Prediction of Mortality in Septic Shock; Comparison of Tissue Doppler and Different Biomarkers

MERVAT M. KHALAF, M.D.; MARWA ELSAID, M.Sc.; EMAD OMAR, M.D.; KHALID HUSSIEN, M.D. and WAHID RADWAN, M.D.
The Department of Critical Care, Faculty of Medicine, Cairo University, Egypt

Abstract

Background: Assessment of the diastolic dysfunction by tissue Doppler imaging (TDI) and cardiac biomarkers such as B-type natriuretic peptide BNP together can be a good tools for prediction of hospital outcome in septic shock patients.

Purpose: To evaluate and compare the prognostic significance of (TDI) particularly E/é (peak early diastolic transmitral/peak early diastolic mitral annular velocity), cardiac biomarkers (N- terminal proBNP (NTproBNP); cardiac troponin I (cTnI)) and high sensitive C- reactive protein (hs CRP) in septic shock.

Methodology: Twenty eight patients with septic shock were involved in a prospective randomized clinical study (mean age were 62±9.3 yrs, 62% male) were divided into 2 groups according to mortality and were subjected to all fluid resuscitation, transthoracic echocardiography TTE and laboratory measurement of the mentioned cardiac biomarkers.

Results: There were 20 pt (71.4%) died Group A, 8 patients (28.6%) survived Group B. E/é ratio was significantly lower in survivors than non-survivors (8.59 ±2.29 vs. 12.32±3.7, p-value = 0.001), hs CRP was found to be significantly lower between survivals and non survivals (33.49 ±10.82 vs. 41.65 ±7.33, p-value = 0.02). There was a strong positive correlation between E/e' and (PMR, DT, LA size and FiO2) (p-value = 0.002, 0.0001, 0.007 and 0.003 r=0.5, 0.6 respectively). There was a positive correlation between hs-CRP with both (PMR and DT) (p-value = 0.01 and 0.03, r=0.4 respectively). By cox regression analysis 5 parameters were found to be independent predictors of mortality in septic shock which were: E/e ratio, APACHE IV, SOFA 1, SOFA 3 and DT as p-value (0.009, 0.002, 0.003, 0.007 and 0.0001) respectively.

Conclusions: E/e and DT obtained by PW and TDI both offer independent and better prognostic prediction of hospital outcome in septic shock as compared with cardiac biomarkers (NT, proBNP & cTnI).

Key Words: TDI – Septic shock – Mortality – Pro BNP – Hs CRP – Ctnl.

Introduction

SEPTIC shock is defined as a state of sepsis induced circulatory failure which is not responsive to adequate fluid resuscitation [1]. The pathogenesis of cardiac dysfunction in septic shock is very complex and multifactorial that leads finally to changes in both systolic and diastolic ventricular performance [2]. Depressed systolic function of the myocardium has been identified as the main cause of circulatory failure in septic shock, but the contribution of diastolic dysfunction to cardiovascular morbidity and mortality in septic shock is not fully understood [3].

Measurement of cardiac biomarkers such as N-terminal proBNP (NTproBNP) and cardiac troponin (cTnI) are mostly used to diagnose diastolic dysfunction of the heart in septic patients and heart failure and both have diagnostic and prognostic values [4-8].

TDI is an echocardiographic technique that measures low velocity motions of the myocardium [9], which are low frequency, high-amplitude signals filtered from conventional Doppler imaging [10]. TDI proved to be a very useful technique for the evaluation of diastolic function [11] and E/é (peak early diastolic transmitral / peak early diastolic mitral annular velocity) represented an accurate diastolic function indices reflecting left ventricular filling pressure LVFP [12], that is used as a powerful predictor of mortality after myocardial infarction [13], however the application of these TDI indices in septic patients still limited.

Aims of this study were to assess and compare the prognostic significance of (TDI) particularly E/e, cardiac biomarkers (N- terminal proBNP (NT-proBNP); cardiac troponin I (cTnI) and high sensitive C- reactive protein (hs_CRP) in septic shock.
Patients and Methods

A prospective, randomized & comparative study was conducted as a single-center analysis of the Critical Care department, Cairo University hospitals including 28 consecutive adult patients admitted with septic shock (or developed septic shock during their ICU stay) from Sept 2010 to Feb. 2012 for a period of eighteen months.

Septic shock was diagnosed when the patient had a mean arterial pressure (MAP) < 60 mmHg or a reduction in systolic blood pressure (SBP) > 40 mmHg from baseline) despite adequate volume resuscitation in the absence of other causes for hypotension [14].

Excluded from the study any patient aged younger than 18 years, any patient who had moderate to severe valvular heart disease and any cause of left ventricular systolic dysfunction.

All included patients were subjected to the following: Full clinical evaluation including history and physical examination with special emphasis on:

- Vital signs (BP, HR, Temperature and RR, CVP).
- Arterial blood pressure: (diastolic blood DBP pressure; systolic blood pressure SBP& mean arterial blood pressure and MAP = diastolic blood pressure+1/3 pulse pressure)
- Height, weight and body surface area (BSA: was calculated by Mosteller, square root method) = sqrt (Height * Weight/ 3600) [15].
- Scoring systems:
  - APACHE IV: Illness severity will be quantified using (Acute Physiology and Chronic Health Evaluation) which were developed because the accuracy of APACHE III changed significantly over the last decade. The APACHE IV model has excellent discrimination (AU-ROC=0.88). Was done at 1st; day of septic shock [16].
  - SOFA SCORE: Sequential Organ Failure Assessment (SOFA) scores collected at day one & day three is used to track a patient's status during the stay in an intensive care unit (ICU). It is one of several ICU scoring systems.
- Modalities of therapy: Vasopressor/inotropic infusion rates, fluid resuscitation therapy, ventilation mode & settings, need for haemodialysis, need for blood or platelet transfusion.
- 28 days of hospital outcome included: length of ICU stay (LOS), mortality and need for organ supportive measures (mechanical ventilation, hemodialysis, and blood transfusion) were reported for all patients until ICU discharge or demise up to a total of 28 days.

Two-dimensional echocardiography TTE: Each patient was examined in the left lateral decubitus position according to the recommendations of the American Society of Echocardiography. The study was conducted using an ATL HDI 5000 colored echocardiographic machine with TDI software incorporated in the device using 2.5 to 3.5 MHz transducer.

Systolic function:
- LV end-diastolic volume (LVEDV); will be calculated using the biplane method of disks (modified Simpson's rule) from the apical four-chamber. N = female range 56-104ml. male range 67-155ml.
- LV end-systolic volume (LVESV); will be calculated using the biplane method of disks (modified Simpson's rule) from the apical four-chamber. N = female range 19-19 ml. male range 22-58ml.
- (LVEDVI and LVESVI, respectively): indexed to BSA. N = 35-75ml/m². N = 12-30ml/m². Respectively.
- LV ejection fraction (LVEF); will be calculated as (LVEDV- LVESV)/LVEDV x 100. Systolic dysfunction was defined as EF below 55%.
- Tissue Doppler: Myocardial velocities will be obtained using tissue Doppler settings, with the pulsed-wave Doppler sample volume at the septal mitral annulus in the apical four-chamber view. The Peak systolic (s') wave contraction which ranges between 8-18 cm/sec.
- LV outflow tract diameter (OTD); will be recorded as the maximum measurement from parasternal long axis view.

Diastolic function:

Doppler echocardiography; Transmitral flow velocities will be recorded with pulsed-wave Doppler with the sample volume placed at the mitral valve tips from the apical four-chamber view.

- E wave: Peak early filling diastolic transmitral flow velocity.
- A wave; diastolic atrial peak velocity.
- (DT) wave deceleration time; interval between the peak of the E wave to the zero baseline. Age-dependent thresholds for deceleration time (<40 years <220ms; 40 to 60 years 140 to 250ms; >60 years 140 to 275ms) will be used to determine impaired relaxation (DT above normal
limit) and restrictive patterns (DT below normal limit)
E to A ratio (E/A); will be calculated. N = 0.75 → 1.5, ≤0.75 = Grade I diastolic dysfunction,
0.75 < E/A <1.5 with DT >140 = Pseudonormal,
E/A >1.5 & DT ≤140 = Restrictive pattern.
Tissue Doppler: Myocardial velocities will be
taken using tissue Doppler settings, with the
pulsed-wave Doppler sample volume at the septal
mitral annulus in the apical four-chamber view.
Peak Early diastolic septal mitral annulus veloc-
ity (e') and peak active late diastolic septal mitral
annulus velocity (a') myocardial velocities will
be measured. E/e' will be calculated. In the
presence of atrial dysrhythmia, transmitral and
tissue Doppler velocities will be measured over
five consecutive cardiac cycles. Abnormal dias-
tolic TDI were accepted as e' less than 9.6 cm/s
(myocardial relaxation below the lower 95%
confidence limit of normal subjects) or E/e' more
than 10 [17].
Cardiac output:
Doppler interrogation of LV outflow tract ve-
locity will be guided by apical five-chamber view
[18]. Heart rate (HR), velocity time integral (VTI)
and peak velocity (V peak) will be measured.
Stroke volume was calculated as the production of
VTI & cross-sectional area of the LV outflow
tract \( \mu \), \( \text{OTD}/2 \).
Cardiac output; will be calculated as the product
of stroke volume and HR. Stroke volume N = 75 → 100ml, Cardiac output 4 → 8 L/min re-
spectively.
SVI and CI, respectively; Stroke volume and
cardiac output measurements will be indexed to
body surface area.
Velocity time integrity (VTI): N = 18 → 22.
Left atrial area: (>20cm²) will be used as a
marker of raised LV filling pressure.
Statistical analysis:
• The data was coded and entered using the statis-
tical package SPSS version 15.
• The data was summarized using descriptive sta-
tistics: Mean, standard deviation, minimal and
maximum values for quantitative variables and
number and percentage for qualitative values.
• Statistical differences between groups were tested
using Chi Square test for qualitative variables,
independent sample t-test for quantitative nor-
mally distributed variables while Nonparametric
Mann Whitney test was used for quantitative variables which aren’t normally distributed.
• Correlations were done to test for linear relations
between variables.
• Discrimination between hospital survivors and
non-survivors was evaluated by receiver operating
characteristic (ROC) curve analysis. Kaplan-
Meier survival analysis was done and Log Rank
test was used to test for equality of survival
distributions among different levels of indepen-
dent variables.
• Cox proportional hazards regression was used to
test for significant predictors of time to event
outcomes (hospital survival).
• Sensitivity, specificity, positive and negative
predictive values together with Odds ratio.
• p-values less than or equal to 0.05 were considered
statistically significant.
Results
The study included 28 patients admitted with
or developed septic shock during the stay in ICU.
The mean age of the studied patients were 56.86 ±
21.15 yrs, they were 16 females 57.1% and 12
males 42.9%. The mean of body mass index BMI
were 28.44 ±5.73. Co-morbid conditions (DM, HTN
and AF) and source of sepsis are shown below in
Table (1).
The follow-up 28 days mortality showed that
there were 20 pt (71.4%) died, 8 patients (28.6%)
survived, comparison between survivals and non-
survivals were made as shown in Table (2).
Fluid therapy and vasopressors:
As regarding the management of septic patients
we found that, in the group A they needed a larger
amount of fluid replacement around 5 liters but in
group B they needed about 4 liters with non sig-
nificant \( p \)-value=0.536.
As regarding the dose of nor adrenaline there
was no statistically significant difference between
2 groups (\( p \)-value=0.313). The mean of dopamine
dose in group A was 5.5 ± 1.0 mc/kg/min while in
group B it was 11.25±2.5 mc/kg/min which was
statistically significant (\( p \)-value=0.005).
Need for mechanical ventilation was more
significantly in non survivors than survivors (\( p-
value=0.003).
Scoring systems:

Comparison between the two groups was made in relation to scoring system (APACHE IV and SOFA), prediction mortality rate (PMR) and length of stay (LOS) Table (2).

Trans-thoracic echocardiography TTE:

It was observed that $e'$ wave was significantly higher in survivors than non-survivors ($8.73 \pm 1.75 \text{ cm/s}$ vs. $6.99 \pm 1.5 \text{ cm/s}$, $p$-value=0.014) Table (3).

$E/e'$ ratio was significantly lower in survivors than non-survivors ($8.59 \pm 2.29$ vs. $12.32 \pm 2.37$, $p$-value=0.001). The CI was significantly lower in survivors than non-survivors ($4.89 \pm 1.52$ vs. $6.54 \pm 1.83 \text{ l/min/m}^2$ with $p$-value=0.03) Table (3).

As regarding echo parameters including (LVEDVI, LVESVI, OTD, EF, SVI, E wave, A wave, DT, E/A, a, s, LA area) of both group there were no significant difference, ($p$-value=0.443, 0.277, 0.278, 0.055, 0.053, 0.380, 0.274, 0.382, 0.939, 1.000, 0.380, 0.380) respectively.

Cardiac biomarkers:

only high sensitive C reactive protein CRP proved to be significantly lower in survivors than non survivals ($p$-value=0.02), Table (3).

Correlative results:

There was a strong positive correlation between $E/e'$ and (PMR, DT, LA size and FiO2) as shown in Table (4).

Predictories of mortality:

By cox regression analysis we found that 5 parameters were found to be independent predictors of mortality in septic shock which were: $E/e$ ratio, APACHE IV, SOFA 1, SOFA 3 and DT as $p$-value (0.009, 0.002, 0.003, 0.007 and 0.0001) respectively Table (5).
E/e ratio is a good tool for prediction the mortality in septic shock patients at cutoff point 10.02 where AUC is 0.884, a significant p-value=0.002, sensitivity 85%, specificity 75%, PPV 95.4%, NPP 75% & but NTproBNP may be used with borderline AUC 0.634, non significant p-value=0.634, sensitivity 75 %, specificity 62.5%, PPV 83.3%, NPP 50% (Fig. 1).

Although by cox regression analysis hs-CRP is not predictor of mortality in septic shock pts, but by ROC curve it had a significant AUC=0.725, p-value=0.05, sensitivity 85% & specificity 75% at cutoff point 34.05mg/l.

On other hand TnI could not be used at as a tool for prediction the mortality in septic shock patients at cutoff point 0.4 where AUC is 0.478, a non significant p-value=0.859, sensitivity 50%, specificity 50% (Fig.1).

Classification of studied group according to E/e’ cutoff point 10.02:

Of the studied 28 patients with septic shock, it was found that 7 patients 25% had normal diastolic function, 2 patients 7.1% had grade I diastolic dysfunction (impaired relaxation), 11 patients 39.3% had grade II diastolic dysfunction (pseudo-normal) and 8 patients 28.6% had grade III diastolic dysfunction (restrictive type) by using both PW Doppler and TDI.

It was found that 9 patients 32.2% who had normal or type I diastolic dysfunction had also had normal LVFP as reflected by E/é <10, while 19 patients 67.8% who had type II or III diastolic dysfunction also had high LVFP as reflected by high E/e >10.

When the studied patients were classified into two groups: Those who had E/é <10.02 (normal LVFP) & the other who had E/é >10.02 (high LVFP) to assess the impact of E/é (utilizing the cutoff point 10.02) on scoring systems, ICU duration, Parameters of diastolic dysfunction & Biomarkers between two groups. The mortality rate in group A was 33.3% & in group B was 89.5%, so the highest mortality rate was among group B with impaired diastolic function.

There was high statistically significant difference between the 2 groups as regards scoring systems Table (6).

Also through the using Kaplan Meier plot of association between E/é & hospital survive in septic shock pts, we found that the estimation of survival time of group E/é ratio <10.02 was 45.4 days while in group E/é <10.02 was 15 days with a statistically significant difference between the two groups p-value=0.003.

![ROC Curve](image)

Fig. (1): ROC curve analysis of E/é, NTproBNP, TnI, hs-CRP as prognostic markers of septic shock pt.
Discussion

B-type natriuretic peptide (BNP) is a protein released by the ventricles in the presence of myocyte stretch, and has been correlated to LV filling pressure, so its measurement accurately diagnoses left ventricular dysfunction and heart failure [19]. Noninvasive estimation of left ventricular filling pressure by e/e’ is a powerful predictor of survival after acute myocardial infarction [13].

Biomarkers including BNP [20,21], cardiac troponin I [22,23] and high sensitive C-reactive protein [24] potentially offer prognostic information in septic patients. Recently, studies which compare between TDI and these biomarkers (BNP, cTnI and hs CRP) as regard prediction of hospital outcome in septic shock are still very limited, so this study aimed to discover the prognostic value of diastolic function indices (e’, e/e’, DT) and other biomarkers (NT-pro-BNP, cTnI and HS CRP) in septic shock patients. The cornerstone finding of this study is that E/é offers independent and better prognostic prediction of hospital outcome in septic shock as compared with cardiac biomarkers (NT, proBNP & cTnI).

The predictors of mortality proved statistically in our study were 5 parameters: Diastolic function indices (E/é & DT) in addition to scoring systems (APACHE IV & SOFA) & finally hs-CRP.

In the present study we found that the diastolic function indices including (E/é & DT) are superior than conventional measures of systolic function including (EF and SVI) in discrimination between hospital survivors and non survivors. These finding are correlated with Praker and colleagues in a radionuclide cineangiographic study, who documented that non-survivors did not demonstrate LV dilation (preload adaptation) and therefore were unable to maintain stroke volume and cardiac output [25].

In the present study we demonstrate the value of é wave as diastolic function indices where the mean of é wave in group A was 9.14±4 cm/s while in group B was 9.75±2.6 cm/s with p-value=0.0 1, this results is similar to Sturgess study which included 21 pts, with septic shock, where é wave (survivor 10.4±3.4cm/s, non survivor 6.8±1.9cm/s; p=0.025) [26].

In the present study we also found a trend toward an association between DT and hospital mortality where univariate cox regression analysis yielded DT is independent predictor of mortality where (p=0.0001).

And these results are similar to Munt & colleagues who demonstrated DT as independent predictor of mortality in sever sepsis [27].

The following relations are aiming to demonstrate the importance of the effect diastolic of diastolic dysfunction on the morbidity of septic shock where; a strong positive correlation between DT & E/é with p=0.0001 & r=0.6, another a positive correlation between DT& ventilation duration where p=0.01 & finally a positive strong correlation between DT & ICU duration where p=0.0001 & r=0.6.

Another diastolic function indices is E/é ratio which found to be highly predictor of mortality in septic shock as we found that the mean of E/é ratio in group A (survivors) was 8.59±2.29 while in group B (non survivors) was 12.32±2.37 with a highly statistically significant difference between the two groups  p-value= 0.001.

Also we found that there was a strong positive correlation between E/é & PMR where  r= 0.6 & a significant p-value=0.002.

By cox regression analysis E/é ratio is independent predictor of mortality of septic shock pts, where B=0.292 & a significant p-value=0.009.

By using ROC curve analysis E/é ratio is a very good tool for predicting the mortality in septic shock patients at cutoff point 10.02 where AUC is 0.884, a significant p-value=0.002, sensitivity 85%, specificity 75%, PPV 89.5%, NPP 66.7% & DA is 82%.

These results are more or less similar to Sturgess and his colleagues results who studied 21 pts, with septic shock & they found that significant differences were observed between survivors & non survivors with respect to E/é (survivor 9.05 ±2.75, non survivor 15.32±2.74; p=0.0002), The area under the ROC curve was 0.94 for E/é. An E/é cutoff value of 14.5 offered sensitivity of 100% and specificity of 83% [26].

Mokart and coworkers study also examined 58 mechanically ventilated patients with no history of heart failure. They found that systolic, é, and E/é correlated with age, By multivariate analysis E/é was a reliable predictor of LV diastolic dysfunction (p=0.017) defined as a composite of é wave less than or equal to 8 cm/s and/or mean E/é greater than or equal to 13 (area under the curve,
This study is different from our study in E/é ratio at cutoff point ≥ 10.02 is indicator of diastolic dysfunction & independent predictor of mortality in septic shock patients only but in the previous study they only enrolled patients with mild sepsis.

Also Mclean and colleagues used E/é as an estimate of LV filling pressure in their prognostic study of BNP in patients with severe sepsis and septic shock [29]. They reported E/é to be non-significantly lower in non-survivors (survivors 14.8 ± 7.4, non-survivors 12.1 ± 4.6; p = 0.452). However, their study incorporated a number of patients with severe sepsis (lower severity of illness compared with the current study).

Bouhemad and colleagues used TDI to demonstrate isolated and reversible impairment of ventricular relaxation in septic shock with increased plasma troponin I concentration but association with mortality were not assessed [30].

Another TDI parameter which is peak systolic velocity measured at mitral annulus Sa, (one of LV systolic function indices) serve as useful tool to predict mortality in patients with septic shock as in Weng L study who investigated 61 Patients with septic shock in a medical intensive care unit by transthoracic echocardiography with TDI within 24 hours after the onset of septic shock. Baseline clinical, Laboratory and echocardiographic variables were prospectively collected [31].

In the present study E/é ratio at 10.02 there were two groups, group A which E/é ratio < 10.02 included 9 pts, with normal filling pressure. But group B which E/é ratio ≥ 10.02 included 19 pts, with impaired diastolic function.

The mortality rate in group A was 33.3% & in group B was 89.5%, so the highest mortality rate was among group B with impaired diastolic function.

Also through the using Kaplan Meier plot of association between E/é & hospital survive in septic shock pts, we found that the estimation of survival time of group E/é ratio < 10.02 was 45.4 days while in group E/é < 10.02 was 15 days with a statistically significant difference between the two groups (p-value = 0.003).

In comparison to the cardiac biomarkers (NT-proBNP & TnI) there are not statistically difference between the survivors & non survivors where p-value = 0.273 & 0.858.

By using cox regression analysis we found that they were not independent predictors of mortality in septic shock patients where B = 0.000 & –0.073 & p-value = 0.484 & 0.931.

By using ROC curve analysis NT proBNP may be used with borderline AUC 0.634, non significant p-value = 0.634, sensitivity 75 %, specificity 62.5 %, PPV 83.3 % & NPP 50 %. On other hand TnI could not be used at all as a tool for prediction the mortality in septic shock patients at cutoff point 0.4 where AUC is 0.478, a non significant p-value = 0.859, sensitivity 50 %, specificity 50 %.

These results are more or less similar to Sturgess results who studied 21 pts, with septic shock & they found that ROC curve analysis of NTproBNP was 0.67 but for TnT was 0.78. As regard univariate cox regression analysis yielded significant associations between survival to hospital discharge and E/é (p = 0.005), and TnT (p = 0.03) [26].

Contrary to our results cardiac troponin I found to be an independent predictor of hospital mortality in Mehta study who found that serum cTnI and APACHE II score were independent predictor of death and length of stay in intensive care unit [32]. John et al., also found that Elevated cTnI was an independent prognosticator of mortality (odds ratio, 2.020; 95% confidence interval, 1.153-3.541) after adjusting for other significant variables [33].

Although by cox regression analysis hs-CRP is not predictor of mortality in septic shock pts, but by ROC curve it had a significant AUC = 0.725, p-value = 0.05, sensitivity 85 % & specificity 75 % at cutoff point 34.05 mg/l.

These might correlate with Cai et al., results in a prospective and randomized controlled study in patients receiving early goal directed therapy (EGDT), they found a positive correlation between hs-CRP and cTnI with p-value = 0.05, also there was positive correlation with APACHE II & mortality rate [34].

Conclusion:
E/é and DT obtained by PW and TDI both offer independent and better prognostic prediction of hospital outcome in septic shock as compared with cardiac biomarkers (NT-proBNP & cTnI).

References


