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# Echocardiographic assessment of diastolic function in non-ST elevation acute coronary syndrome patients and its association with in-hospital diagnosis

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**Abstract:** **Objective:** This study was conducted to evaluate the association of echocardiographic parameters used in left ventricular (LV) diastology with the early results of non-ST elevation acute coronary syndrome (NSTE-ACS) workup in the hospital.

**Methods:** This cross-sectional study was performed on patients presenting with acute chest pain and a diagnosis of NSTE-ACS including only patients with unstable angina (UA) and non-ST elevation myocardial infarction (NSTEMI). All patients underwent transthoracic echocardiography in the emergency room (ER) within 12 hours of the last episode of chest pain. An invasive approach was not uniformly pursued in all of the patients so analysis was performed in two different settings. First, analysis was performed in the patients that underwent coronary angiography (CAG) and echocardiographic data were compared between those with normal and abnormal CAG results. Finally, echocardiographic data of the patients with normal diagnostic results (i.e., normal exercise tolerance test (ETT), myocardial perfusion imaging (MPI) or coronary angiography (CAG) results) were compared with the data of the patients with abnormal test results.

**Results:** Eighty patients with a mean age of 54.43 ± 12.38 years were included in the study, of whom 57 (71.2%) were male. Fifty-three patients underwent CAG. In these 53 patients, there was significant difference in mitral annular velocity in early diastole (e'), ratio of mitral inflow velocity to e' (E/e'), left ventricular end-diastolic diameter (LVEDD) and left ventricular end-diastolic pressure (LVEDP) between patients with coronary artery involvement and those with normal coronary artery ($P<0.05$). The area under the receiver operating characteristic (ROC) curve to predict CAG results for e', E/ e', LVEDD and LVEDP was more than 0.65. The sensitivity and specificity of the LV diastolic dysfunction for predicting coronary involvement was 94.4% and 35.29%, respectively. Comparison of echocardiographic data between patients with normal test results (non-invasive and invasive) and those with abnormal diagnostic tests showed a significant difference in e', E/e', acceleration time of E, LV end-diastolic diameter index, size of interventricular septum and left atrial volume.

**Conclusion:** The results suggest that diastolic dysfunction data can be used as an adjunctive method to evaluate ACS patients in the ER.

**Keywords:** Acute Coronary Syndrome; Diastole; Echocardiography; Emergency Department; Left Ventricular Dysfunction

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## 1. Introduction

Acute coronary syndrome (ACS) is a prevalent leading cause of death worldwide (1-3). Based on electrocardiography (ECG) and biochemical findings, it has different presentations such as ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA). In patients with UA, cardiac biomarkers remain unchanged, adding more challenge to the diagnosis (4-6). Better management of non-ST elevation ACS (NSTE-ACS) cases, including NSTEMI and UA, is achieved by early risk stratification. Current guidelines recommend that high-risk patients should undergo coronary angiography (CAG) within 24 hours whereas those with lower risk may undergo CAG within 72 hours (5).

Studies have shown that following ACS, the diastolic function of the left ventricle changes as a result of alteration in the myocardial structure, and NSTE-ACS patients show changes in the trans-mitral blood flow due to left ventricular (LV) dysfunction (7). Although the diastolic dysfunction may be corrected following the removal of occlusion, a mild dysfunction is likely to persist for 24 hours (4). The role of echocardiography and, in particular, diastolic dysfunction assessment in early risk stratification has not yet been defined in NSTE-

ACS patients. As diastolic dysfunction occurs soon after coronary artery occlusion, it is hypothesized that diastolic function assessment may provide information that can be used in early risk stratification in the emergency room (ER), especially when the results of cardiac biomarkers are not yet ready. This study was conducted to evaluate the association of echocardiographic parameters used in diastology with the early results of NSTE-ACS workup in the hospital.

## 2. Methods

### *2.1. Study design and setting*

A cross-sectional study was conducted in an educational medical center in Tehran, Iran. Clinical Research Ethics Committee of the hospital approved the study and written informed consent was obtained from the patients. Management of the patients and decision-making regarding adoption of invasive vs. non-invasive testing were done by the in-charge attending cardiologist and the researchers had no contribution to the patients' workup.

### *2.2. Study population*

The current study was conducted on patients with acute chest pain presenting to the ER in whom a diagnosis of acute coronary syndrome was made based on the history, ECG findings, and/or biomarker results. The exclusion criteria were STEMI, non-sinus rhythm, more than moderate mitral regurgitation, mitral stenosis, any factor preventing precise assessment of diastolic function, diagnoses other than ACS in the course of hospitalization, history of diuretic consumption, and a left ventricular ejection fraction (LVEF) below 45%. Eighty consecutive patients were enrolled in this research.

Based on the Thrombolysis in Myocardial Infarction (TIMI) risk score, ACS patients were categorized into three groups of low risk (score: 0-2), intermediate risk (score: 3-4) and high risk (score: 5-7). CAG was done in intermediate and high-risk patients, whereas low-risk patients underwent non-invasive methods including exercise tolerance test (ETT) or myocardial perfusion imaging (MPI) with dipyridamole or dobutamine infusion. Echocardiography was performed for all patients within 12 hours of the last episode of chest pain. Although CAG is the gold standard method for evaluation of coronary artery disease, an invasive approach was not considered in low-risk patients or patients with negative non-invasive test results. No follow-up was considered after discharge in this research.

### *2.3. Patients' assessment and data collection*

Upon admission, the patients were visited by the ER physicians and proper testing and management were implemented. For each patient, a detailed history regarding cardiac risk factors was taken. Further diagnostic workup was considered after cardiology consultation. An invasive approach was not uniformly pursued in all the patients; therefore, analysis was carried out in two different settings. First, analysis was performed in the patients that underwent CAG and echocardiographic data were compared between those with normal and abnormal CAG findings including mild CAD, single-vessel, two-vessel, three-vessel and multi-vessel CAD. Finally, the echocardiographic data of the patients with normal diagnostic results (i.e., normal ETT, MPI or CAG results) were compared with the data of the patients with abnormal test results.

#### 2.3.1. 2D Echocardiography

Transthoracic echocardiography (TTE) was performed in the ER within 12 hours after the last episode of the chest pain. All echocardiographic examinations were performed and saved by one cardiologist who was aware of the purpose of the study but had no role in medical management or clinical decision-makings. Measurement of parameters and analysis of diastolic function were performed offline by another expert echocardiography fellow who was blind to the patients' history and had no contribution to their medical management. Echocardiography was done using the General Electric Vivid S5 or Affinity 50 (Philips) machine. Evaluation of a normal or abnormal LV diastolic pattern was done according to the 2009 American Society of Echocardiography (ASE) guideline (8).

Echocardiographic parameters are shown in figure 1. In the apical four-chamber view, a 3-mm sample volume was placed in the tip of mitral leaflets and peak velocity in early diastole (E wave), late diastole (A wave) and deceleration time (DT) of the E wave to the baseline were measured. The velocity of the septal mitral annulus in early (e') and late (a') diastole were also measured in tissue Doppler imaging (TDI). Other parameters that aided in the assessment of LV diastolic dysfunction included LA volume index, and TR velocity. To evaluate pulmonary venous (PV) flow, a 3-mm sample volume was placed in the orifice of right lower pulmonary vein in the apical four-chamber view to measure peak velocity and velocity time integral (VTI) of systolic, diastolic and atrial flow reversal of the pulmonary vein.

Abnormal LV diastolic patterns include mild, moderate and severe LV diastolic dysfunction based on the ASE guideline (9). Multiple supplementary indices that are not routinely measured in clinical diastology including peak acceleration rate of mitral E wave and peak acceleration rate of mitral e' wave were also measured using echocardiography (Affinity 50) or were calculated by the operator in the GE vendor (Figure 1. B, D) using the following formula:

Peak acceleration rate ($cm/sec^2$) = Velocity (cm/sec) divided by acceleration time (sec)

#### 2.3.2. Coronary angiography

Patients with a TIMI score ≥3 as well as those with high-risk clinical presentations or positive results of non-invasive test underwent coronary angiography. In the cath lab, left ventricular end-diastolic pressure (LVEDP) was measured in all patients at the start of the procedure with a pigtail catheter before contrast injection. Routine administration of intra-

venous (IV) crystalloid fliud 1cc/kg/min was started in the cath lab after inavasive measurement of LVEDP.

### *2.4. Statistical analysis*

Quantitative data are reported as mean and standard deviation (SD) while qualitative data are described as frequency and relative frequency. Data were analyzed using independent t-test (parametric variables) and Mann-Whitney test (non-parametric variables). The normality assumption was assessed using the Kolmogorov-Smirnov test. P values less than 0.05 were considered significant. The discrimination power of echocardiography variable for diagnosis of CAG abnormality was assessed using the area under the receiver operating characteristic (ROC) curve (AUC-ROC). In addition, the AUC-ROC was calculated for a combination of significant echocardiographic variables and significant difference was checked with the chi-square statistic. The sensitivity, specificity, positive and negative likelihood ratios (PLR and NLR), and positive and negative predictive values (PPV and NPV) with their 95% confidence intervals (CI) were calculated in different cut-off points for significant AUC-ROC echocardiographic variables. The best cut-off point of each echocardiographic variable for diagnosis of "abnormal CAG" was selected using the Youden's J statistic. All analyses were performed using the SPSS software version 20 and STATA software version 14.

## 3. Results

### *3.1. Patients' characteristics*

Eighty patients with a mean age of 54.43 ± 12.38 years were included in the present study. Fifty-seven patients (71.2%) were male. Baseline characteristics are presented in table 1. Only 14 patients (17.5%) were considered intermediate- or high-risk for adverse events based on the TIMI risk score (TIMI score ≥ 3). Fifty-three patients (66.2%) underwent coronary angiography based on the TIMI score, clinical presentation, or non-invasive test results.

### *3.2. Diagnostic workup of acute coronary syndrome*

All of the subjects underwent transthoracic echocardiography (TTE) in the emergency room (ER) within a maximum of 12 hours from last chest pain episode.

Further assessment of chest pain was done using different modalities including exercise tolerance test (ETT), myocardial perfusion imaging (MPI) and coronary angiography (CAG). The diagram of the ACS workup is presented in figure 2. After diagnostic evaluation, coronary artery involvement was confirmed by CAG in 45% (36/80) of the study population (Table 1).

The mean left ventricular end-diastolic pressure (LVEDP) measured invasively in the cath lab was 14.54 mmHg (SD: 1.75, IQR= 12.0-18.0). Table 2 presents a summary of the echocardiographic parameters of the study population.

**Table 1** Baseline characteristics of participants

| Characteristics (n = 80) | Mean ± SD or n (%) |
|---|---|
| **Age** | 54.43 ± 12.38 |
| **Sex, men** | 57/80 (71.2) |
| **Weight (kg)** | 77.78 ± 13.05 |
| **Height (cm)** | 171.26 ± 8.24 |
| **BMI (kg/m$^2$ )** | 26.48 ± 3.93 |
| **Time to echo (hours)** | 7.04 ± 2.01 |
| **CAG** | 53 (66.2) |
| Normal | 17 (21.3) |
| Mild CAD | 10 (12.5) |
| Single-vessel | 1 (1.3) |
| Two-vessels | 6 (7.5) |
| Three-vessels | 14 (17.5) |
| Multi-vessels | 5 (6.3) |
| **LVDD by echo** | 63 (78.7) |
| Normal | 17 (21.3) |
| Mild | 44 (55.0) |
| Moderate | 18 (22.5) |
| Severe | 1 (1.3) |
| **MPI** | 8 (10.0) |
| Normal | 6 (7.5) |
| Positive* | 2 (2.5) |
| **ETT** | 27 (33.7) |
| Normal | 20 (25.0) |
| Positive | 7 (8.7) |
| Diabetes | 18 (22.5) |
| Dyslipidemia | 41 (51.2) |
| Hypertension | 24 (30.0) |
| Aspirin use within the last week | 20 (25.0) |
| Positive cardiac biomarker | 7 (8.8) |
| ST changes | 17 (21.3) |
| **Angina pectoris in the hospital course** | |
| None | 5 (6.3) |
| Once | 25 (31.3) |
| Twice | 41 (51.2) |
| Three times | 9 (11.2) |
| History of known CAD | 11 (13.8) |
| **TIMI risk score** | |
| 0 | 18 (22.5) |
| 1 | 27 (33.7) |
| 2 | 21 (26.3) |
| 3 | 4 (5.0) |
| 4 | 4 (5.0) |
| 5 | 6 (7.5) |
| **Body surface area** | 1.89 ± 0.18 |

BMI: Body mass index; CAD: Coronary artery disease; CAG: Coronary angiography; ETT: Exercise tolerance test; LVDD: Left ventricular diastolic dysfunction; MPI: Myocardial perfusion imaging; SD: Standard derivation; TIMI: Thrombolysis in Myocardial Infarction risk score

* Only patients who underwent MPI as the initial diagnostic test were included. In another 2 patients with positive ETT results, MPI was also done and the results were positive for ischemia.

In the remaining patients including those with negative results of non-invasive tests or those with normal CAG, other diagnoses including coronary spasm, microvascular involvement, and non-cardiac causes of chest pain were considered (no patient with obvious non-cardiac or non-anginal diagnosis was enrolled in the study). Of 53 patients that underwent

**Table 2** Echocardiographic data of study population

| Variable | Mean (SD) | Median (IQR) |
|---|---|---|
| Variable | Mean (SD) | Median (IQR) |
| E velocity (cm/s) | 66.43 (17.94) | 65.50 (57.25-75.88) |
| A velocity (cm/s) | 71.55 (24.92) | 71.0 (55.0-82.75) |
| E deceleration time (msec) | 237.39 (100.78) | 219.50 (162.0-287.25) |
| E acceleration time (msec) | 72.40 (21.94) | 70.0 (60.0-85.0) |
| Peak acceleration rate of mitral E velocity | 971.39 (424.56) | 925.0 (688.0-1186.25) |
| Septal e'(cm/s) | 6.85 (2.54) | 6.65 (5.0-7.78) |
| Septal a'(cm/s) | 9.08 (6.60) | 8.10 (7.0-9.75) |
| Septal e'acceleration time (msec) | 54.90 (15.68) | 53.0 (42.0-67.0) |
| Peak acceleration rate of mitral e' velocity | 151.71 (122.04) | 130.50 (100.0-163.50) |
| E/e' | 10.91 (3.84) | 10.0 (8.40-12.30) |
| LVEDV ($cm^3$) | 115.58 (36.27) | 113.0 (90.0-130.25) |
| LVESV ($cm^3$) | 53.24 (19.42) | 51.0 (40.0-64.5) |
| LVEF % (by Simpson's method) | 54.69 (7.17) | 53.85 (48.88-60.0) |
| LV end-diastolic diameter (cm) | 4.67 (0.39) | 4.70 (4.50-4.90) |
| Septum (cm) | 0.98 (1.05) | 0.80 (0.80-1.00) |
| LV end-systolic diameter (cm) | 3.30 (2.73) | 3.0 (2.60-3.30) |
| Posterior wall (cm) | 0.94 (1.04) | 0.80 (0.75-0.90) |
| Left atrial volume ($cm^3$) | 55.33 (17.06) | 56.20 (43.0-66.0) |
| Left atrial volume index | 29.43 (9.05) | (23.69-34.35) |
| Pulmonary vein S velocity (cm/s) | 54.08 (14.36) | 54.45 (42.0-63.0) |
| Pulmonary vein D velocity (cm/s) | 42.62 (11.50) | 40.0 (35.25-47.75) |
| Pulmonary vein S VTI (cm) | 14.24 (3.40) | 14.40 (12.20-17.0) |
| Pulmonary vein D VTI (cm) | 10.41 (3.40) | 10.0 (8.0-12.0) |
| A reversal velocity (cm/s) | 23.28 (5.30) | 22.0 (20.0-26.75) |
| A reversal duration (msec) | 133.8 (33.54) | 134.0 (113.75-155.0) |

SD: Standard derivation; CI: Confidence interval; IQR: Interquartile range (Q1-Q3);
LVEDV: Left ventricular end-diastolic volume; LVESV: Left ventricular end-systolic volume;
LVEF: Left ventricular ejection fraction; VTI: velocity time integral

invasive approaches, CAG findings were normal in 17 (32.1%) and abnormal in the remaining 36 (67.9%) patients.

### *3.3. Comparison of echocardiographic findings between patients with normal and abnormal CAG results*

Considering CAG results and a "normal" vs. "abnormal" LV diastolic pattern, a significant difference (P value=0.010) was observed in the LV diastolic pattern (normal/abnormal) between patients with normal and abnormal CAG results. Assessment of 36 patients with abnormal CAG and 17 patients with normal CAG showed LV diastolic dysfunction in 34 (94.4%) and 11 (64.7%) patients, respectively. The sensitivity and specificity for LV diastolic dysfunction for predicting coronary involvement was 94.44% (95%CI: 81.3 to 99.3) and 35.29% (95%CI: 14.2 to 61.7), respectively. In addition, the positive and negative likelihood ratios (PLR and NLR) were 1.46 (95%CI: 1.0 to 2.1) and 0.16 (95%CI: 0.04 to 0.7) and positive and negative predictive values (PPV and NPV) were 75.6% (95%CI: 60.5 to 87.1) and 75.0% (34.9 to 96.8), respectively.

The septal e' was significantly higher in the normal CAG category compared to abnormal CAG (mean: 7.82 vs 6.01 cm/s, P=0.002). In addition, the E/e' (mean: 8.92 vs 12.43, P<0.001), LV end-diastolic diameter (mean: 4.45 vs 4.79 cm, P=0.030), and invasive measurement of LVEDP in the cath lab (mean: 13.31 vs 15.08 mmHg, P<0.001) were significantly lower in the normal versus abnormal CAG group. There were no significant differences in other echocardiographic variables between normal and abnormal CAG groups (Table 3).

The area under the ROC curve was more than 0.65 for e' (0.768), E/e' (0.838), LV end-diastolic diameter (0.685), and invasive LVEDP measured in the cath lab (0.806) in the abnormal CAG group, which was significant (Table 3).

The best cut-off point of e' for abnormal CAG was ≤7.4 cm/s with 94.44% sensitivity and 58.82% specificity. The best cut-off point of E/e' for abnormal CAG was >9.5 with 80.56% sensitivity and 88.24% specificity. The best cut-off points of LV end-diastolic diameter and invasive LVEDP were >4.9 cm (36.11% sensitivity and 88.24% specificity) and >14 mmHg

**Table 3** Echocardiography results according to CAG category and area under ROC curve for these parameters

| Variable | Normal CAG (n=17) | Abnormal CAG (n=36) | P | Area under the ROC Curve (95% CI) | P |
|---|---|---|---|---|---|
| E velocity (cm/s) | 63.52 (9.94) | 68.19 (18.69) | 0.242 | 0.580 (0.43, 0.72) | 0.350 |
| A velocity (cm/s) | 70.35 (33.30) | 73.78 (21.91) | 0.499* | 0.558 (0.38, 0.74) | 0.499 |
| E deceleration time (msec) | 207.59 (103.68) | 251.25 (101.19) | 0.152 | 0.627 (0.46, 0.79) | 0.137 |
| E acceleration time | 76.29 (21.11) | 68.36 (26.93) | 0.084 | 0.648 (0.49, 0.80) | 0.062 |
| Peak acceleration rate of mitral E velocity | 832.24 (335.86) | 1043.31 (519.70) | 0.133 | 0.634 (0.48, 0.79) | 0.118 |
| e' (cm/s) | 7.82 (2.29) | 6.01 (2.37) | 0.002* | 0.768 (0.61, 0.93) | 0.001 |
| a' (cm/s) | 9.02 (2.44) | 9.70 (9.58) | 0.345* | 0.581 (0.41, 0.75) | 0.342 |
| e'acceleration time (msec) | 54.47 (14.45) | 53.89 (17.37) | 0.660* | 0.538 (0.37, 0.70) | 0.657 |
| Peak acceleration rate of mitral e' velocity | 156.47 (74.12) | 161.33 (169.11) | 0.905* | 0.623 (0.46, 0.79) | 0.140 |
| E/e' | 8.92 (3.89) | 12.43 (4.07) | <0.001* | 0.838 (0.70, 0.97) | <0.001 |
| LVEDV ($cm^3$) | 110.68 (42.38) | 123.55 (38.38) | 0.315* | 0.588 (0.41, 0.77) | 0.315 |
| LVESV ($cm^3$) | 51.46 (20.84) | 55.09 (19.91) | 0.565 | 0.567 (0.39, 0.74) | 0.461 |
| LVEF% (by Simpson's method) | 53.66 (6.30) | 54.43 (7.08) | 0.705 | 0.512 (0.37, 0.69) | 0.892 |
| LV end-diastolic diameter (cm) | 4.45 (0.48) | 4.79 (0.39) | 0.030* | 0.685 (0.53, 0.84) | 0.031 |
| Septum | 0.84 (0.15) | 1.16 (1.53) | 0.403 | 0.639 (0.47, 0.81) | 0.113 |
| LV end-systolic diameter (cm) | 2.88 (0.62) | 3.77 (4.01) | 0.104* | 0.639 (0.48, 0.80) | 0.105 |
| Posterior wall | 0.83 (0.10) | 1.10 (1.54) | 0.648* | 0.533 (0.37, 0.70) | 0.696 |
| Left atrial volume | 49.64 (18.06) | 59.93 (18.37) | 0.067 | 0.684 (0.52, 0.85) | 0.036 |
| Pulmonary vein S velocity (cm/s) | 54.08 (15.23) | 55.00 (16.37) | 0.846 | 0.525 (0.36, 0.69) | 0.768 |
| Pulmonary vein D velocity (cm/s) | 43.98 (7.94) | 45.19 (13.18) | 0.717* | 0.533 (0.37, 0.70) | 0.687 |
| Pulmonary vein S VTI (cm) | 13.48 (3.37) | 14.03 (3.82) | 0.615 | 0.512 (0.35, 0.68) | 0.891 |
| Pulmonary vein D VTI (cm) | 9.51 (2.52) | 11.45 (4.05) | 0.077 | 0.639 (0.48, 0.79) | 0.105 |
| A reversal velocity (cm/s) | 25.43 (6.93) | 22.83 (4.38) | 0.462* | 0.569 (0.39, 0.75) | 0.740 |
| A reversal duration (msec) | 130.35 (42.97) | 135.72 (32.71) | 0.652 | 0.603 (0.41, 0.80) | 0.230 |
| Invasive LVEDP measured in cath lab (mmHg) | 13.31 (1.58) | 15.08 (1.55) | <0.001 | 0.806 (0.67, 0.94) | <0.001 |

*P-value based on non-parametric test

SD: Standard derivation; CI: Confidence interval; LVEDV: Left ventricular end-diastolic volume; LVESV: Left ventricular end-systolic volume; LVEF: Left ventricular ejection fraction; VTI: Velocity time integral; LVEDP: Left ventricular end-diastolic pressure

**Table 4** Accuracy of LVEDP, E/e', e', and LVEDD for diagnosis of abnormal coronary angiography (CAG)

| Cut-off | Sensitivity | Specificity | PLR | NLR | PPV | NPV |
|---|---|---|---|---|---|---|
| | (95% CI) | | | | | |
| e' (cm/s) | | | | | | |
| ≤6.5 | 63.89 (46.2, 79.2) | 82.35 (56.6, 96.2) | 3.62 (1.3, 10.4) | 0.44 (0.3, 0.7) | 88.5 (69.8, 97.6) | 51.9 (31.9, 71.3) |
| ≤7 | 77.78 (60.8, 89.9) | 64.71 (38.3, 85.8) | 2.20 (1.1, 4.3) | 0.34 (0.2, 0.7) | 82.4 (65.5, 93.2) | 57.9 (33.5, 79.7) |
| ≤7.2 | 86.11 (70.5, 95.3) | 64.71 (38.3, 85.8) | 2.44 (1.3, 4.7) | 0.21 (0.09, 0.5) | 83.8 (68.0, 93.8) | 68.8 (41.3, 89.0) |
| ≤7.4* | 94.44 (81.3, 99.3) | 58.82 (32.9, 81.6) | 2.29 (1.3, 4.1) | 0.09 (0.02, 0.4) | 82.9 (67.9, 92.8) | 83.3 (51.6, 97.9) |
| ≤7.7 | 94.44 (81.3, 99.3) | 52.94 (27.8, 77.0) | 2.01 (1.2, 3.3) | 0.10 (0.03, 0.4) | 81.0 (65.9, 91.4) | 81.8 (48.2, 97.7) |
| ≤7.8 | 94.44 (81.3, 99.3) | 47.06 (23.0, 72.2) | 1.78 (1.1, 2.8) | 0.12 (0.03, 0.5) | 79.1 (64.0, 90.0) | 80.0 (44.4, 97.5) |
| E/e' | | | | | | |
| >9 | 86.11 (70.5, 95.3) | 70.59 (44.0, 89.7) | 2.93 (1.4, 6.2) | 0.20 (0.08, 0.5) | 86.1 (70.5, 95.3) | 70.6 (44.0, 89.7) |
| >9.2 | 83.33 (67.2, 93.6) | 82.35 (56.6, 96.2) | 4.72 (1.7, 13.3) | 0.20 (0.09, 0.4) | 90.9 (75.7, 98.1) | 70.0 (45.7, 88.1) |
| >9.5* | 80.56 (64.0, 91.8) | 88.24 (63.6, 98.5) | 6.85 (1.8, 25.4) | 0.22 (0.1, 0.4) | 93.5 (78.6, 99.2) | 68.2 (45.1, 86.1) |
| >9.8 | 77.78 (60.8, 89.9) | 88.24 (63.6, 98.5) | 6.61 (1.8, 24.6) | 0.25 (0.1, 0.5) | 93.3 (77.9, 99.2) | 65.2 (42.7, 83.6) |
| >10 | 63.89 (46.2, 79.2) | 88.24 (63.6, 98.5) | 5.43 (1.4, 20.4) | 0.41 (0.3, 0.7) | 92.0 (74.0, 99.0) | 53.6 (33.9, 72.5) |
| >10.5 | 61.11 (43.5, 76.9) | 88.24 (63.6, 98.5) | 5.19 (1.4, 19.6) | 0.44 (0.3, 0.7) | 91.7 (73.0, 99.0) | 51.7 (32.5, 70.6) |
| Left ventricular end-diastolic diameter (cm) | | | | | | |
| >4.6 | 58.33 (40.8, 74.5) | 64.71 (38.3, 85.8) | 1.65 (0.8, 3.3) | 0.64 (0.4, 1.1) | 77.8 (57.7, 91.4) | 42.3 (23.4, 63.1) |
| >4.7 | 47.22 (30.4, 64.5) | 76.47 (50.1, 93.2) | 2.01 (0.8, 5.1) | 0.69 (0.5, 1.0) | 81.0 (58.1, 94.6) | 40.6 (23.7, 59.4) |
| >4.9* | 36.11 (20.8, 53.8) | 88.24 (63.6, 98.5) | 3.07 (0.8, 12.1) | 0.72 (0.5, 1.0) | 86.7 (59.5, 98.3) | 39.5 (24.0, 56.6) |
| >5 | 25.00 (12.1, 42.2) | 94.12 (71.3, 99.9) | 4.25 (0.6, 30.9) | 0.80 (0.6, 1.0) | 90.0 (55.5, 99.7) | 37.2 (23.0, 53.3) |
| Left ventricular end-diastolic pressure (mmHg) | | | | | | |
| >13 | 88.89 (73.9, 96.9) | 50.00 (24.7, 75.3) | 1.78 (1.1, 2.9) | 0.22 (0.08, 0.6) | 80.0 (64.4, 90.9) | 66.7 (34.9, 90.1) |
| >14* | 61.11 (43.5, 76.9) | 93.75 (69.8, 99.8) | 9.78 (1.4, 66.4) | 0.41 (0.3, 0.6) | 95.7 (78.1, 99.9) | 51.7 (32.5, 70.6) |
| >15 | 47.22 (30.4, 64.5) | 93.75 (69.8, 99.8) | 7.56 (1.1, 52.0) | 0.56 (0.4, 0.8) | 94.4 (72.7, 99.9) | 44.1 (27.2, 62.1) |

*Best cut-off point

CI: Confidence interval; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; PPV: Positive predictive value; NPV: Negative predictive value

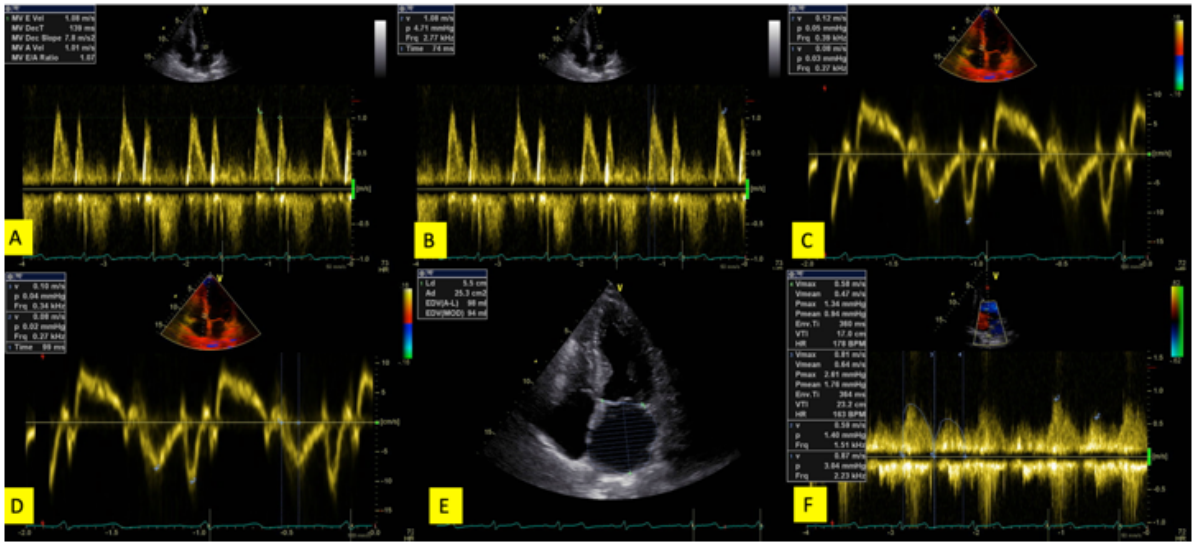


**Figure 1** Different echocardiographic parameters used for evaluation of left ventricular diastolic dysfunction A. The sample volume of pulse wave Doppler was placed in the tip of the mitral leaflets and blood velocity in early diastole (E) and late diastole (A) and deceleration time of E velocity to baseline (msec) were measured.
B. In GE vendors, acceleration time of E wave was measured and peak acceleration rate (cm/sec$^2$) was calculated as velocity (cm/sec) divided by acceleration time (sec). In the Philips vendors, direct measurement of this slope was possible.
C. In tissue Doppler imaging (TDI), the sample volume was placed on the septal annulus of the mitral valve and tissue velocity was measured in early (e') and late diastole (a').
D. As in figure 1.B, peak acceleration rate of e' was calculated or measured directly.
E. The left atrial volume was measured in biplane views (2-chamber view not shown here).
F. The velocity of the pulmonary vein flow was measured in early diastole (D wave), systole (S wave) and late diastole (A reversal wave). The velocity time integral (VTI) of D and S wave was also measured.

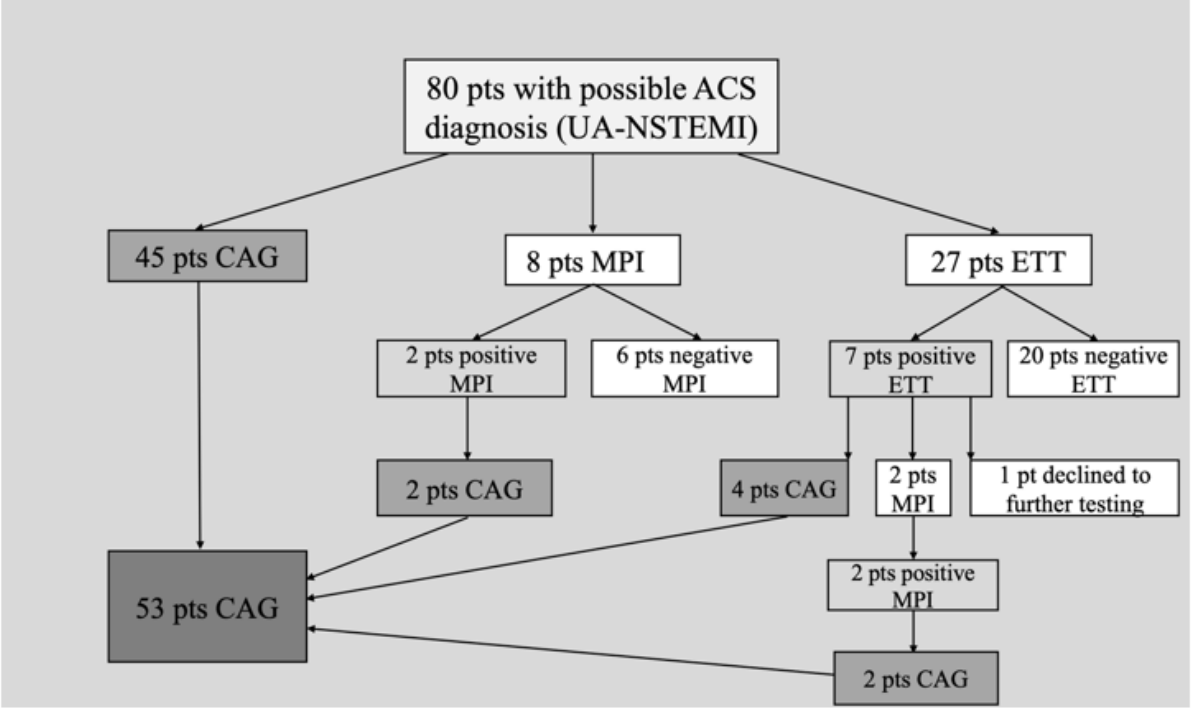


**Figure 2** Summary of diagnostic workup

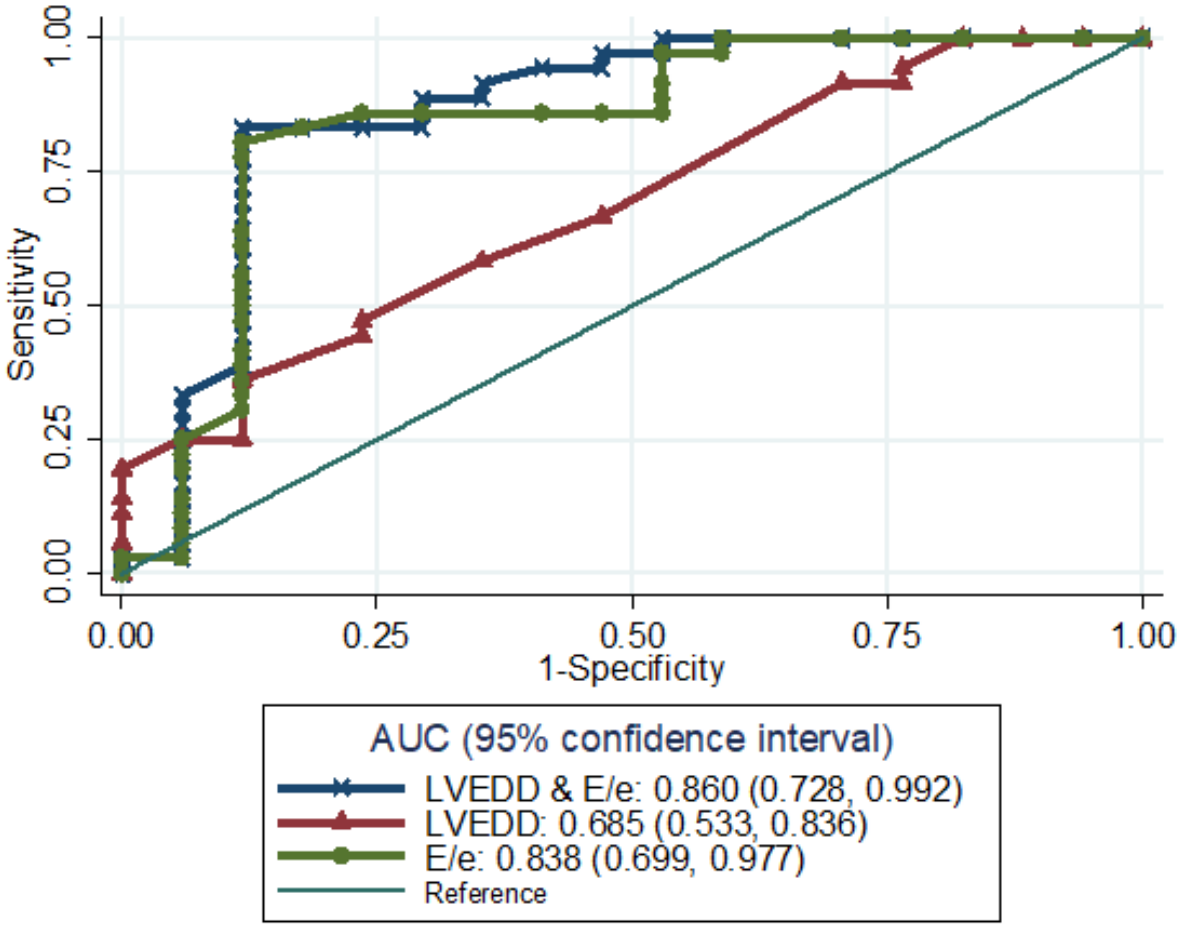


**Figure 3** ROC curve of left ventricular end-diastolic diameter, E/e' and models combining echocardiographic data for prediction of CAG abnormality

(61.11% sensitivity and 93.75% specificity), respectively (Table 4).

Significant echocardiographic variables, including E/e' and LVEDD, were combined to find out if it was possible to achieve a larger area under the curve (AUC). LVEDP was not included in these combination models because it was measured invasively during CAG in the cath lab (not in the ER) and a diagnosis of the CAD was already made after LVEDP measurement. The AUC-ROC of this combination model was 0.860, but it had no significant difference with LVEDD (P=0.106) and E/e' (P=0.182) (Figure 3).

### *3.4. Comparison of echocardiographic findings between patients with normal and abnormal diagnostic tests*

Diagnostic tests were normal in 43 patients, including 20 normal ETT, 6 normal MPI, and 17 normal CAG results. Abnormal diagnostic tests were reported in 36 patients with abnormal CAG findings and one patient with a positive ETT who refused further testing. Comparison of the echocardiographic data between these two groups of patients showed significant differences in the following variables: LVEDD index [mean (SD) in normal vs abnormal: 2.41 (0.23) vs 2.57 (0.21); P=0.001], e' [mean (SD) in normal vs abnormal: 7.49 (2.51) vs 6.11 (2.41); P=0.002], E/e' [mean (SD) in normal vs abnormal: 9.68 (3.19) vs 12.35 (4.04); P<0.001], E acceleration time [mean (SD) in normal vs abnormal: 75.91 (16.54) vs 68.32 (26.55); P=0.016], size of interventricular septum [mean (SD) in normal vs abnormal: 0.83 (0.14) vs 1.15 (1.51); P=0.049], left atrial volume [mean (SD) in normal vs abnormal: 51.73 (15.14) vs 59.43 (18.36); P=0.045] and pulmonary vein D velocity [mean (SD) in normal vs abnormal: 9.58 (2.58) vs 11.41 (4.0); P=0.038].

## 4. Discussion

The present study was conducted to investigate the association of echocardiographic data with the in-hospital results of coronary workup in NSTE-ACS patients. Although previous reports focused on diastolic dysfunction in acute coronary syndrome, a limited number of studies evaluated the role of echocardiographic data in predicting the results of in-hospital ACS workup. In 2008, Richardson et al. (9) evaluated

the prognostic value of E/e' (parameter of LV filling pressure) in 239 ACS patients. The predictors of E/e'>15 in ACS patients were older age, diabetes mellitus, non-ST-segment elevation ACS, and decreased LVEF. Survival free from cardiac death was lower in patients with E/e'>15. A study by Lassen et al. (10) found that E/e' could be an independent predictor of cardiovascular mortality and morbidity in ACS patients with preserved systolic function.

In 2019, Gc et al. (11) reported that adding tissue Doppler imaging data (E/e') and risk stratification based on E/e'>14 to conventional care, led to earlier coronary angiography and subsequent reduction in hospital stay and costs in 51 NSTE-ACS patients. In our study, only one patient had severe LV diastolic dysfunction and most importantly, echocardiographic data of diastolic function were not used to determine the need for invasive workup. Moreover, hospital costs and length of stay were not evaluated in the present study.

In 2019, Gitting et al (12) assessed the association between LV diastolic dysfunction and severity of coronary involvement in 110 patients with NSTEMI using the SYNTAX score. A significant difference was observed in LVEF, LVEDD, E/A, E/e', tricuspid regurgitation (TR) velocity and left atrial volume index between patients with low SYNTAX scores versus those with intermediate or high syntax scores. The estimated prevalence of LV diastolic dysfunction was 85% (45.5% mild, 27.3% moderate and 27.3% severe). Although this study had rather similar objectives as to our study, no patient with unstable angina was included in this study and all the NSTEMI patients underwent invasive coronary angiography. We observed a significant difference in e', E/e', LVEDD, and LVEDP between normal and abnormal CAG groups. The diagnostic performance of E/e' to predict abnormal CAG was excellent while e' had an acceptable diagnostic ability to differentiate normal from abnormal CAG results. A cut-off value of >9.5 for E/e' and <7.4 for e' helped to identify patients with abnormal CAG with a sensitivity of above 80%. In the present study, 78.7% (63/80) of the recruited patients had echocardiographic diastolic dysfunction (55% mild, 22.5% moderate, 1.3% severe) and about 66.2% (53/80) of the study cohorts underwent both echocardiography and coronary angiography. The sensitivity and specificity of LV diastolic dysfunction for predicting coronary artery involvement were 94.4% and 35.29% respectively, indicating that significant coronary involvement is unlikely in a patient with a normal echocardiographic LV diastolic pattern. Our study population consisted mostly of ACS patients with low to intermediate risk whose LVEF was ≥45%. Only 17.5% of the participants had TIMI scores ≥3 and significant coronary artery involvement was observed in 32.5%.

It should be mentioned that despite a significant difference in LVEDD, E/e' and e' between patients with normal and abnormal CAG and AUC > 0.8 for E/e', the positive LR of diastolic dysfunction for prediction of coronary involvement was only 1.46 (CI: 1.02-2.09), indicating that the probability of the CAD does not change significantly with this LR. Further research is required to determine which group of ACS patients will benefit from combining echocardiographic data with the routine ACS diagnostic approach.

## 5. Limitations

A major limitation of this study was its small sample size. Cardiac troponin I was measured in the emergency room while other biomarkers including high-sensitive cardiac troponin and N-terminal pro BNP were not measured. The patients with LVEF below 45% were excluded from the study to prevent interference with LV diastolic assessment and most of the study participants were categorized as low/intermediate risk. Coronary angiography was not done in all of the patients. Indications for CAG were determined by non-invasive test results, TIMI score and/or clinical judgment. Theoretically, the measured sensitivity and specificity of diastolic dysfunction are not influenced by the prevalence of diastolic dysfunction in ACS patients; however, the clinical characteristics of the participants prevent generalization of the results to other ACS groups. To incorporate echocardiography in routine risk stratification tools in ACS, larger studies with focus on low-risk and high-risk NSE-ACS patients are required to facilitate decision-making regarding hospital discharge or early invasive approaches with the aid of echocardiographic data.

## 6. Conclusion

Left ventricular diastolic parameters can be added to the routine risk stratification strategy in non-ST elevation ACS, especially in low-risk patients. Measurement of both E/e' and LVEDD is easy and accessible in the ER setting. Early use of echocardiography along with other risk assessment scores and non-invasive diagnostic modalities might lead to faster management of NSE-ACS patients.

## 7. Declarations

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### *7.2. Authors' contribution*

LF: preparing research proposal, recruiting study population, data gathering; SBH: recruiting study population; FL: designing the research, preparing the manuscript; FAA: preparing the manuscript; AM: analyzing the data.

### *7.3. Conflict of interest*

The authors declare no conflict of interest.

### *7.4. Funding*

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## References


1. Eisen A, Giugliano RP, Braunwald E. Updates on acute coronary syndrome: a review. JAMA Cardiol. 2016;1(6):718-30.
2. Salehi N, Heidari Moghadam R, Rai A, Montazeri N, Azimivghar J, Janjani P, et al. Daily, monthly, and seasonal pattern of ST-segment elevation myocardial infarction (STEMI) occurrence in western Iran; a cross-sectional study. Fron Emerg Med. 2021;5(3):e28.
3. karbalai Saleh S, Oraii A, Soleimani A, Saraee E, Ashraf H. The primary angioplasty registry of Sina (PARS); a brief report of design and rationale. Fron Emerg Med. 2021;5(1):e13.
4. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130(25):2354-94.
5. Leistner DM, Dietrich S, Erbay A, Steiner J, Abdelwahed Y, Siegrist PT, et al. Association of left ventricular end-diastolic pressure with mortality in patients undergoing percutaneous coronary intervention for acute coronary syndromes. Catheter Cardiovasc Interv. 2020;96(4):E439-E46.
6. Ashraf H, Sadatnaseri A, Aminorroaya A, Kuhi Z, Zandi N, Karbalai Saleh S. Left ventricular pseudoaneurysm as a complication of myocardial infarction; a case series and review of the literature. Front Emerg Med. 2021;5(3):e30.
7. Maslovskyi VI, Mezhiievska IA. Types of remodeling and assessment of myocardial diastolic function in patients with ACS and CCS. Eur J Prev Cardio. 2021;28(1s).
8. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr. 2009;10(2):165-93.
9. Richardson-Lobbedez M, Maréchaux S, Bauters C, Darchis J, Auffray JL, Bauchart JJ, et al. Prognostic importance of tissue Doppler-derived diastolic function in patients presenting with acute coronary syndrome: a bedside echocardiographic study. Eur J Echocardiogr. 2008;9(5):594-8.
10. Lassen MCH, Skaarup KG, Iversen AZ, Jørgensen PG, Olsen FJ, Galatius S, et al. Ratio of transmitral early filling velocity to early diastolic strain rate as a predictor of cardiovascular morbidity and mortality following acute coronary syndrome. Am j cardiol. 2019;123(11):1776-82.
11. Gc VS, Alshurafa M, Sturgess DJ, Ting J, Gregory K, Oliveira Gonçalves AS, et al. Cost-minimisation analysis alongside a pilot study of early tissue Doppler evaluation of diastolic dysfunction in emergency department non-ST elevation acute coronary syndromes (TEDDy-NSTEACS). BMJ open. 2019;9(5):e023920.
12. Caram LM, Ferrari R, Naves CR, Tanni SE, Coelho LS, Zanati SG, et al. Association between left ventricular diastolic dysfunction and severity of chronic obstructive pulmonary disease. Clinics. 2013;68(6):772-6.