L thoracic diameter, measured by the cardiologist, were slightly larger than those derived from CXR by the radiologist.

Both groups of subjects showed a moderate prevalence of the most common cardiovascular risk factors. Hypertension and dyslipidemia were detected in approximately two-third of subjects with obesity, whereas smoking and type 2

Table 1 Demographics, anthropometrics, biochemical and clinical parameters recorded in subjects with obesity and controls at basal evaluation

	Subjects with obesity ($n=100$)	Controls ($n=60$)	P value
Demographics and anthropometrics			
Age (yrs)	57.2 ± 13.8	55.1 ± 11.2	0.32
Female sex (%)	57 (57.0)	32 (53.4)	0.65
BSA (m^2)	2.07 ± 0.23	1.85 ± 0.15	< 0.001
BMI (Kg/m^2)	36.0 ± 5.6	24.5 ± 4.5	< 0.001
Waist circumference (cm)	115.4 ± 10.8	90.6 ± 11.8	< 0.001
Class 1 obesity (%)	52 (52.0)	/	/
Class 2 obesity (%)	28 (28.0)	/	/
Class 3 obesity (%)	20 (20.0)	/	/
Conventional radiological Haller index			
L–L thoracic diameter (cm)	26.7 ± 3.2	26.1 ± 3.2	0.25
A–P thoracic diameter (cm)	15.7 ± 2.0	13.7 ± 1.9	< 0.001
Haller index	1.7 ± 0.2	1.9 ± 0.1	< 0.001
Nonradiological Haller index			
L–L thoracic diameter (cm)	31.6 ± 4.5	30.6 ± 3.1	0.13
A–P thoracic diameter (cm)	16.5 ± 2.0	14.5 ± 1.8	< 0.001
Modified Haller index	1.9 ± 0.2	2.1 ± 0.2	< 0.001
Cardiovascular risk factors			
Hypertension (%)	73 (73.0)	40 (66.6)	0.39
Smoking (%)	29 (29.0)	15 (25.0)	0.58
Type 2 diabetes mellitus (%)	42 (42.0)	24 (40.0)	0.80
Dyslipidemia (%)	63 (63.0)	32 (53.3)	0.23
OSAS (%)	24 (24.0)	2 (3.3)	< 0.001
Biochemical parameters			
eGFR ($ml/min/m^2$)	111.2 ± 27.9	98.4 ± 16.6	0.001
Glycosylated hemoglobin (mmol/mol)	41.5 ± 12.3	38.8 ± 5.6	0.11
LDL cholesterol (mg/dl)	127.6 ± 31.7	121.5 ± 25.6	0.21
Triglycerides (mg/dl)	142.2 ± 67.7	135.3 ± 51.1	0.49
Hemodynamics			
HR (bpm)	75.9 ± 11.3	73.6 ± 10.5	0.20
SBP (mmHg)	137.5 ± 16.5	133.6 ± 11.2	0.11
DBP (mmHg)	89.0 ± 11.8	86.8 ± 9.1	0.22
Current medical treatment			
Antiplatelets (%)	12 (12.0)	6 (10.0)	0.69
ACEIs/ARBs (%)	34 (34.0)	18 (30.0)	0.60
Calcium channel blockers (%)	17 (17.0)	9 (15.0)	0.74
Beta blockers (%)	16 (16.0)	15 (25.0)	0.16
Diuretics (%)	17 (17.0)	9 (15.0)	0.74
Statins (%)	12 (12.0)	6 (10.0)	0.69
Antidiabetic drugs (%)	36 (36.0)	20 (33.3)	0.73

Data are expressed as mean ± SD or as a number (percentage)

A–P antero-posterior, *ACEIs* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *BMI* body mass index, *BSA* body surface area, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *HR* heart rate, *LDL* low-density lipoprotein, *L–L* latero-lateral, *OSAS* obstructive sleep apnea syndrome, *SBP* systolic blood pressure

Significant *P* values are in bold

diabetes were found in 29% and 42% of total, respectively. Prevalence of OSAS in our study population was 24%.

Overall, blood tests revealed good glycemic control, normal serum levels of eGFR and a mild increase in serum level of LDL cholesterol in both groups of subjects.

Analysis of hemodynamic indices showed that both groups of subjects had normal resting heart rate and suboptimal blood pressure control; notably, among subjects with obesity, 40% of total were found with blood pressure ≥ 140/90 mmHg.

As regards current medical treatment, 12% of subjects with obesity were regularly treated with antiplatelets, 34% with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, 17% with calcium channel blockers, 16% with beta blockers, 17% with diuretics, 12% with statins, and finally 36% with antidiabetics.

Bland–Altman analysis (Fig. 2), performed for comparing invasive and noninvasive thoracic measurements in subjects with obesity, revealed a bias (the difference between the means) of − 4.91 cm for L–L thoracic diameter (Panel A), of − 0.74 cm for A–P thoracic diameter (Panel B) and of − 0.22 for Haller index assessment (Panel C). The larger limits of agreement were observed for L–L thoracic diameter estimation (+ 1.63; − 11.45) (Panel A), whereas the limits of agreement were narrower for A–P thoracic diameter (+ 2.09; − 3.57) (Panel B) and for Haller index (+ 0.17; − 0.60) (Panel C) assessment. These results suggested a systematic overestimation of the nonradiological methodology in comparison to the standard radiological methodology, especially in the assessment of L–L thoracic diameter and to a lesser extent in the measurement of A–P thoracic diameter and of Haller index. The Pearson's correlation analysis indicated a good correlation between the two measurement methods in the assessment of L–L thoracic diameter ($r = 0.67$, $p < 0.001$), of A–P thoracic diameter ($r = 0.74$, $p < 0.001$) and of Haller index ($r = 0.58$, $p < 0.001$).

Main conventional and functional echocardiographic variables measured in subjects with obesity and controls at basal evaluation are summarized in Table 2.

Compared to the accepted reference ranges [30], biventricular and biatrial cavity sizes were normal in both groups of subjects. In comparison to controls, subjects with obesity were found with significantly greater RWT and LVMi and significantly increased prevalence of LV concentric remodeling. Biventricular systolic function, as assessed by LVEF, MAPSE and TAPSE, was similar in both groups of subjects, whereas stroke volume was significantly lower in subjects with obesity than controls. No subject was found with LVEF < 55% nor with TAPSE < 20 mm. Analysis of LV diastolic function revealed that the impaired LV relaxation pattern was the most commonly detected LV diastolic filling pattern in both groups of subjects. However, subjects with obesity showed an increased degree of diastolic dysfunction, expressed by significantly greater values of E/A ratio and average E/e' ratio than controls.

Concerning myocardial deformation variables, LV-GLS and LV global longitudinal strain rate (LV-GLSR) were adequately measured in all subjects with obesity. In comparison to controls, subjects with obesity were diagnosed with significantly impaired LV-GLS and LV-GLSR. Compared to the accepted reference ranges for Philips QLAB software [34], LV-GLS resulted to be impaired in 76% subjects with obesity and in 25% of controls.

At univariate logistic regression analysis (Table 3), the main variables independently associated with the abnormality of LV-GLS (LV-GLS less negative than -20%) were the following: waist circumference (OR 1.15, 95%CI 1.06–1.24, $p < 0.001$), radiological L–L thoracic diameter (OR 0.82, 95%CI 0.71–0.95, $p = 0.01$), radiological A–P thoracic diameter (OR 0.59, 95%CI 0.44–0.78, $p < 0.001$), nonradiological L–L thoracic diameter (OR 0.83, 95%CI 0.74–0.93, $p = 0.002$) and finally nonradiological A–P thoracic diameter (OR 0.46, 95%CI 0.33–0.67, $p < 0.001$). At multivariate logistic regression analysis (Table 3), waist circumference (OR 1.13, 95%CI 1.04–1.22, $p = 0.002$) and nonradiological A–P thoracic diameter (OR 0.51, 95%CI 0.28–0.93, $p = 0.02$) retained statistical significance. ROC curve highlighted the following cut-offs as the cut-offs with maximum sensitivity and specificity for predicting the above-mentioned LV-GLS abnormality: waist circumference ≥ 100.5 cm (82% sensitivity and 83% specificity, AUC = 0.86) and nonradiological A–P thoracic diameter ≤ 17 cm (82% sensitivity and 83% specificity, AUC = 0.81).

Multiple linear regression models built to describe the relationship between LV-GLS and extrinsic mechanical factors,

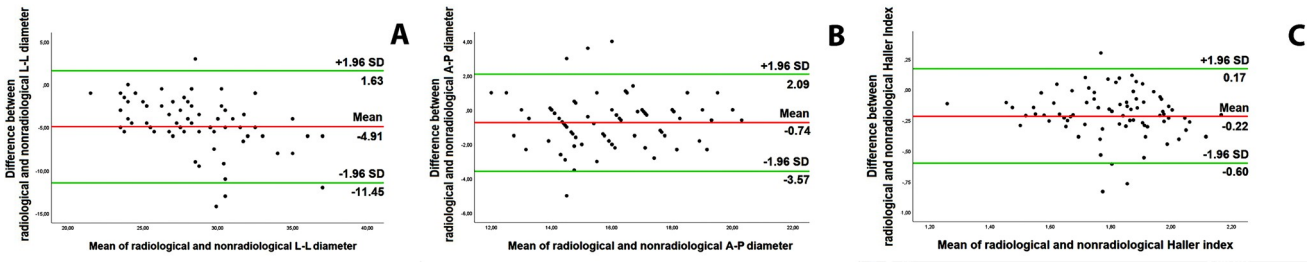


Fig. 2 Bland–Altman analysis to compare the nonradiological thoracic diameters and Haller index with the radiological measurements in subjects with obesity. A–P, antero-posterior; L–L, latero-lateral

Table 2 Conventional echoDoppler parameters and functional myocardial deformation indices measured in subjects with obesity and controls at basal evaluation

	Subjects with obesity ($n=100$)	Controls ($n=60$)	P value
Conventional echoDoppler parameters			
RWT	0.39 ± 0.05	0.37 ± 0.04	0.009
LVMi (g/m^2)	92.5 ± 20.8	85.5 ± 15.2	0.02
LV concentric remodeling (%)	22 (22.0)	5 (8.3)	0.02
LV concentric hypertrophy (%)	9 (9.0)	3 (5.0)	0.35
LV eccentric hypertrophy (%)	12 (12.0)	6 (10.0)	0.69
Normal LV geometric pattern (%)	57 (57.0)	46 (76.7)	0.01
LVEDVi (ml/m^2)	38.9 ± 6.9	40.5 ± 4.4	0.11
LVESVi (ml/m^2)	12.9 ± 2.7	13.5 ± 2.6	0.17
LVEF (%)	66.5 ± 3.0	67.0 ± 2.8	0.29
MAPSE (mm)	18.2 ± 2.5	18.5 ± 2.2	0.44
SVi (ml/min/m^2)	34.7 ± 8.1	38.1 ± 7.2	0.008
COi (L/min/m^2)	2.7 ± 0.6	2.8 ± 0.8	0.37
E/A ratio	0.96 ± 0.31	0.85 ± 0.25	0.02
Average E/e' ratio	11.4 ± 4.3	8.6 ± 3.5	< 0.001
LAVi (ml)	31.6 ± 9.7	30.5 ± 8.2	0.46
Moderate MR (%)	6 (6.0)	5 (8.3)	0.57
Moderate AR (%)	4 (4.0)	5 (8.3)	0.25
RVIT (mm)	30.3 ± 5.8	28.8 ± 5.5	0.11
TAPSE (mm)	24.5 ± 3.8	25.1 ± 3.6	0.33
Moderate TR (%)	10 (10.0)	8 (13.3)	0.52
SPAP (mmHg)	27.2 ± 11.0	26.6 ± 8.8	0.72
2D-STE variables			
LV-GLS (%)	17.3 ± 2.8	20.5 ± 1.5	< 0.001
LV-GLSR (s^{-1})	0.99 ± 0.18	1.25 ± 0.22	< 0.001
LV-GLS less negative than -20% (n, %)	76 (76.0)	15 (25.0)	< 0.001

Data are expressed as mean ± SD or as number (percentage)

2D two-dimensional, *AR* aortic regurgitation, *COi* cardiac output index, *GLS* global longitudinal strain, *GLSR* global longitudinal strain rate, *LAVi* left atrial volume index, *LV* left ventricular, *LVEDVi* left ventricular end-diastolic volume index, *LVEF* left ventricular ejection fraction, *LVESVi* left ventricular end-systolic volume index, *LVMi* left ventricular mass index, *MAPSE* mitral annular plane systolic excursion, *MR* mitral regurgitation, *RV* right ventricular, *RVIT* right ventricular inflow tract, *RWT* relative wall thickness, *SPAP* systolic pulmonary artery pressure, *STE* spekcle tracking echocardiography, *SVi* stroke volume index, *TAPSE* tricuspid annular plane systolic excursion, *TR* tricuspid regurgitation

Significant *P* values are in bold

are depicted in Fig. 3, panels A and B, respectively. The two models confirmed the strong correlation of LV-GLS with thoracic measurements (including L–L diameter, A–P diameter and Haller index) and waist circumference, with similar behavior for the model that included radiological thoracic measurements (Panel A) and for the one that included non-radiological thoracic measurements (Panel B), showing mild overestimation for the lower values and mild underestimation for the greater values of LV-GLS.

Measurement variability

Intra- and inter-rater variability, expressed as ICC with 95%ICc, ranged from 0.82 to 0.90 and from 0.79 to 0.84, respectively.

Table 3 Univariate and multivariate logistic regression analysis for identifying the main demographic, anthropometric, clinical, biochemical and conventional echoDoppler variables independently associated with impaired LV-GLS, defined as an absolute value less negative than −20%, in subjects with obesity

	Univariate logistic regression analysis			Multivariate logistic regression analysis		
Variables	OR	95% CI	*P* value	OR	95% CI	*P* value
Demographics						
Age (yrs)	1.01	0.97–1.04	0.71			
Male sex	0.55	0.22–1.39	0.21			
Anthropometrics						
BMI (Kg/m^2)	1.03	0.98–1.08	0.33			
Waist circumference (cm)	1.15	1.06–1.24	< 0.001	1.13	1.04–1.22	0.002
Conventional radiological Haller index						
L–L thoracic diameter (cm)	0.82	0.71–0.95	0.01	1.08	0.86–1.36	0.49
A–P thoracic diameter (cm)	0.59	0.44–0.78	< 0.001	0.85	0.54–1.35	0.49
Haller index	2.12	0.19–16.4	0.55			
Nonradiological Haller index						
L–L thoracic diameter (cm)	0.83	0.74–0.93	0.002	0.97	0.80–1.17	0.51
A–P thoracic diameter (cm)	0.46	0.33–0.67	< 0.001	0.51	0.28–0.93	0.02
Modified Haller index	2.16	0.23–20.5	0.50			
Cardiovascular risk factors						
Hypertension	1.93	0.72–5.16	0.18			
Smoking	1.75	0.58–5.25	0.32			
Type 2 diabetes mellitus	1.38	0.55–3.47	0.49			
Dyslipidemia	1.40	0.44–4.49	0.57			
OSAS	1.44	0.43–4.79	0.55			
Biochemical parameters						
eGFR	0.99	0.98–1.01	0.45			
Glycosylated hemoglobin	1.01	0.96–1.05	0.69			
Triglycerides	1.00	0.99–1.01	0.31			
ECG parameters						
Heart rate (bpm)	1.01	0.96–1.05	0.79			
Conventional echoDoppler parameters						
LVMi (g/m^2)	0.99	0.98–1.00	0.15			
LVEF (%)	0.94	0.85–1.05	0.29			
MAPSE (mm)	0.97	0.81–1.16	0.75			
SVi (ml/m^2)	0.99	0.96–1.03	0.90			
Average E/e' ratio	1.00	0.90–1.12	0.93			
Current medical treatment						
ACEIs/ARBs	2.45	0.76–7.93	0.13			
Beta blockers	1.18	0.30–4.65	0.81			
Statins	0.40	0.13–1.28	0.12			

ACEIs angiotensin-converting enzyme inhibitors, *A–P* antero-posterior, *ARBs* angiotensin II receptor blockers, *BMI* body mass index, *CI* confidence interval, *COi* cardiac output index, *eGFR* estimated glomerular filtration rate, *GLS* global longitudinal strain, *HR* heart rate, *HDL* high-density lipoprotein, *LAVi* left atrial volume index, *LDL* low-density lipoprotein, *L–L* latero-lateral, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *LVMi* left ventricular mass index, *MAPSE* mitral annular plane systolic excursion, *OR* odds ratio, *OSAS* obstructive sleep apnea syndrome, *SVi* stroke volume index

Significant *P* values are in bold

Discussion

The present study demonstrated the reliability of modified Haller index as nonradiological method for assessing chest wall conformation in a consecutive series of 100 subjects with obesity and without overt heart disease. Despite a systematic overestimation of the noninvasive technique in comparison to the radiological method, both L–L and A–P thoracic diameters and MHI showed a satisfying correlation with the measurements derived by the CXR.

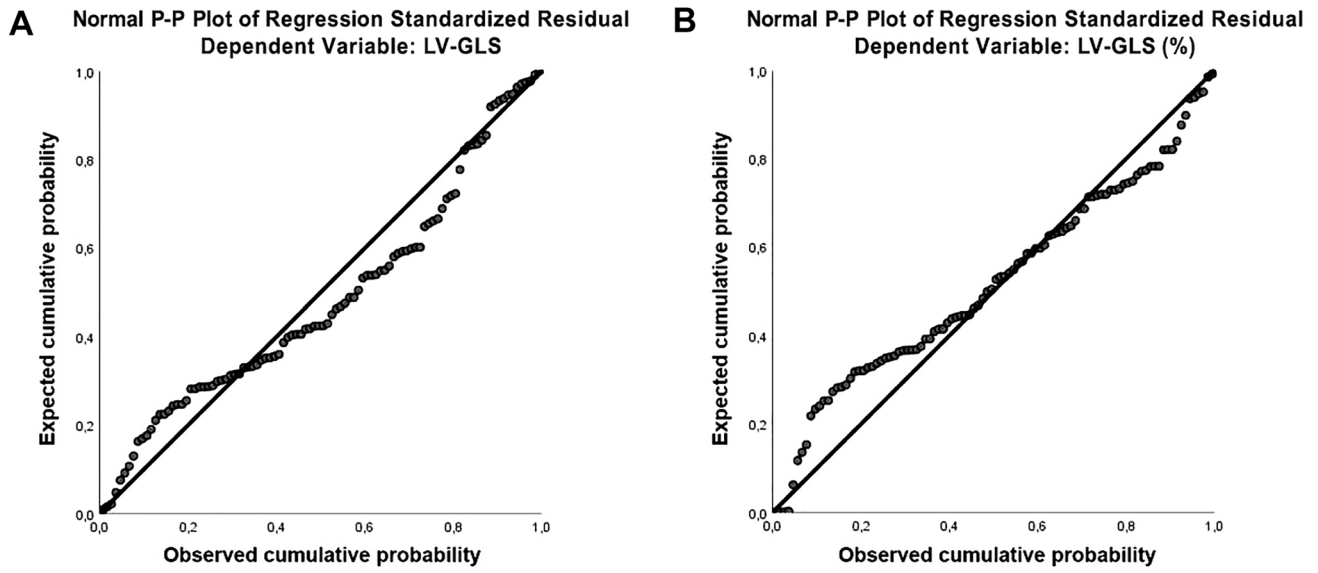


Fig. 3 Multiple linear regression models for evaluating the correlation of LV-GLS with waist circumference and both the radiological (Panel A) and nonradiological (Panel B) thoracic measurements (including A–P diameter, L–L diameter and Haller index), in subjects with obesity. *A–P* antero-posterior, *GLS* global longitudinal strain, *L–L* latero-lateral, *LV* left ventricular

After validating the MHI methodology in subjects with obesity, this study evaluated not only the influence of the main clinical, biochemical and conventional echoDoppler variables on subclinical myocardial dysfunction (defined as a LV-GLS value less negative than − 20%), but also the role of anthropometrics, such as BMI, waist circumference and chest shape (assessed by both radiological and nonradiological chest diameters and Haller index), in potentially influencing myocardial strain parameters in the same study population.

Our findings revealed that the waist circumference and the nonradiological A–P thoracic diameter were the only variables independently associated with an impaired LV-GLS in subjects with obesity. Notably, a waist circumference ≥ 100.5 cm and a nonradiological A–P thoracic diameter ≤ 17 cm were the best cut-off values for predicting a reduced left ventricular myocardial strain in our study population. On the other hand, BMI, conventional risk factors, biochemical parameters, LVMi and other conventional echocardiographic indices did not show any statistically significant correlation with the above-mentioned LV-GLS abnormality. Finally, we demonstrated that the set of anthropometrics, including radiological and nonradiological thoracic measurements and waist circumference, showed a strong correlation with LV-GLS, confirming the assumption that extrinsic mechanical factors may play a key role in determining an impairment in myocardial strain parameters [21–24].

To the best of our knowlegde, this is the first study that evaluated the influence of both abdominal adiposity (assessed by waist circumference) and chest wall conformation (assessed by both conventional radiological and nonradiological Haller index) on left ventricular global longitudinal strain in subjects with obesity.

Modified Haller index has been developed in our echo Lab in 2011 and has been validated in 2018 [20]. The validation study compared the radiological measurements of Haller index derived from CXR with the nonradiological findings obtained using a measuring device (for L–L thoracic diameter assessment) and conventional transthoracic echocardiography (for A–P thoracic diameter assessment). A mild systematic overestimation of L–L thoracic diameter (bias of − 3.4 cm), A–P thoracic diameter (bias of − 1.1 cm) and Haller index (bias of − 0.07) by the nonradiological method was demonstrated in comparison to the conventional radiological method. However, the validation study did not include subjects with obesity.

Similar to the validation study results, the present study revealed a general overestimation of thoracic diameters, especially of the L–L thoracic diameter, by the nonradiological technique in subjects with obesity. Indeed, the bias for the L–L thoracic measurement was greater than that observed in the validation study (− 4.91 vs. − 3.4 cm). The imprecision in the assessment of L–L thoracic diameter by the measuring device (a rigid ruler coupled to a level) in subjects with obesity should be primarily related to the excessive fat accumulation in both sides of the lateral thoracic region, with consequent significant amplification of the overestimation problem. On the other hand, the bias for the A–P thoracic estimation was similar to that obtained in the

validation study (− 0.74 vs − 1.1 cm). Our results confirmed low bias, narrow limits of agreement and strong linear correlation between the radiological and nonradiological A–P thoracic diameter. The resultant Haller index was much more overestimated by the nonradiological method in subjects with obesity, in comparison to what observed in subjects without obesity in the validation study (bias of − 0.22 vs − 0.07). Despite the limits of the nonradiological method in the assessment of chest shape, the correlation between the two techniques for the Haller index estimation in subjects with obesity was moderate ($r = 0.58$).

To date, several echocardiographic studies conducted in subjects with obesity aimed at investigating subclinical characteristics of systolic and diastolic function assessed by 2D-STE analysis. These studies identified following clinical, biochemical and echocardiographic parameters to be independently associated with impaired left ventricular mechanics: hypertension and type 2 diabetes [38, 39], hyperglycaemia [40], BMI [41, 42], insulin resistance and hypertriglyceridemia [43–46], microalbuminuria [47], left ventricular hypertrophy and left ventricular mass [48–50].

Different from the above-mentioned studies, the present study employed the MHI as new anthropometric index for evaluating the influence of the anterior chest wall conformation on left ventricular myocardial strain in subjects with obesity. The results of our study would exclude the existence of a metabolic cardiomyopathy/intrinsic myocardial dysfunction in the early stages of obesity and would support the concept of "metabolically healthy" obesity, as emphasized by previous authors [51, 52]. Indeed, compared to conventional clinical, biochemical and echoDoppler variables, the main anthropometrics, such as waist circumference and A–P thoracic diameter, showed a superior independent prognostic value for predicting an impaired left ventricular global longitudinal strain in subjects with obesity. A possible explanation for our findings could be related to an extrinsic thoracic compression on cardiac chambers, likely exerted by the combined action of abdominal adiposity (expressed by waist circumference) and a narrow A–P chest diameter. This "mechanical theory" was supported by the evidence of a strong correlation of LV-GLS with both radiological and nonradiological thoracic diameters and waist circumference. The reason for which BMI did not show any statistically significant correlation with LV-GLS in our study population may be related to a different model of obesity, android versus gynoid type, which may have contributed to a different degree of extrinsic thoracic compression and which was not specifically investigated in the present study.

Despite the evidence of an intimate relationship between OSAS and obesity which sinergically contribute to systemic arterial hypertension, as well as carotid and brachial atherosclerosis, and modify the original architecture and function of heart [53, 54], in our findings the presence of OSAS was not found to be independently associated with subclinical myocardial dysfunction. A possible explanation for this finding was related to the fact that the present study was conducted on a consecutive cohort of subjects with obesity, but otherwise healthy, without significant comorbidity and with a low prevalence of grade 3 obesity.

Consistent with our previous researches conducted in both adults [21] and infants [22] with pectus excavatum, in subjects with mitral valve prolapse [23] and in healthy pregnant women [24], the present study confirmed the important role exerted by the chest shape in influencing cardiac kinetics and function in subjects with obesity, also. Even in presence of a more circular transversal thoracic shape, a shorter A–P thoracic diameter was responsible for the impairment in left ventricular deformation indices due to a compressive phenomenon, in the absence of any intrinsic myocardial dysfunction, in subjects with obesity.

Chest shape assessment should be implemented in the clinical evaluation of subjects with obesity and without structural heart disease. The eventual impairment in myocardial strain indices observed in these subjects appears to be primarily related to anthropometrics such as waist circumference and a narrow A–P thoracic diameter. These factors may also be responsible for symptoms such as dyspnea and fatigue which are commonly detected among subjects with obesity. Physical exercise, hypocaloric diet and weight loss should be recommended in these subjects at an early stage of obesity.

A number of limitations of the present study should be aknowledged. First, noninvasive thoracic measurements were compared to CXR rather than to computed tomography (CT) scan. The latter would have provided a more accurate assessment of thoracic diameters. Second, the present study did not perform HI and MHI assessment in subjects with obesity who were unable to stand in an upright position. Third, the sample size of subjects with obesity enrolled was limited and did not inlcude an external validation cohort. Moreover, the ruler employed for measuring the L–L thoracic diameter, designed by A.S. and GL.N., was constructed for our Cardiology Division only and is not available in other Cardiology Centers. In addition, the obesity duration was not assessed in our study population. Finally, insulin resistance determined by Homeostasis Model Assessment (HOMA) was not examined in all participants, because at our Center it is not used for non-diabetic individuals.

Conclusions

Despite a systematic overestimation of the nonradiological methodology in comparison to the standard radiological methodology, the MHI techique may provide a reliable

assessment of both thoracic diameters and Haller index in subjects with obesity.

This technique allows the clinicians a more immediate comprehension of the possible influence of chest wall conformation on the cardiac kinetics and function in subjects with obesity and without overt heart disease.

The impairment in left ventricular myocardial strain observed in subjects with obesity appears to be primarily related to extrinsic abdominal and thoracic compressive phenomena, rather than intrinsic myocardial dysfunction.

Further studies are needed to evaluate the relationship between myocardial strain indices and the type of obesity (android versus gynoid) and if a number of non-pharmacological measures, such as physical exercise, hypocaloric diet and weight loss, would improve myocardial strain parameters in subjects with obesity.

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Author contributions AS: Conceptualization; Data curation; Investigation; Methodology; Software; Visualization; Writing—original draft. RT and AG: Conceptualization; Data curation; Methodology; Software. GLN, MZ and ML: Conceptualization; Supervision; Validation; Writing—review and editing.

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Declarations

Conflict of interest We wish to confirm that there are no conflicts of interest associated with this publication. Andrea Sonaglioni declares that he has no conflict of interest. Gian Luigi Nicolosi declares that he has no conflict of interest. Roberta Trevisan declares that she has no conflict of interest. Alberto Granato declares that he has no conflict of interest. Maurizio Zompatori declares that he has no conflict of interest. Michele Lombardo declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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