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Predicting Clinical and Echocardiographic Response After Cardiac Resynchronization Therapy With a Score Combining Clinical, Electrocardiographic And Echocardiographic Parameters

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Running title: A score to predict clinical and echocardiographic response after cardiac resynchronization therapy

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Abstract

The L₂ANDS₂ score was previously found to be able to assess the probability of left ventricular (LV) remodeling. We sought to evaluate this score in terms of clinical outcomes: 275 heart failure patients, from 2 centres, implanted with a cardiac resynchronization therapy (CRT) device were followed at least 2 years after implantation. Baseline clinical, electrocardiographic and echocardiographic characteristics including left bundle branch block (LBBB), age >70 years, non-ischemic aetiology, LV end-diastolic diameter <40 mm/m², and septal flash by echocardiography were integrated in 4 scoring systems. Non-response to CRT was left ventricular reverse remodeling <15% at 6 months' follow-up and/or occurrence of major cardiovascular event (cardiovascular death or transplantation or assistance) during a clinical follow-up of at least 2 years. 97 patients (36%) demonstrated non-response to CRT. The L₂ANDS₂ score demonstrated the best predictive value (C-statistic of 0.783) for predicting absence of LV reverse remodeling and/or occurrence of major cardiovascular event during the 2 years follow-up compared to other scoring systems that don't include septal flash. A L₂ANDS₂ score ≤4 was associated with a worse outcome (38% survival vs 81% survival, hazard ratio 4.19, 95% CI 2.70-6.48, p <0.0001). In conclusion, the L₂ANDS₂ score is able to assess the probability of non-response to CRT in terms of no reverse LV remodeling and/or major cardiovascular event at long-term follow-up. Integrating septal flash in a scoring system adds value over LBBB only.

Key words: cardiac resynchronization therapy, heart failure, echocardiography, septal flash

Introduction

Despite the expected benefits of cardiac dyssynchrony imaging explored in numerous publications, no role has been allocated to optimize cardiac resynchronisation therapy (CRT) response.¹ However still ~30% of patients do not benefit from CRT even in latest trials, whatever criteria of response used.^{2,3} Recent guidelines mentioned that CRT is contra-indicated in patients with a QRS duration <130 ms.⁴ A multi-parametric approach with cardiac imaging could have additional value in some selected cases to help for clinical decision.^{5,6} It has been recently proposed to predict response to CRT throughout scores integrating clinical, electrical or echocardiographic parameters. In 2014, we described a score combining clinical parameters such as age, etiology of cardiomyopathy, QRS-morphology, left ventricular (LV) size and one qualitative parameter of LV-dyssynchrony that is the septal flash.⁷ Adding septal flash to clinical parameters and left bundle branch block (LBBB) morphology increased significantly its predictive value in terms of LV reverse remodeling 6 months after CRT. Hence, the aim of this study was to evaluate the impact of the L₂ANDS₂ score on clinical and echocardiographic detrimental mid-term outcomes after CRT.

Methods

The initial cohort consisted of 207 heart failure patients included retrospectively in 2 centers (Rennes University Hospital, Rennes and Saint Philibert Catholic University Hospital, Lille, France).⁷ Inclusion criterion was patient requiring a CRT device implantation according to recommendations: patients in NYHA functional class II, III or ambulatory class IV with LV ejection fraction $\leq 35\%$, QRS duration ≥ 120 ms.¹ Then 68 more patients were included according to same inclusion criteria for a final bicentric cohort of 275 heart failure patients. This study was performed in accordance with the principles outlined in the Declaration of

Helsinki on research in human subjects and with the procedures of the local Medical Ethics Committee.

Flow chart of the study is presented in Figure 1. All patients underwent clinical evaluation, 12-lead ECG, and echocardiography prior to implant. QRS duration and QRS morphology were measured and assessed by 2 clinical experts. QRS morphology was classified as either LBBB or non-LBBB (including right bundle branch block and non-specific intra-ventricular conduction delay).^{8,9} At 6-month follow-up, all patients were reassessed by echocardiography to determine LV reverse remodeling. Echocardiographic non responders were defined as those with <15% decrease in LV end-systolic volume as compared with baseline.^{10,11} Patients were seen for a medical visit at each time they required further evaluation due to a worsened clinical condition for a clinical follow-up of at least 2 years. Major cardiovascular events were defined as cardiovascular death, heart transplantation or ventricular assistance.

Overall non-response to CRT was defined by a combined end-point including a <15% decrease in LV end-systolic volume at 6 months follow-up and/or occurrence of major cardiovascular event at the end of follow-up.

Each patient had a complete baseline echocardiography (GE, Vingmed System 7 or e9, Horten, Norway) including standard grey-scale apical views (grey-scale frame rate ≥ 50 Hz; 2-, 3-, and 4-chamber apical views). Off-line analysis was performed using a previously validated software pack (BT12-EchoPAC PC, GE Healthcare). Two-dimensional echocardiographic parameters were measured according to the guidelines of the American Society of Echocardiography.¹² LV volumes and ejection fraction were calculated using the biplane modified Simpson method. All measurements were averaged for 3 cardiac cycles.

Two clinical experts (AB, AM) visually assessed the presence of septal flash, which was validated if both were in agreement. Septal flash was defined as an early septal thickening/thinning within the isovolumic contraction period as detected both visually from the grey-scale short-axis view and 4 chamber views and from the parasternal long-axis view, short-axis view, and 4 chamber views obtained by M-mode. Basal, mid and apical septal segments were checked.¹³ Patients were categorized according to the presence or absence of septal flash. All the echocardiographic measurements were done at the echographic core laboratory (CIC-IT, INSERM, U1414, CHU Rennes). The analysis of the echo-recording was blinded from the clinical status and was performed according to a random way.

In all patients, the implantation procedure was performed during the month following the qualifying echocardiography. When required, patients received an implantable cardiac defibrillator. Devices were implanted with LV and right ventricular lead placement left to the discretion of the physician.

Patients' characteristics were given as percentages and means \pm standard deviation. Statistical analysis was carried out using the software Statview 5.0 (Abacus Concepts, Berkeley CA, USA) and Medcalc version 9.3.0 (MedCalc Software, Mariakerke, Belgium). Chi-square tests were employed to compare categorical variables between the 2 groups, and the 2 groups' continuous variables were compared, where appropriate, using the Student t test or the non-parametric Kruskal Wallis test. Cumulative incidence rates of events were calculated for all patients by subgroups of interest. A Cox proportional hazards regression model was used to calculate the hazard ratio (HR) of predictive factors and their 95% confidence interval (CI) for the incidence of events. A *P* value <0.05 was considered statistically significant.

The L₂ANDS₂ score has been validated in a previous publication.⁷ L₂ANDS₂ is an acronym for LBBB morphology on ECG (2 points awarded), Age \geq 70 years old, Non-ischemic etiology of the cardiomyopathy, left ventricular end-diastolic Diameter indexed (LVEDDi) <40 mm/m², Septal Flash (2 points). We then calculated the C statistic as a measurement of the predictive accuracy of the model incorporating CRT response factors (with regard to LV reverse remodeling and no cardiovascular event). The C statistics were compared with others using the DeLong test.¹⁴

Results

A total of 275 patients were included in the study. 65% of patients had a non-ischemic cardiomyopathy. Mean QRS duration was 161 ± 26 ms and 73% of patients had LBBB morphology on ECG. All patients were on stable, maximally tolerated, heart failure medication: 93% with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, 92% with a Beta-blocker, and 88% with a diuretic treatment. 92 patients (33%) demonstrated no LV remodeling at 6-month follow-up with $<15\%$ decrease in LV end-systolic volume (Figure 1). Six patients (2.2%) were lost to follow-up and excluded from analysis due to the impossibility of checking their vital status. Consequently, 269 patients with at least 2-year follow-up were analysed. During a median follow-up duration of 720 days (25% percentile: 720 days – 75% percentile: 1071 days), 21 (8%) major cardiovascular events were recorded. Sixteen patients died from a cardiovascular cause and 5 patients had a transplantation or ventricular assistance. No major cardiovascular event occurred before the echocardiographic evaluation at 6-month' follow-up. Of the cardiovascular deaths, 6% (1/16) occurred during the first 12 months, increasing to 63% (10/16) at 24 months and to 31% (5/16) after 24-month' following CRT implantation.

Overall, 97 patients (36%) demonstrated non-response (absence of LV reverse remodeling and/or occurrence of a major cardiovascular event) and 172 patients (64%) demonstrated positive response to CRT (LV reverse remodeling and no major cardiovascular event during follow-up) (Figure 1). Among the 183 patients with LV reverse remodeling, six of them demonstrated a major cardiovascular event during follow-up (29% of patients with a major cardiovascular event). Baseline characteristics of patients with positive CRT response versus patients with no response are displayed in Table 1. Patients who were classified responders were predominantly women, had a non-ischemic cardiomyopathy, had LBBB morphology on ECG and demonstrated more frequently septal flash on echocardiography than non-responders.

Four different scoring systems including either clinical and electrocardiographic or clinical, electrocardiographic and echocardiographic parameters were applied to the population and tested for positive response to CRT (Table 2). The population consisted of 259 patients (septal flash assessment available in 265 patients and 2 years clinical follow-up in 259 patients finally). The L₂ANDS₂ score had the best predictive value with C statistic of 0.783. There was an increased predictive value for each scoring system, particularly when adding septal flash parameter to a scoring system including LBBB morphology only (difference between areas: 0.101, $p < 0.001$) (Table 2). A scoring system including septal flash did better even if LBBB was quoted 2 in the LAND scoring system (difference between areas: 0.077, $p < 0.001$) (Figure 2). A L₂ANDS₂ score ≤ 4 was associated with a worse outcome than a score > 4 (38% survival vs 81% survival, hazard ratio 4.19, 95% CI 2.70-6.48, $p < 0.0001$) (Table 3 and Figure 3). After adjusting for QRS duration ≥ 130 ms and for medical therapy (angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers, Beta-blockers or diuretic use), a L₂ANDS₂ score ≤ 4 was still associated with a worse outcome (HR 5.35, 95% CI 3.24-8.85, $p < 0.0001$).

Discussion

This study confirms the clinical value of the L₂ANDS₂ score to assess the risk of non-response to CRT in terms of no LV reverse remodeling at 6 months or no major cardiovascular event. More than only assessing the probability of LV remodeling, it is also efficient in assessing the probability of a combined response to CRT, which might be valuable for the clinician. Our study also confirms the interest of combining multiple parameters including electrocardiographic but also echocardiographic parameters of LV dyssynchrony.

CRT have been demonstrated to improve long-term morbidity and mortality rates,¹⁵⁻¹⁷ changing the clinical management of heart failure patients. CRT, by restoring more synchronous contraction, induces LV-reverse remodeling and so LV-performance. Beyond the importance of LV-remodeling after CRT that has been demonstrated as a key factor for CRT response,^{10,18} prediction of long-term prognosis remains the main objective for physicians. Both LV remodeling and long-term prognosis are related as demonstrated in the REVERSE study.^{11,18} This relationship is not-linear but remains a valuable objective.²

We previously found that the L₂ANDS₂ score was able to assess the probability of LV reverse remodeling at 6-month' follow-up with a c-statistic of 0.75 in the validation cohort. The present study focused on non-response to CRT with a combined end-point including no LV remodeling at 6-month' follow-up and/or major cardiovascular event at long-term follow-up. Avoiding non-response to CRT is, in fact, a major issue for clinicians.² The L₂ANDS₂ score assessed the probability of non-response to CRT and was still valuable after adjustment for QRS duration and medical therapy.

After single echocardiographic predictors failed to predict CRT response, multi-parametric approaches have been proposed.^{6,19} The MADIT-CRT score integrated clinical parameters and LBBB morphology, amongst others, to LV volume.¹⁹ Park *et al.* evaluated the

combination of several echocardiographic parameters of LV and right ventricular dimensions and functions.²⁰ Other scoring systems have been proposed, combining only clinical parameters,²¹ or combining LV dyssynchrony parameters and LV function in addition with LV lead position such as the one proposed by Kydd *et al.*²² or Kang *et al.*²³

LBBB morphology is a key factor for predicting prognosis in CRT as it has been well demonstrated.²⁴ However, some observational studies including mechanical dyssynchrony parameters and/or inefficient deformation parameters^{25,26} have demonstrated a benefit for CRT patient selection. Assessment of septal flash is a simple way to visually identify an intra-ventricular dyssynchrony and demonstrated to provide significantly more incremental value than clinical characteristics for predicting LV reverse remodeling.^{13,27,28} The L₂ANDS₂ score takes in both these electrical and echocardiographic characteristics. It offers a well-balanced tool combining clinical, electrocardiographic and a qualitative dyssynchrony parameter.

Variability in echocardiographic measurements outside of an experienced echo lab setting is a concern; however, the inclusion of septal flash as a LV dyssynchrony parameter may help overcome this issue. Experience of visual assessment of septal flash can easily be achieved.^{26,29} Septal flash can be analysed off-line on a dedicated parasternal short-axis or an apical 4-chamber view. Other sophisticated parameters of heart function or structure, such as scar, could have been included in the model but the aim was to develop a simple and easy-to-use tool that can be displayed as an application for smartphone or tablet.

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Figure legends

Figure 1. Flow-chart of the study. CRT, cardiac resynchronization therapy; LV, left ventricular; MCVE, major cardiovascular events.

Figure 2. Receiver operating characteristics curve analysis testing the incremental value of a score including dyssynchrony indices over a score system including only clinical and electrocardiographic characteristics for predicting positive response to cardiac resynchronization therapy. LAND (blue), Left Bundle Branch Block, Age >70, Non-ischemic aetiology, Diameter (Left ventricular end-diastolic diameter indexed <40 mm) (1 point each); L₂AND (red), Left Bundle Branch Block (2 points), Age >70, Non-ischemic aetiology, Diameter (Left ventricular end-diastolic diameter indexed <40 mm) (1 point each); LANDS (orange), Left Bundle Branch Block, Age >70, Non-ischemic aetiology, Diameter (Left ventricular end-diastolic diameter indexed <40 mm), Septal Flash (1 point each); L₂ANDS₂ (green), Left Bundle Branch Block (2 points), Age >70, Non-ischemic aetiology, Diameter (Left ventricular end-diastolic diameter indexed <40 mm), Septal Flash (2 points).

Figure 3. Cardiovascular death, heart transplantation or ventricular assistance or lack of echo response during follow-up in patients with L₂ANDS₂ score >4 (blue) or ≤4 (red). L₂ANDS₂, Left Bundle Branch Block (2 points), Age >70, Non-ischemic aetiology, Diameter (Left ventricular end-diastolic diameter indexed <40 mm), Septal Flash (2 points).

Table 1. Baseline characteristics of patients with positive response to cardiac resynchronization therapy versus patients with no response. Non-response to cardiac resynchronization therapy was defined by a combined end-point including <15% decrease in LV end-systolic volume and/or occurrence of major cardiovascular event (cardiovascular death, ventricular assistance or heart transplantation) at the end of follow-up ($n = 269$).

Variable	CRT Responder		<i>P</i> -value
	YES ($n = 172$)	NO ($n = 97$)	
Age (years)	67 ± 11	68 ± 10	0.47
Men	109 (63%)	79 (81%)	0.002
NYHA functional class II/III/IV	59/111/2	22/73/2	0.19
Non-ischaemic cardiomyopathy	129 (75%)	46 (47%)	<0.001
Heart rate (bpm)	70 ± 13	69 ± 14	0.71
QRS duration (ms)	162 ± 24	160 ± 29	0.78
LBBB morphology	140 (81%)	56 (58%)	<0.001
NT-proBNP (ng/L)*	1468 (566-3500)	1973 (994-3700)	0.38
LV ejection fraction (%)	31 ± 10	28 ± 8	0.005
LV end-diastolic diameter indexed (mm/m ²)	36 ± 6	37 ± 6	0.08
LV end-diastolic volume (mL)	233 ± 67	240 ± 72	0.39
LV end-systolic volume (mL)	171 ± 54	178 ± 62	0.37
Septal flash ($n = 259$)	140 (84%)	43 (46%)	<0.001
LAND score	2.9 ± 0.8	2.4 ± 0.9	<0.001
LANDS score	3.7 ± 0.9	2.6 ± 1.0	<0.001

L ₂ ANDS ₂ score	5.3 ± 1.3	3.7 ± 1.6	<0.001
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*Median (Interquartile range); LAND, Left Bundle Branch Block, Age >70, Non-ischemic aetiology, Diameter (Left ventricular end-diastolic diameter indexed <40 mm) (1 point each); LANDS, Left Bundle Branch Block, Age >70, Non-ischemic aetiology, Diameter (Left ventricular end-diastolic diameter indexed <40 mm), Septal Flash (1 point each); L₂ANDS₂, Left Bundle Branch Block (2 points), Age >70, Non-ischemic aetiology, Diameter (Left ventricular end-diastolic diameter indexed <40 mm), Septal Flash (2 points); LBBB, Left Bundle Branch Block; LV, Left ventricular; NYHA, New York Heart Association.

Table 2. Comparison of c-statistics (95% confidence intervals) for predicting positive response to cardiac resynchronization therapy. Non-response to cardiac resynchronization therapy was defined by a combined end-point including <15% decrease in LV end-systolic volume and/or occurrence of major cardiovascular event (cardiovascular death, ventricular assistance or heart transplantation) at the end of follow-up ($n = 259$).

	C statistics*	95% Confidence Interval	
LAND	0.665	0.604 to 0.722	
L₂AND	0.706	0.647 to 0.761	
LANDS	0.767	0.710 to 0.817	
L₂ANDS₂	0.785	0.730 to 0.833	
	Difference between areas	95% Confidence Interval	P-value
LAND vs L₂AND	0.042	0.006 to 0.078	$P = 0.023$
LAND vs LANDS	0.102	0.059 to 0.144	$P < 0.001$
L₂AND vs L₂ANDS₂	0.078	0.038 to 0.119	$P < 0.001$

*C statistic calculated as area-under-the-curve for the receiver-operator characteristic (ROC)

LAND, Left Bundle Branch Block, Age > 70, Non-ischemic aetiology, Diameter (Left ventricular end-diastolic diameter indexed < 40 mm) (1 point each); LANDS, Left Bundle Branch Block, Age > 70, Non-ischemic aetiology, Diameter (Left ventricular end-diastolic diameter indexed < 40 mm), Septal Flash (1 point each); L₂ANDS₂, Left Bundle Branch

Block (2 points), Age > 70, Non-ischemic aetiology, Diameter (Left ventricular end-diastolic diameter indexed < 40 mm), Septal Flash (2 points).

Table 3. Sensitivity, specificity and likelihood ratios of L₂ANDS₂ for non-response to cardiac resynchronisation therapy: no LV reverse remodeling and/or occurrence of major cardiovascular event (*n* = 259*)

L ₂ ANDS ₂ [†] score	Nb of patients	(%)	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
<1	0	0	0,00	0,0 - 3,9	100,00	97,8 - 100,0	-	1,00
≤1	11	4	10,75	5,3 - 18,9	99,4	96,7 - 99,9	17,85	0,9
≤2	30	11	24,73	16,4 - 34,8	95,78	91,5 - 98,3	5,86	0,79
≤3	58	22	45,16	34,8 - 55,8	90,36	84,8 - 94,4	4,69	0,61
≤4	102	39	67,74	57,2 - 77,1	76,51	69,3 - 82,7	2,88	0,42
≤5	158	61	86,02	77,3 - 92,3	53,01	45,1 - 60,8	1,83	0,26
≤6	230	89	97,85	92,4 - 99,7	16,27	11,0 - 22,8	1,17	0,13
≤7	259	100	100,0	96,1 - 100,0	0,00	0,0 - 2,2	1,00	-

*Data lacking for 6 patients; [†]L₂ANDS₂ is an acronym for Left bundle branch block (doubled), Age >70, Non ischemic etiology, Diameter (indexed LVEDD <40 mm), Septal flash (doubled) ; +LR : Positive likelihood ratio ; -LR : Negative likelihood ratio.

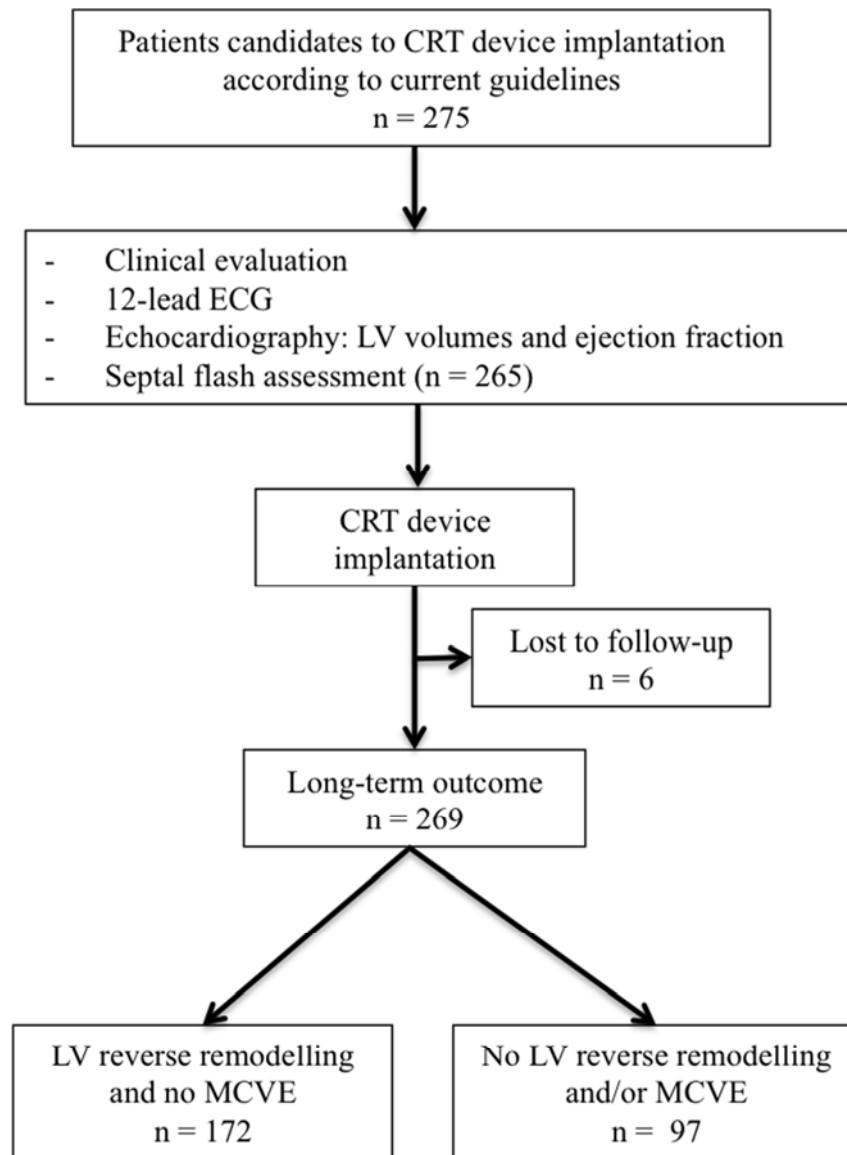
Figure 1.

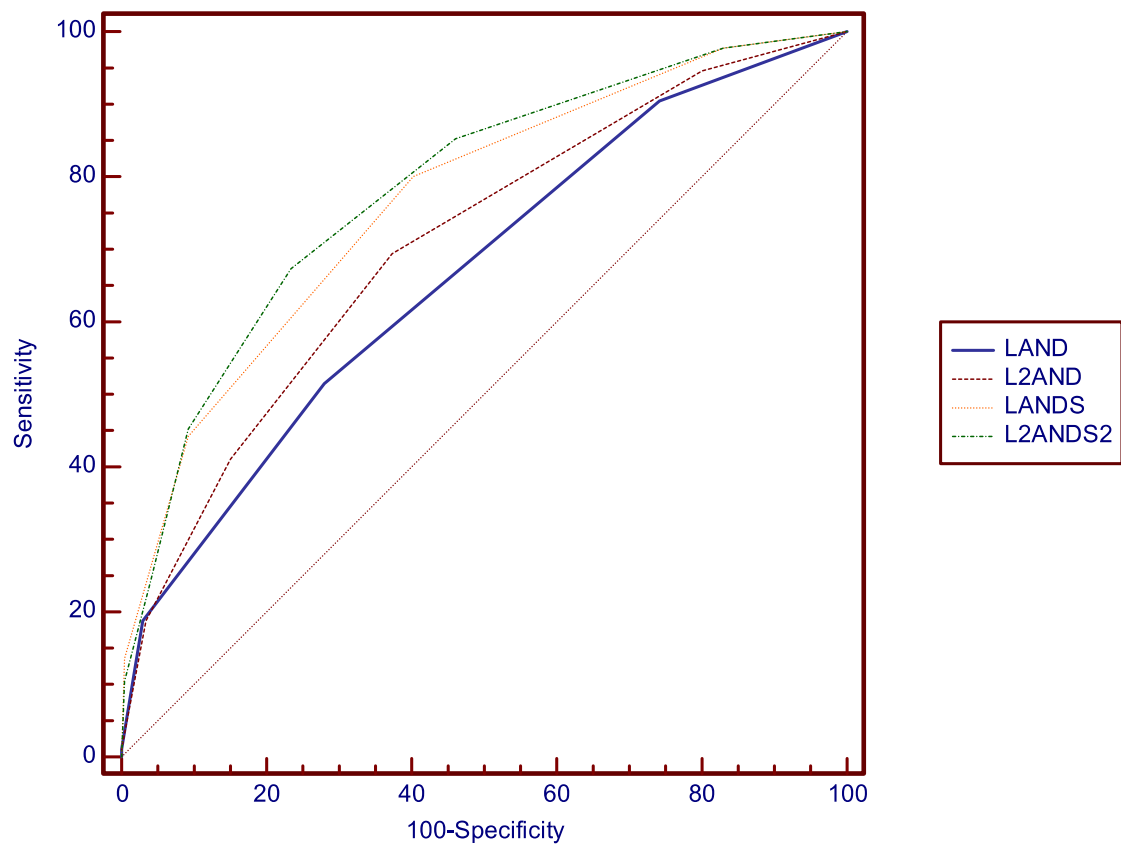
Figure 2.

Figure 3.

