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The Diagnostic and Prognostic Value of Mitral Annular Plane Systolic Excursion (MAPSE) as an Echocardiographic Indicator of Myocardial Dysfunction in Sepsis and Septic Shock

Mohamed Saleh Gomaa[1*], Maher A. El-Amir[1], Heba M. Zein El-Abedin[1], Gomaa Abdel-Razik[2] and Eman M. Ezzat[1]

[1]Department of Internal Medicine, Fayoum University, Egypt.
[2]Department of Cardiology, Fayoum University, Egypt.

Authors' contributions

This work was carried out in collaboration between all authors. Authors MSG, MAEA, HMZEA and GAR designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. All authors managed the analyses of the study. Author EME managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Objectives: Validation of mitral annular plane systolic excursion (MAPSE) as a rapid easy marker of left ventricle (LV) systolic function in general, and as an independent predictor of systolic function and mortality among patients with septic shock.
Background: Sepsis-induced myocardial dysfunction is one of the major predictors of morbidity and mortality in sepsis. Cardiac ultrasonography has become an indispensible tool in ICU for management of hemodynamically unstable critically ill patients, and MAPSE has been suggested as a surrogate measurement for LV function.
Methods: Prospective analysis of 50 septic shock patients by transthoracic echocardiography was carried out. MAPSE, LV ejection fraction (LVEF) measured by modified Simpson's method, and

**Corresponding author: E-mail: sgformicu@gmail.com;*

mitral annular systolic velocity by tissue Doppler imaging TDI were measured every other day for 1 week, and they were correlated with cardiac injury biomarkers and mortality predictors.

Results: MAPSE values correlated significantly with sequential organ failure assessment score (SOFA score) among survived and non-survived patients (average; r – 0.95 with p-value <0.001 and average; r – 0.85 & 0.84 with p-value <0.001 respectively), with high percentage of non-survivor group had MAPSE < 9 mm, on the other hand high percentage of survivor group had MAPSE ≥ 9 mm, and regarding receiver operating characteristic (ROC) curves for mortality prediction; MAPSE was (95.5% sensitivity, 67.9% specificity, and 92% accuracy for cut-off value of ≤ 8.8 mm). Also, it was found that there was statistically significant positive correlation with p-value <0.05 between MAPSE with LVEF and systolic mitral annular velocity TDI S' values, with high percentage of LVEF value ≤ 50% had MAPSE < 9 mm and TDI S' ≤ 8 cm/sec, on the other hand high percentage of LVEF value > 50% had MAPSE ≥ 10 mm and TDI S' > 8 cm/sec, and regarding ROC curve for prediction of LVEF of value ≤ 50%; MAPSE measurement was (98.1% sensitivity, 90.9% specificity, and 96.4% accuracy for cut-off value of ≤ 9 mm).

Conclusion: MAPSE value is thought to be an independent tool for LV systolic function assessment generally, as well as myocardial injury in patients with sepsis induced myocardial dysfunction, and also a predictor of mortality in patients with severe sepsis and septic shock.

Keywords: Septic shock; sepsis induced myocardial dysfunction; MAPSE; mortality outcome.

1. BACKGROUND

Sepsis syndromes and sepsis-induced mortality are major health concerns worldwide, accounting for more than $75 billion (13%) of total world-wide hospital costs yearly [1]. Septic shock is a kind of distributive shock with pathologic vasoplegia, leading to hemodynamic instability with the presence of perfusion abnormalities, resulting in multiple organ dysfunctions [2]. The combined effect of the primary process (hypo-perfusion and 1st hit of multiple organs dysfunction syndrome MODS) and self-reinforcing processes (the 2nd hit of MODS) determine acute phase (mortality outcome) and chronic critical phase illness and morbidity of severe sepsis [3].

Sepsis-induced myocardial dysfunction (SIMD) is one of the major predictors of morbidity and mortality in sepsis, presenting more than 40% of cases of sepsis, with increasing the mortality rate up to 70% [4]. According to the current evidence, it is generally accepted that SIMD may be a result of the interaction of many factors, including inflammation, metabolic disruption and neuro-immunomodulation [5]. It has recently been suggested that SIMD can be defined as the global reversible intrinsic myocardial systolic and diastolic dysfunction of both the left and right sides of the heart induced by sepsis [6].

The use of cardiac ultrasound has proven to be invaluable in order to rapidly establish a diagnosis and provide optimal treatment; important tool for the critical care physician to assess cardiac preload, afterload and contractility in order to fine tune treatment with fluids, inotropes and vasopressors [7]. A quick method to estimate LVEF is to measure systolic movement of the mitral annulus ring [8].

MAPSE represents the amount of systolic long-axis directed displacement of the mitral annular plane towards; assessing the global change in size of the LV cavity. Thus, it can be interpreted as the volume change during ejection and therefore a close association between the long-axis shortening and ejection fraction has been suggested in different patient groups with normal or reduced LV function [9].

The average normal value of MAPSE ranges between 12-15 mm, and a value of MAPSE < 8 mm is associated with a depressed LV EF (< 50%), and value of MAPSE of ≥ 10 mm is linked with preserved EF (≥ 55%). In addition, MAPSE value of < 7 mm could be used to detect an EF < 30% [10].

Also, MAPSE is an easy and rapid tool; when used by untrained personnel for poor window patients, for LV systolic function assessment, and can be an early detector of LV dysfunction with preserved EF [11].

The aim of this study was to investigate if MAPSE is of prognostic value in septic shock patients. Furthermore, we wanted to examine if MAPSE correlates well with other markers of LV systolic function.

2. METHODS

This study was approved by our medical ethics committee and institutional review board, and informed written consents were obtained from all patients enrolled in the study.

This single-center study was designed as a prospective observational study, which included 50 adult patients with septic shock; patients admitted with sepsis (systemic inflammatory response syndrome SIRS criteria plus evidence of infection) with concurrent shock (where shock was defined as failure to maintain mean arterial pressure MAP ≥ 70 mmHg, despite adequate volume/fluid resuscitation), admitted to Medical-ICU of Fayoum university hospital FUH from Feb-2015 to Apr-2016; total number of patients was 86 → 7 patients died within 6 hours of admission before performing echocardiography examination, 5 patients were excluded due to lack of written consent, 8 patients were excluded due to morbid obesity (trans-thoracic echo examination was not possible to be performed), 6 patients were transferred to other ICUs, and 10 patients were excluded because they died before the first week after admission (not completed follow up examinations). Exclusion criteria were patients with large pericardial effusion, severe right ventricular dysfunction, paradox septal motion, mitral valve disease or prosthetic mitral valve, and after cardiac surgery.

After initial resuscitation, hemodynamic and supportive therapies were delivered to patients according to each patient`s clinical scenario . Then all study patients were screened by clinical (demographic and previous health status, diagnostic category, physiological parameters, organs with dysfunction, and ongoing supportive therapies), hemodynamic (MAP, volume status, and dose of inotropic or vasoactive drugs), laboratory (parameters of sepsis, organs dysfunction, and myocardial injury), and transthoracic echocardiographic assessment.

Prognostic scores of sepsis: simplified acute physiology score (SAPS III score) at day 1 of admission, and SOFA score at days 1-3-5-7 of admission. LV systolic function markers: LVEF (by modified biplane Simpson`s method), TDI-S (measured mitral annular peak systolic velocity by TDI-PW), and MAPSE (M-mode of LV medial and lateral walls at MA level) were performed at days 1-3-5-7 of admission, then mean/average value of every variable/marker was recorded. Cardiac injury marker: troponin-I TPN-I at days 1-3-5-7 of admission.

Transthoracic echocardiography (TTE) examinations were performed by well experienced ICU staff under supervision of senior cardiology experienced echocardio-grapher, within 1st 12 hours of admission then every other day for the 1st week of ICU stay (study period), then every 1 week until discharge or death. Images were obtained using Philips (HD-11-XE; revision 2.0.8) US system machine.

2.1 LVEF

LVEF was measured by modified Simpson`s method at A4C and A2C views; biplane traced average EDD and ESD (from endocardial border) then equated and transformed to volume measuring LVEF% equal to (EDV-ESV)/EDV X 100.

2.2 MAPSE

MAPSE was measured at M-mode; images were obtained in A-4C view, longitudinal curser along lateral and medial walls of LV → cutting MV annuli → trace line at level of MV → MAPSE at this level from end-diastole (lowest point) to end-systole (highest point), and average MAPSE value was calculated (mm).

2.3 TDI-Ś

TDI-Ś peak systolic mitral annular velocity; measuring velocity during systole using pulsed wave tissue Doppler imaging at mitral annulus of medial and lateral LV walls (cm/sec).

2.4 Statistical Analysis

Data were coded and analyzed using the SPSS program (Statistical Package for Social Sciences software version 18, Windows 7).

Qualitative data were presented using the numbers and its related percentage (using Chi-square test), while quantitative data were presented using the mean and standard deviation (using Student t-test, Paired t-test, and Mann-Whitney test).

Correlations between MAPSE and SOFA score or between MAPSE and LVEF/TDI-S were performed using the bivariate and multivariate Pearson correlation coefficient. Multiple linear regressions were done to test association between quantitative dependent and in-dependent variables and detection of risk factors.

A receiver operating characteristic (ROC) curve was used to identify the cutoff points, and the

area under the curve was calculated. Average MAPSE cutoff points with the highest balanced sensitivity and specificity for the different LVEF values or SOFA scores were obtained. A P-value of <0.05 was chosen as the level of significance.

3. RESULTS

The study included 50 adult septic shock patients admitted to medical ICU of Fayoum University Hospital, and they were divided into 2 groups: Group I which included 28 survived patients and Group II which included 22 non-survived patients (patients who died within 30 days of ICU stay; due to refractory shock with hypoperfusion status and complicated MODS; refractory to vasoactive infusions and supportive interventions; there were *10 patients who were excluded from this study because they died before the first week after admission* with not completed follow up echocardiographic examinations).

Co-morbidities included: diabetes mellitus (15; 30%), liver cirrhosis (6; 12%), chronic kidney disease/end stage renal disease (8; 16%), hypertension (11; 22%), pre-existing cardiac disease (13; 26% → with LV systolic dysfunction LVEF ≤ 45%), auto-immune disorders (4; 8%), chronic obstructive pulmonary disease/interstitial lung disease (12; 24%), malignancy (2; 4%), cerebrovascular stroke/bed-ridden (7; 14%), and trauma patients (9; 18%).

The most frequent causes of sepsis were infections involving lungs (n = 16, 32%) and urinary tract (n = 12, 24%); moreover, intra-abdominal (n = 8, 16%), vascular (n = 5, 10%), dermal-articular-muscular (n = 4, 8%), cerebral-facial (n = 3, 6%), and other (n = 5, 10%) causes of sepsis occurred.

Identified microbiological isolates included *Staphylococcus aureus 42%, MRSA 26%, S. epidermidis 12%, VRSA 10%, Strep. pneumonia 10%, Acinetobacter spp. 38%, E. coli 14%, Pseudomonas spp. 22%, MDR-organisms 20%, and others/non-identified 38%.*

3.1 Regarding the Markers of LV Systolic Function, Myocardial Injury, and Mortality Predictors

In Group I; average LVEF (mean ± SD; 53.8 ± 4.2 %), average MAPSE (mean ± SD; 12.1 ± 1.6 mm), average TDI Ś (mean ± SD; 9.3 ± 0.93 cm/sec), average TPN-I (mean ± SD; 0.053 ± 0.03 ng/ml), average SOFA score (mean ± SD; 10.7 ± 1.9), and SAPS III score (mean ± SD; 50.3 ± 12.1), but in Group II; average LVEF (mean ± SD; 47.6 ± 4.6 %), average MAPSE (mean ± SD; 8.7 ± 1.5 mm), average TDI Ś (mean ± SD; 7.3 ± 1 cm/sec), and average TPN-I (mean ± SD; 0.16 ± 0.07 ng/ml), average SOFA score (mean ± SD; 16.2 ± 1.9), and SAPS III score (mean ± SD; 92.6 ± 8).

There was statistically significant negative correlation with p-value <0.05 between TNP-I level with MAPSE values (day 1, day 7, and average) in all study patients and among

Table 1. Clinical, hemodynamic, and echocardiographic characteristics of studied patients of each group

Variables	Study group (n=50)	Survivor (n=28)	Non-survivor (n=22)	p-value	Sig.
Age (years)	61.1±7.9	59±6.9	63.9±8.2		
Sex (M/F)	27/23	17/11	10/12		
SOFA	**13.1±3.3**	**10.7±1.9**	**16.2±1.9**	**<0.001**	**HS**
SAPS III	**68.9±23.6**	**50.3±12.1**	**92.6±8.02**	**<0.001**	**HS**
ARDS	29(58%)	11(39.2%)	18(81.8%)		
Needed MV	24(48%)	8(72.7%)	16(88.8%)		
AKI	33(66%)	14(50%)	19(86.3%)		
Needed RRT	17(34%)	6(42.8%)	11(57.8%)		
MAP (mmHg)	76.6±7.1	80.9±5.9	71.2±4.1	<0.001	HS
NE dose (Mc/kg/min)	0.19±0.09	0.15±0.07	0.25±0.07		
Average LVEF %	**51.1±5.3**	**53.8±4.2**	**47.6±4.5**	**<0.001**	**HS**
Average TDIS' (cm/sec)	8.4±1.4	9.3±0.9	7.3±1.03	<0.001	HS
Average MAPSE (mm)	**10.6±2.3**	**12.1±1.6**	**8.7±1.5**	**<0.001**	**HS**
Average TPN-I (ng/ml)	**0.099±0.07**	**0.053±0.03**	**0.16±0.07**	**<0.001**	**HS**

ARDS (Acute respiratory distress syndrome), MV (Mechanical ventilation), AKI (Acute kidney injury), RRT (Renal replacement therapy), NE (Nor-epinephrine)

survivor group (day 1; r – 0.84, day 7; r – 0.90, and average; r – 0.88 with p-value <0.001), and non-survivor group (day 1; r – 0.82, day 7; r – 0.95, and average; r – 0.93 with p-value <0.001); which indicated that the decrease in MAPSE value was associated with increase in TNP-I level. So, MAPSE value was thought to be an independent tool for LV systolic function assessment generally, as well as myocardial injury in patients with septic shock and sepsis induced myocardial dysfunction.

3.2 Regarding Mortality Outcomes Prediction

There was statistically significant negative correlation between SOFA and SAPS III scores levels with MAPSE values among Group I survived patients (average; r – 0.95 with p-value <0.001), and the same results were shown among Group II non-survivor patients (average; r – 0.85 & 0.84 with p-value <0.001). Also, there was statistically significant difference with p-value <0.05 between survivor and non-survivor groups as regards to MAPSE values; with high percentage of non-survivor group had MAPSE < 9 mm, on the other hand high percentage of survivor group had MAPSE ≥ 9 mm.

Regarding ROC curves for mortality prediction; MAPSE was (95.5% sensitivity, 67.9% specificity, and 92% accuracy for cut-off value of ≤ 8.8 mm), and SOFA score was (95.5% sensitivity, 89.3% specificity, and 98.5% accuracy for cut-off value of 13.5).

3.3 Regarding LV Systolic Function Prediction

There was statistically significant positive correlation with p-value <0.05 between MAPSE with LVEF and TDI S' values among survivor and non-survivor groups.

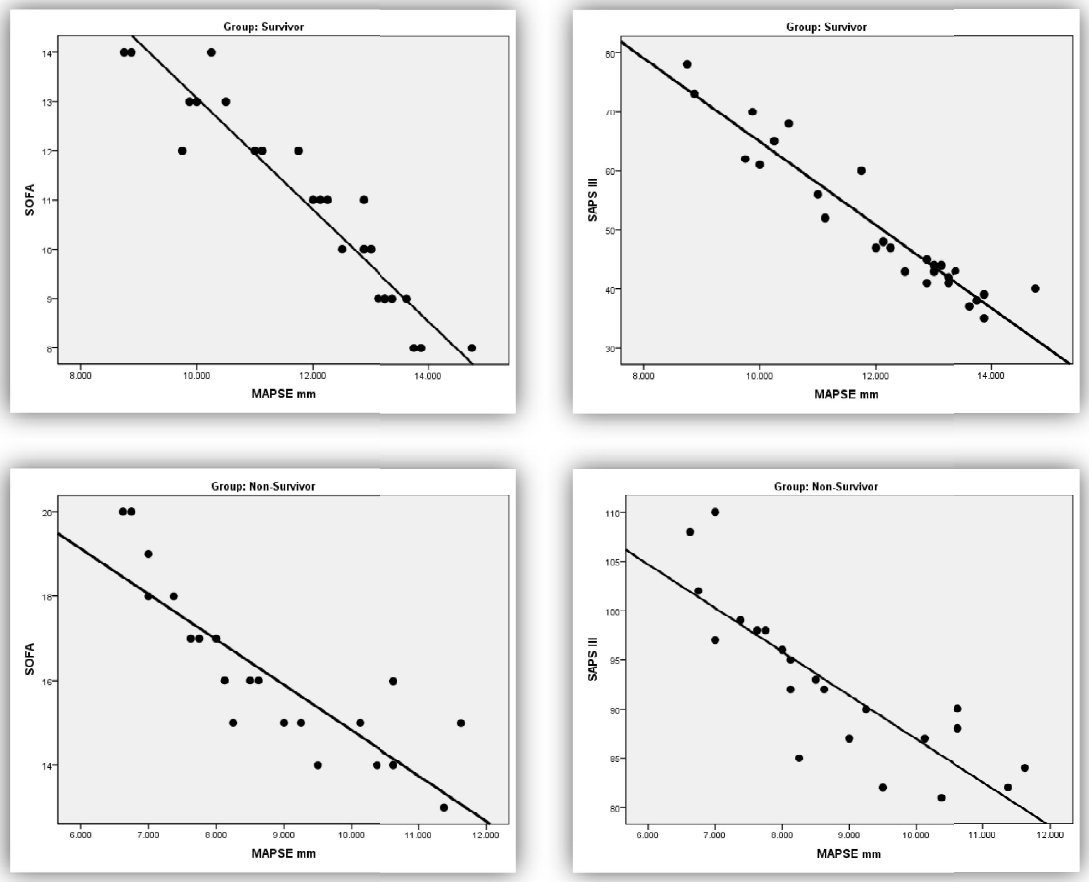
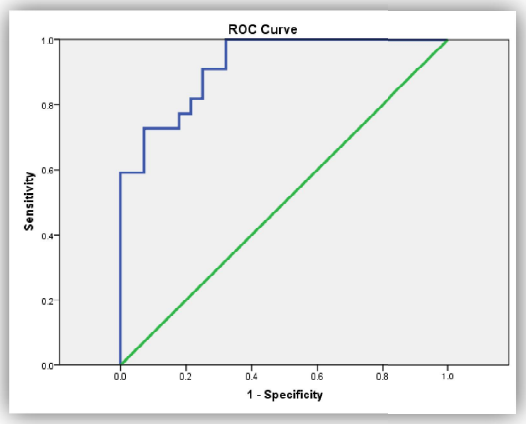


Diagram 1. Correlation between MAPSE and mortality predictors among studied patients of each group

MAPSE



SOFA

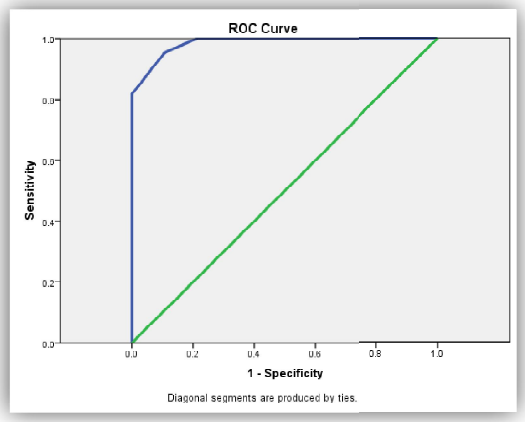


Diagram 2. ROC curves for MAPSE and SOFA score for mortality prediction

Table 2. Comparison of MAPSE, LVEF, and TDI-S categories among study groups

	Mortality outcomes				p-value	Sig.
	Survivor		Non- survivor			
	No.	%	No.	%		
MAPSE						
<9 mm	4	14.3%	**16**	**72.7%**	<0.001	**HS**
≥10 mm	**24**	**85.7%**	6	27.3%		
LVEF						
≤50 %	7	25%	**15**	**68.2%**	0.004	**HS**
>50 %	**21**	**75%**	7	31.8%		
TDI S'						
≤8 cm/sec	4	14.3%	**18**	**81.8%**	<0.001	**HS**
>8 cm/sec	**24**	**85.7%**	4	18.2%		

Table 3. Comparison of LVEF categories among MAPSE categories in study groups

	LVEF				p-value	Sig.
	≤50		>50			
	No.	%	No.	%		
MAPSE						
<9	**19**	**86.4%**	1	3.6%	<0.001	**HS**
≥10	3	13.6%	**27**	**96.4%**		
TDI S'						
≤8	**18**	**81.8%**	4	14.3%	<0.001	**HS**
>8	4	18.2%	**24**	**85.7%**		

Also, there was statistically significant difference with p-value <0.05 between LVEF values as regards to MAPSE and TDI S' values; with high percentage of LVEF value ≤ 50% had MAPSE < 9 mm and TDI S' ≤ 8 cm/sec, on the other hand high percentage of LVEF value > 50% had MAPSE ≥ 10 mm and TDI S' < 8 cm/sec.

Regarding ROC curve for prediction of LVEF of value ≤ 50%; MAPSE measurement was (98.1% sensitivity, 90.9% specificity, and 96.4% accuracy for cut-off value of ≤ 9 mm).

The multivariate logistic regression model analysis was conducted to explore the explanatory power of MAPSE in prediction of LVEF value; it illustrates that there was statistical significance prediction with p-value <0.001; according to this equation: EF= 27.6 + (2.2 × MAPSE).

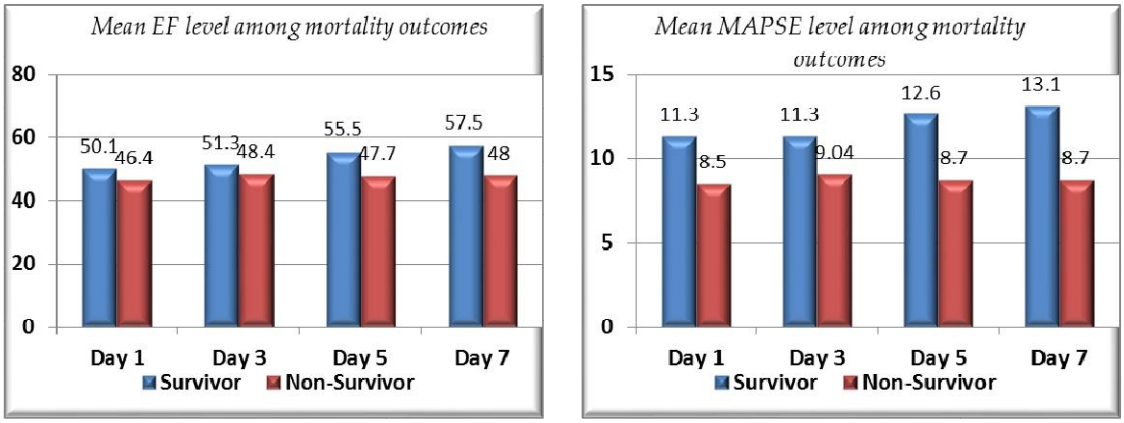


Diagram 3. Comparison of LVEF and MAPSE (every other day) follow up among mortality outcomes

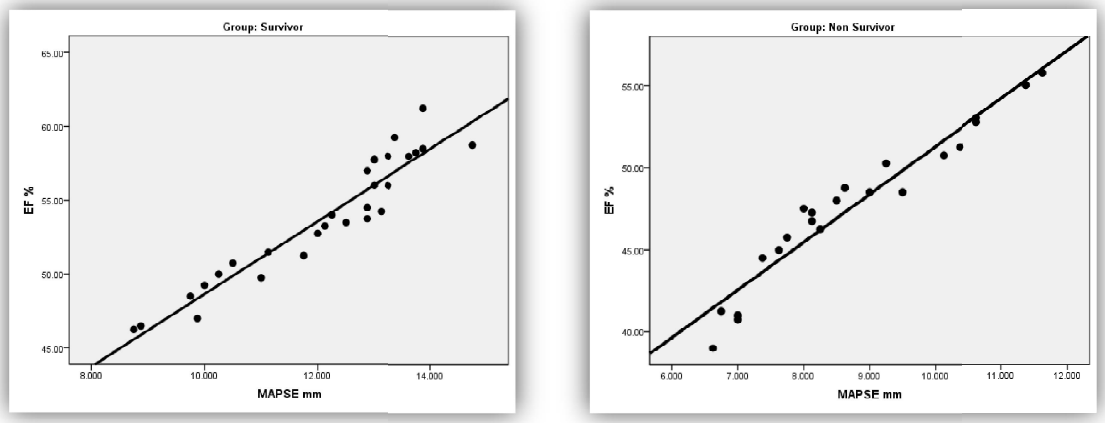


Diagram 4. Correlation between LVEF and MAPSE values in study groups

4. DISCUSSION

From the above data, MAPSE was found to be an independent predictor of LV systolic function in patients with sepsis induced myocardial dysfunction, and independent predictor of mortality in patients with septic shock. Furthermore, LVEF value could be predicted and calculated from MAPSE value. Furthermore, another goal of this study was to define a simple echocardiographic method that can be used (even by inexperienced observers) for a quick estimation of global EF, not to replace other more advanced/sophisticated techniques.

4.1 MAPSE in Relation to Mortality Outcome

It was found that MAPSE was significantly lower in non-survivors compared to survivors in most days of the 7-day observation with cut-off value ≤ 8.8 mm, and could be identified as an independent predictor of mortality in septic shock patient with SIMD.

Our results were consistent with those of Bergenzaun et al. who stated that MAPSE was an independent predictor of 28-day mortality in critically ill patients with shock and SIRS with cut-off value < 8 mm, and combining MAPSE with SOFA increased the predictive value for mortality [12]. Also, a study by Kai Hu et al. demonstrated that reduced MAPSE values were also related to poor outcomes in patients with various cardiovascular diseases; showed that 10 years survival was significantly better in heart failure patients with highest MAPSE > 9 mm than in heart failure patients with the lowest MAPSE < 5 mm [10].

Our results disagreed with data conducted by Huang et al. who suggested that mortality does

not depend on whether patients have SIMD or not, but it depends on whether the patient's heart is hyperkinetic or not [13]. Also, more recent meta-analysis by Sanfilippo et al. [14] found that there was no significant difference in mortality rates in septic patients with reduced LV systolic function compared to patients with normal LV systolic function.

4.2 MAPSE in Relation to LV Systolic Function

This study suggested MAPSE as a surrogate measurement for LVEF with both normal and reduced LV function, with a mean value MAPSE of equal or more than 10 mm in patients preserved EF, and in those with reduced EF had a mean value MAPSE of less than 9 mm.

These data agreed with those included by Matos et al. who found that MAPSE measurements by an untrained observer were highly accurate predictor of LVEF values [9]. Kai Hu et al. [10] demonstrated that the average normal value of MAPSE derived from previous studies ranges from 12 to 15 mm, and MAPSE < 8 mm was associated with a depressed LVEF < 50%, while MAPSE ≥ 10 mm was linked with preserved LVEF ≥ 55%. In addition, MAPSE < 7 mm could detect an LVEF < 30% with dilated cardiomyopathy with severe congestive heart failure.

The current study showed that an average MAPSE cutoff value of less than or equal to 9 mm predicted EF < 50%, and MAPSE cutoff value of less than or equal to 6 mm could determine EF < 40% in 100% of the patients. Our results were similar to results by of Matos et al. and Adel et al. [9] and [11]; who stated that a MAPSE cutoff value of less than or equal to 5 mm provided the best balanced sensitivity (67.1%) and specificity (76.5%) to predict EF < 30%, and a cutoff value of MAPSE less than or equal to 3.9 mm could determine EF < 30% in 100% of the patients.

Although MAPSE and LVEF may be related, they are not entirely interchangeable. MAPSE is suggested to be primarily representative of sub-endocardial longitudinally oriented myocardial fibres (long-axis function), compared to the other subepicardial circumferential and oblique fibres (radial function) measured by LVEF. So, MAPSE is known to detect more subtle abnormalities of LV function [15].

Wenzelburger et al. [15] stated that MAPSE correlated well with more sophisticated measurements of ventricular function in heart failure with preserved ejection fraction HFpEF patients; MAPSE was potentially useful and easily acquired measurement for the diagnosis of HFpEF. Kai Hu et al. [10] demonstrated that MAPSE seemed to be more sensitive than LVEF, for detecting early abnormalities of LV systolic function, especially useful in patients with poor imaging qualities.

4.3 MAPSE and Septic Cardiac Depression

The current study showed that MAPSE was independent predictor of LV systolic function in patients with sepsis induced myocardial dysfunction.

Similar results were conducted by de Geer et al. [16] who stated that MAPSE was the least user-dependent and most reproducible systolic parameter used to identify cardiac dysfunction in septic shock.

However, Zaky et al. [17] revealed a complicated and contradictory picture about myocardial dysfunction in septic patients, due to the limitations of currently used indices of ventricular function, because LVEF and MAPSE are load-dependent indices that do not reflect the intrinsic myocardial contractile function during sepsis.

5. RECOMMENDATIONS

The influence of vasopressors, inotropes, and mechanical ventilation on echocardiographic measurements is uncertain, and needs to be investigated. Whether or not diastolic dysfunction could affect MAPSE-derived measurements remains another area of future research.

Comparing MAPSE-derived EF with cardiac magnetic resonance CMR, speckle-tracking imaging, or 3D TTE-derived LVEF by volumes should be considered in future studies as these modalities represent the gold standard for quantification of LV function and are sought to be much more accurate than the current 2D quantification methods.

6. CONCLUSION

Despite routine use of newer and more refined echocardiographic technologies nowadays, the use of MAPSE measurement is still especially

helpful to evaluate LV systolic function in case of poor sonographic windows with minimal inter- and intra-observer variability.

MAPSE is thought to be an independent predictor of LV systolic function in patients with sepsis induced myocardial dysfunction, and independent predictor of mortality in patients with septic shock. Furthermore, LVEF value can be predicted and calculated from MAPSE value.

The goal of this study is to define a simple echocardiographic method that can be used (even by inexperienced observers) for a quick estimation of global EF, not to replace other more advanced/sophisticated techniques.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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