ZargisCardioscan™ Aided Heart Murmurs Recognition has high negative predictive values when correlated and validated with Echocardiography: A Potential Dawn for Valvular Heart Disease Prevalence Studies in Rural India

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Original Article

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Abstract

Background

The purpose of this open-label study was to correlate the auscultation findings of ZargisCardioscan™ with the echocardiographic findings in our patient population who were referred for echocardiography so as to investigate and ensure the validity of this technology before instituting its applicability in community health events among rural Indian population.

Materials and Methods

This was a double blinded prospective correlation study in outpatients presenting for echocardiography. Methods: One hundred patients, who had presented for echocardiography at Cardiology Center of an academic university hospital in rural India, were enrolled in this double blinded prospective correlation study. Principal investigator who is a community medicine physician performed the auscultation of patients' hearts in sitting position. Subsequently, the

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www.nepjol.info/index.php/NJE
eISSN 2091-0800

ZargisCardioscan™ software was used to analyze the heart sounds auscultated by the 3M™ Littmann® Model 3200 stethoscope. Thereafter, the scheduled echocardiography for which the patient had presented to hospital was performed by co-investigator cardiologist who was blinded to the results obtained by the ZargisCardioscan™.Finally, all these data were statistically analyzed by blinded investigator for the presence of correlation between the two modalities.

Results

The most important finding was the high 90s negative predictive values when the stethoscope-software combination was used for auscultation and analysis of heart murmurs. Additionally, presence of isolated systolic murmurs had higher incidence of appreciable significant valvular lesions and presence of isolated diastolic murmurs primarily had underlying minimal-mild regurgitant valvular lesion, if any. The Bland-Altman Plot confirmed good correlation between stethoscope-echocardiography findings.

Conclusion

Stethoscope-software combination, 3M™ Littmann® Model 3200 and ZargisCardioscan™, accurately predicts the absence of valvular heart disease on echocardiography.

Keywords: ZargisCardioscan™; 3M™ Littmann® Model 3200;

Background

Rheumatic heart disease is highly prevalent in India [1-2] similar to other developing countries. A recent echocardiography based study [2] has further elucidated this fact that routine clinical examination misses out on appreciation of murmurs in clinically asymptomatic patients and has recommended more echocardiography based screening in general population for early recognition of rheumatic heart disease in asymptomatic patients. The only limitation to the echocardiography based screening is the involvement of highly skilled professionals (cardiologists) to perform and read these echocardiography scans; henceforth financial resources and personnel access-time limitations are major obstacle to these echocardiography based screenings in general population. To resolve these issues, ZargisCardioscan™[3] has been developed.

ZargisCardioscan™ (Zargis Medical Corp., Freehold, New Jersey, united States) is a computer based software technology that assists in recognition and differentiation of Class I heart murmurs auscultated by 3M™ Littmann® Model 3200 stethoscope (3M, St. Paul, Minnesota, United States). It had been shown to improve the sensitivity and specificity for specialist referrals by primary care physicians to confirm the diagnoses of the computer-recognized heart murmurs[4]. Moreover, this technology apparently does not depend on the sensitivity of clinician's ears to heart murmurs and hence, community health events that have usually focused in evaluating body mass indices, blood pressure and pulse rate measurements, and blood glucose and lipid profile sampling [5-6] for adjudging cardiovascular risk, can embrace this tool for early diagnosis and referral for valvular heart disease.

The purpose of this open-label study was to correlate the auscultation findings of ZargisCardioscan™ with the echocardiographic findings in our patient population who were referred for echocardiography so as to investigate and ensure the validity of this technology before instituting its applicability in community health events among rural Indian population.

Material and Methods

Study design and the participants:

The study was a Cross-sectional, epidemiological study conducted for six months –from Dec 2011 – April 2012. An open-label correlation study for assessing the feasibility and validity of the ZargisCardioscan™ use for early detection of heart murmurs at the community level was conducted among patients who had presented for echocardiography at Cardiology Center of an academic university hospital in rural India

Inclusion criteria:

The first 100 patients visiting Cardiology OPD and who were advised to undergo echocardiography were included.

Exclusion criteria:

Patients known to have pre-existing heart murmurs were excluded.

Sample size calculation:

A purposive sampling was done for assessing the feasibility and validity of the ZargisCardioscan™ use for early detection of heart murmurs

Ethical committee approval:

An institutional review board approval and written informed consent from all patients was taken before the start of study.

Statistical Analysis and Data Analysis:

The data (ZargisCardioscan™ and echocardiography) were statistically analyzed by investigator (blinded to either data acquisitions) for the presence of correlation between the two modalities. Chi-square test and Fisher Exact Test was applied for comparing proportions and ANOVA test was applied for comparing continuous data. Bland-Altman plot was prepared for correlating the two modalities. $P<0.05$ was considered significant.

Methodology:

After taking informed consent, the principal investigator, a community medicine physician performed the auscultation of patients' hearts in sitting position. Subsequently, the ZargisCardioscan™ software was used to analyze the heart sounds auscultated by the 3M™ Littmann® Model 3200 stethoscope. The heart auscultation was performed at all four auscultation sites on the chest: aortic area in second intercostal space on right parasternal line, pulmonary area

in second intercostal space on left parasternal line, tricuspid area in fourth intercostal space on left parasternal line and cardiac apex (mitral area) in fifth intercostal space on midclavicular line. The analysis by ZargisCardioscan™ about presence and absence of systolic and/or diastolic murmurs were recorded. Sub-analysis by ZargisCardioscan™ further confirmed whether the auscultated systolic murmur was Class I murmur based on its grade and occurrence-time in cardiac cycle; all auscultated diastolic murmurs were considered Class I murmur based on the American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines for the Management of Patients with Valvular Heart Disease[7] that classify murmurs in asymptomatic patients as Class I murmurs if they are diastolic or continuous or holosystolic or late systolic or mid-systolic (grade 3 or higher).

Subsequently, the scheduled echocardiography for which the patient had presented to hospital was performed by a co-investigator cardiologist who was blinded to the results obtained by the ZargisCardioscan™. All the echocardiography results were tabulated according to the presence of valvular lesions (stenoses and/or regurgitations) and other structural as well as functional cardiac abnormalities detected on echocardiography.

Result:

One hundred patients consented for the participation in the study. For comparative and correlation analyses with Class I murmurs as assessed by stethoscope related software, all stenoticvavular lesions were considered significant findings per echo-cardiologists' recommendations and all except minimal-mild regurgitant valvular lesions were considered significant echocardiographic findings.

The stethoscope/software findings were compared and correlated as screening test findings to the confirmatory test findings of echocardiography. The comparative analyses based on these subdivisions are shown in Tables 1-2.

The sample size was too small to correlate the sites of appreciation for murmurs and site-corresponding underlying valvular lesions, and therefore site-specific (for example aortic site murmur to echocardiography confirmed aortic lesion) correlation analysis between the two methods (stethoscope-software vs. echocardiography) was not performed. However, while correlating in the remaining parameters, the most important findings were the high values of negative predictive values during the sub-group analyses in patients irrespective of the absence or presence of structural or functional co-morbidities other than the valvular heart disease (Table 2).

The co-morbidities as reported in echocardiography reports included diastolic dysfunction and its grading, left ventricular hypertrophy, pulmonary hypertension and its severity, regional wall or global hypokinesia of ventricular walls, and dilated heart chambers. Similar sub-group analyses in male patients as well as female patients showed high negative predictive values for the heart murmurs screening with stethoscope-software (3M™ Littmann® Model 3200 and ZargisCardioscan™).

Table 1: Demographics Comparisons for Stethoscope-Software and Echocardiography correlations

STETH-ECHO CORRELATION	PATIENT'S AGE			P Value
	Mean (in years)	Standard Deviation (in years)	Number of Patients	
True Positives	55.66	12.73	64	0.07 (ANOVA)
True Negatives	43.67	15.71	9	
False Negatives	53	10.93	5	
False Positives	56.27	12.71	22	
STETH-ECHO CORRELATION	PATIENT'S SEX			P Value
	Male	Female	Total	
True Positives	42	22	64	0.07 (FISHER EXACT TEST 2x4 Table)
True Negatives	3	6	9	
False Negatives	1	4	5	
False Positives	17	7	22	
Total	61	39	100	
STETH-ECHO CORRELATION	CO-MORBID STRUCTURAL OR FUNCTIONAL ABNORMALITY ON ECHOCARDIOGRAPHY			P Value
	None Present	One or More Present	Total	
True Positives	23	41	64	0.19 (FISHER EXACT TEST 2x4 Table)
True Negatives	1	8	9	
False Negatives	0	5	5	
False Positives	5	17	22	
Total	29	71	100	

Abbreviation: STETH-ECHO means Stethoscope based Software Finding-Echocardiography Finding in regards to Class I Heart Murmurs screened by Software termed as Positive Finding-Valvular Heart Disease confirmed by Echocardiography Termed as Positive Finding

The differences in the predictive values were insignificantly different when the patients were compared based on their age (P=0.07), sex (P=0.07) and echocardiographic co-morbidity (P=0.19) as shown in Table 1. Subdivisions based on the type of murmur (diastolic and systolic murmurs) and severity of the lesion (minimal-mild regurgitation vs. significant valvular lesion including all stenotic lesions and moderate-severe regurgitant lesions) demonstrated that presence of isolated systolic murmurs had higher incidence of appreciable significant valvular lesions and presence of isolated diastolic murmurs primarily had underlying minimal-mild regurgitantvalvular lesion, if any (Table 3).

Based on the abovementioned observations and for graphical correlations, 3M™ Littmann® Model 3200 stethoscope and ZargisCardioscan™ software based murmurs and echocardiography based valvular lesions were graded to generate Bland-Altman plot (Stethoscope: No murmur=Grade 1; Diastolic Murmur=Grade 2; Systolic Class I Murmur=Grade 3) (Echocardiography: No Valvular Lesion=Grade 1; Minimal-to-Mild Regurgitant Valvular Lesion=Grade 2; Any Valvular Lesion except Minimal-to-Mild Regurgitant Valvular Lesion=Grade 3).

Grade Correlation Plot (Figure 1) showed good correlation between stethoscope-echocardiography findings (Pearson coefficient R=0.3232; P<0.01) that was confirmed with Bland Altman Plot (Figure 2; R=0, P>0.99).

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Table 2: Statistical Analyses for Stethoscope-Software as Screening Heart Murmur Modality vs. Echocardiography as Confirmatory Modality

CUMULATIVE COMPARISON				
	ECHO POSITIVE	ECHO NEGATIVE	Total	Statistical Values
STETH POSITIVE	9	22	31	PPV = 0.29
STETH NEGATIVE	5	64	69	NPV = 0.93
Total	14	86	100	Type II Error (BETA)= 0.36
Statistical Values	SENS = 0.64	SPEC = 0.74	Type I Error (ALPHA)= 0.26	Power (1-BETA) = 0.64
COMPARISON IF NO CO-MORBIDITY ON ECHO				
	ECHO POSITIVE	ECHO NEGATIVE	Total	Statistical Values
STETH POSITIVE	1	5	6	PPV = 0.17
STETH NEGATIVE	0	23	23	NPV = 1
Total	1	28	29	Type II Error (BETA)= 0
Statistical Values	SENS = 1	SPEC = 0.82	Type I Error (ALPHA)= 0.18	Power (1-BETA) = 1
COMPARISON IF CO-MORBIDITY PRESENT ON ECHO				
	ECHO POSITIVE	ECHO NEGATIVE	Total	Statistical Values
STETH POSITIVE	8	17	25	PPV = 0.32
STETH NEGATIVE	5	41	46	NPV = 0.89
Total	13	58	71	Type II Error (BETA)= 0.38
Statistical Values	SENS = 0.62	SPEC = 0.71	Type I Error (ALPHA)= 0.29	Power (1-BETA) = 0.62
COMPARISON IN MALE PATIENTS				
	ECHO POSITIVE	ECHO NEGATIVE	Total	Statistical Values
STETH POSITIVE	3	15	18	PPV = 0.17
STETH NEGATIVE	1	42	43	NPV = 0.98
Total	4	57	61	Type II Error (BETA)= 0.25
Statistical Values	SENS = 0.75	SPEC = 0.74	Type I Error (ALPHA)= 0.26	Power (1-BETA) = 0.75
COMPARISON IN FEMALE PATIENTS				
	ECHO POSITIVE	ECHO NEGATIVE	Total	Statistical Values
STETH POSITIVE	6	7	13	PPV = 0.46
STETH NEGATIVE	4	22	26	NPV = 0.85
Total	10	29	39	Type II Error (BETA)= 0.4
Statistical Values	SENS = 0.6	SPEC = 0.76	Type I Error (ALPHA)= 0.24	Power (1-BETA) = 0.6

Abbreviation: STETH means Stethoscope based Software Finding and Class I Heart Murmurs screened by Software termed as STETH POSITIVE;ECHO means Echocardiography Finding and Valvular Heart Disease confirmed by Echocardiography Termed as ECHO POSITIVE;Statistical Abbreviation: SENS=Sensitivity;SPEC=Specificity; PPV=Positive Predictive Value; NPV=Negative Predictive Value

Table 3: Sub-Group Classification Analyses for Stethoscope-Software for Variable Heart Murmur Type vs. Echocardiography for Variable Severity of Valvular Lesion

SUB-CLASSIFICATION BASED ON TYPE OF MURMURS ONLY				
MURMUR TYPE	NO VALVULAR LESION EXCEPT MINIMAL-MILD REGURGITATION	SIGNIFICANT VALVULAR LESION	Total	P Value
None	64	5	69	0.0009 (CHI SQUARE TEST)
Diastolic	14	1	15	
Systolic	6	5	11	
Both Systolic and Diastolic	2	3	5	
Total	86	14	100	
SUB-CLASSIFICATION BASED ON TYPE OF MURMURS AND SEVERITY OF VALVULAR LESION				
MURMUR TYPE	NO VALVULAR LESION	MINIMAL-MILD REGURGITATION	SIGNIFICANT VALVULAR LESION	P Value
None	39	25	5	0.0004 (FISHER EXACT TEST 2x4 Table)
Diastolic	7	7	1	
Systolic	2	4	5	
Both Systolic and Diastolic	1	1	3	
Total	49	37	14	

Discussion:

Background relevant information:

The stethoscope-software combination (3M™ Littmann® Model 3200 and ZargisCardioscan™) [7] has been designed to assist physicians in clinical heart examination. The heart sounds are auscultated by 3M™ Littmann® Model 3200 stethoscope and these sounds are wirelessly communicated to the personal computer (Windows system only) through a blue Universal Serial Bus (USB) Dongle. Subsequently, ZargisCardioscan™ software installed in the personal computer analyzes these sounds to recognize heart murmurs and then classify them for-or-against inclusion as Class I murmurs based on software's algorithm involving murmurs' intensity, timing and location in the cardiac cycle. The Class I murmur identification is primarily employed in asymptomatic patients and is meant to recognize diastolic or continuous or holosystolic or late systolic or mid-systolic (grade 3 or higher) murmurs in these patients so that echocardiography referrals per ACC/AHA recommendations can be initiated in these apparently asymptomatic patients. Even though this stethoscope-software combination has been primarily used in asymptomatic patients, we planned this validation study who had suspected cardiac pathology related symptoms and were referred to our Cardiology Center for echocardiography to rule in or rule out the underlying cardiac pathology if any. The better experimental model could have been the screening larger population at risk for rheumatic heart disease in rural India

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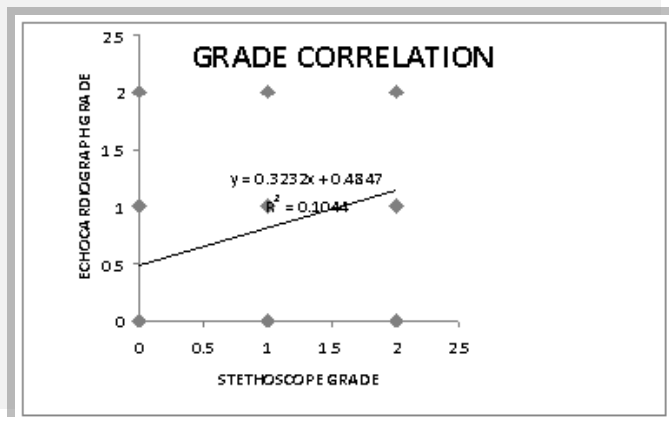
(say school-going children) with stethoscope-software combination, and subsequently correlating with on-site screening echocardiography; but that experimental model would have required a larger research funds especially to compensate for large numbers of on-site screening echocardiography performed by the co-investigator cardiologist. As our study patients were getting an in-hospital echocardiography that was unrelated to his/her inclusion in our research study, we did not require any separate research funds to compensate for in-hospital echocardiography by the co-investigator cardiologist. Therefore, due to paucity of research funds, we planned this small-number in-hospital study to make case for-or-against the larger studies and future use in at-risk population in rural India.

Figure 1: Grade Correlation between Stethoscope-Software Recognized Murmur and Echocardiography Identified Valvular Lesion. Correlation R = 0.3232 (P<0.01). Slope = 0.3232 (P<0.01). Intercept = 0.4847 (P<0.01).

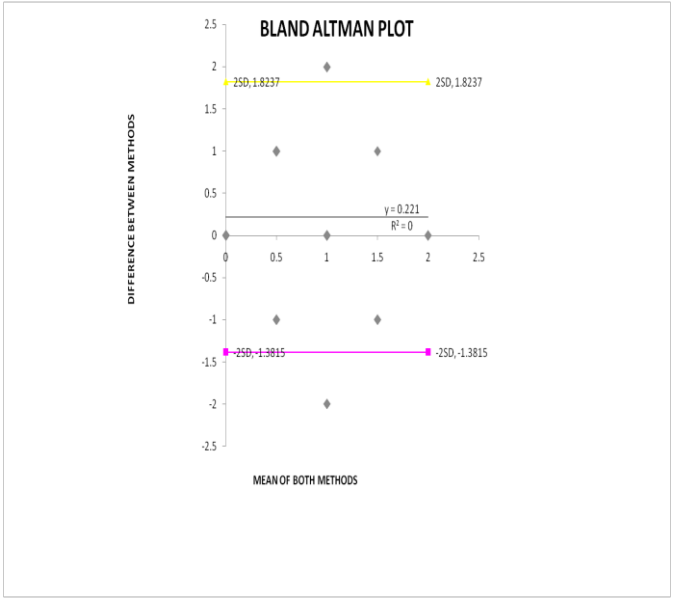


Critical Issues:

As the software graphically display and store the analyzed heart sounds as acoustic signals, the stored phonocardiographic displays can be potentially used to store in electronic medical records as well as paper medical records as printouts. Even though the auscultated heart sounds can be "visible" as waveform displays, few technical issues related to acoustic signal acquisition are needed to be watched for. The acoustic signal acquisition will not be possible in severely obese patients as similar to difficult auscultation with regular analog stethoscope. The heart rates of the patients should fall in the range 50-120 beats per minute and minimum three beats cycle at each auscultation site is essential to completely record the graphical display of heart sounds. Background noises from personnel and unrelated devices as well as operators' hand-motion artifacts will interfere with/or blur the acoustic signal acquisition. However the volume level of electronic stethoscope (3M™ Littmann® Model 3200) will not matter in the acoustic signal acquisition. As communication between the stethoscope and personal computer is through USB dongle, other active but unrelated Wi-Fi networks as well as microwaves will interfere in transmission of acoustic signals from stethoscope to personal computer.

Although these cautions in regards to use of this stethoscope-software combination may appear to be operator dependent, these cautions are much simpler to learn. Even trained personnel under the supervision of licensed physicians can easily master to acquire and analyze these acoustic signals for significant heart murmurs. Although the finality for interpretation of clinical heart examination will still rest upon the licensed physicians; however, the community health events for screening rheumatic heart disease in asymptomatic patients can be completed in abundance and much more rapidity by trained personnel under direct supervision of licensed physicians without relying on licensed physicians' ears personally listening to each and every individual presenting to these community health events. Although the supervising primary care physicians at these stethoscope-software combination based community health events will review patients' medical history before interpreting the results of ZargisCardioscan™ an d deciding for-or-against the need of referral to in-hospital echocardiography, these community health events will be financially more plausible and feasible for assessing prevalence of rheumatic heart disease in the larger populations-at-risk than on-site screening echocardiography based community health events as suggested by Saxena et al [2].

Figure 2: Bland-Altman Plot between Stethoscope-Software Recognized Murmur and Echocardiography Identified Valvular Lesion based on Mean of Methods and Difference between Methods. Correlation R = 0 (P>0.99). Slope = 0 (P>0.99). Intercept = 0.2211 (P=0.05).



Although the ZargisCardioscan™ provides site-specific significance of the detected murmurs, however, our study's sample size was too small to correlate the sites of appreciation for murmurs and site-corresponding underlying valvular lesions, and hence site-specific correlation analysis between the two methods was not performed. The future larger population-at-risk studies can

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elicit the site-specific correlation analysis wherein there can be larger numbers of asymptomatic patients with site-specific murmurs and corresponding valvular lesion as appreciated by stethoscope-software combination and echocardiography respectively. Even evidence (based on earlier reports that most likely had small sample populations) has utilized sensitivity and specificity to patient-level correlation [7] rather than site-level correlation.

Relevant Research Studies:

Compared to other reports which were based on stethoscope-software correlation with echocardiography [4, 7] as well as recent reports based on stethoscope-improvised software correlation with echocardiography [8, 9], our study results had only negative predictive values in high 90s as compared to high 90s sensitivity [4, 7-9] and high 90s positive predictive values [9] reported by those earlier reports. This may be related to our experimental model based on symptomatic patients rather than the asymptomatic patients as studied by other reports. This explanation is further validated by the fact that in our study population wherein there were no co- morbidities appreciable on echocardiography, the sensitivity was 100% (Table 2) suggesting that the co-existence of structural or functional co-morbidity may attenuate the sensitivity scores of stethoscope-software combination based screenings. However, the high 90s negative predictive values appreciable in our study population suggest the validity of stethoscope-software combination based screening in regards of correctly predicting absence of valvular heart disease when there are no Class I murmurs appreciable per stethoscope-software combination.

Conclusion

In summary, stethoscope-software combination, 3M™ Littmann® Model 3200 and ZargisCardioscan™, accurately predicts the absence of valvular heart disease on echocardiography irrespective of patient's sex as well as presence of structural or functional non-valvular co-morbidities on echocardiography.

Limitation:

As the study was conducted among the patients coming to Cardiology OPD and has been advised to undergo ECHO Cardiography, the community based screening for cardiac murmurs will give true prevalence of valvularheart diseases.

Relevance of the study:

The study has provided baseline hospital based data for researchers that will lead way to community level survey to screening population with potential undiagnosed valvular lesions.

Future scope of the study:

A larger multi-centric community based studies are required to be conducted for detailed data collection.

Author's Contribution:

PA designed the study, collected the data and drafted manuscript. RK helped in designing the study and revision of the manuscript. SDK critically revised the manuscript. DG assisted in manuscript write up. TR helped in data analysis and interpretation. All the authors approved the final document.

Acknowledgements:

The authors duly acknowledge the Ethics Committee, HIHT University for giving approval for conducting this research study vide their letter no.: HIHT/PHARMA/E-1/2011/90 dated: 07.03.2011.

No funding was received from any agency for carrying out this research work. However, ZargisCardioscan™ software and 3M™ Littmann® Model 3200 stethoscope were provided by Deepak Gupta, MD, Anesthesiologist, Detroit Medical Center/Wayne State University, Detroit, Michigan, United States from his personally owned equipments' inventory on loan basis (academic / research purposes only) only as a gesture of supporting medical research under the principal investigator at the institution. There was no competing interest between the authors of this research study.

Conflict of interest:

None

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PMid:22956159

Article Information	
Article history	
Received	2nd January 2014
Received in revised form	13th June 2014
Accepted	25th June 2014