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Diastolic Dysfunction and In - Hospital Mortality in Sepsis: A Study from Tertiary Care Rural Hospital

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Abstract: ***Background: Sepsis is a leading cause of mortality with rate eight times more than that due to other causes and is also a major cause of morbidity. Cardiac dysfunction augments the mortality rate in these patients. Diastolic dysfunction can predict long term mortality and morbidity in sepsis and is recognized to be a major cause of heart failure with normal ejection fraction (LVEF>55%). Objectives: Co - relate LVDD with APACHE 2 score and its effect on in - hospital mortality. Methodology: This present study is an observational cross - sectional study from tertiary care rural hospital.140 patients of sepsis were observed for evidence of LVDD. Necessary investigations and cultures were sent. Bedside 2D Echo documented E Wave, A wave and septal e'. Worse APACHE 2 scores during hospital stay were noted. Results: 140 patients of sepsis with mean age is 50.15±16.37 years, 94 (67.14%) were males and 46 (32.86%) females. There were 104 (74.3%) survivors and 36 (25.7%) non - survivors. CKD and DM were important co morbidities.83 patients were culture positive and 88 had positive CRP. Mortality was higher in patients with higher APACHE 2 scores. Presence of LVDD had effect on in - hospital mortality. Conclusions: Mean arterial pressure, positive cultures (from source of infection), APACHE 2 scores and septal e' were strong independent predictors of in - hospital mortality. There is a necessity in monitoring of these parameters to prognosticate in - hospital outcome.***

Keywords: Sepsis, Mortality, Left ventricular diastolic dysfunction, Outcome

1. Introduction

Sepsis is a leading cause of mortality and is a major cause of morbidity causing end organ damage as well as cognitive and physical disability in survivors. [1, 2, 3] Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestation of infection. [4]

The hospital stay of a patient with sepsis is nearly twice and the mortality rate is eight times more than that due to other cause. [2, 5]

Sepsis needs aggressive treatment in the form of early antibiotic therapy, sending relevant cultures and limiting aggressive resuscitative strategies to improve the chances of survival. [6–8]

Patients with sepsis generally have multiple predisposing factors and sources of infection. Cardiac dysfunction adds up to increasing the mortality rate in these patients. [9]

When compared to patients who don't have left ventricular diastolic dysfunction (LVDD) with patients who develop LVDD during sepsis, have worse prognosis. [10, 11]

Management of sepsis is frequently complicated with high prevalence of cardiac disease in hospitalized patients. [12]

The diastole encompasses the time period during which the myocardium loses its ability to generate force and shorten and returns to an unstressed length and force.

Diastolic dysfunction occurs when these processes are prolonged, slowed, or incomplete. Whether this time period is defined by the classic concepts of Wiggers or the constructs of Brutsaert, the measurements that reflect changes in this normal function generally depend on the onset, rate, and extent of ventricular pressure decline and filling and the relationship between pressure and volume or stress and strain during diastole. Moreover, if the diastolic function is truly normal, these measurements must remain normal both at rest and during the stress of a variable heart rate, stroke volume, end - diastolic volume, and blood pressure. [13]

Severe peripheral vasodilatation, absolute or relative decrease in central blood volume, altered left and right ventricular function result in complex and wide ranging hemodynamic consequences. Circulating factors mediate the etiology of these cardiovascular abnormalities that can be systolic or diastolic dysfunctions. [14–17]

Diastolic and systolic dysfunctions have been focused separately in most of the researches on cardiovascular dysfunctions in septic patients. [18–21]

Diastolic dysfunction can predict long term mortality and morbidity in sepsis and is recognized to be a major cause of heart failure with normal ejection fraction (EF>55%).

Only few studies and limited data are available on cardiac dysfunction in sepsis and septic shock and also on the prognostic importance of diastolic dysfunction in sepsis and septic shock. [11, 22–25]

Presence of left ventricular dysfunction in critically ill septic patients complicates the management due to concern about development of pulmonary edema and respiratory failure from excessive fluid administration. [26]

There is sufficient data of LVDD in sepsis and its impact on outcome from developing countries. However, there is insufficient evidence from middle and low income countries.

Severe sepsis is common in Indian ICUs and is mainly due to gram negative organisms. In - hospital mortality documented in this study was high as 63.3% including a mortality of 85 % in severe sepsis. [27] Epidemiological data from sepsis comes from western literature and data from India are sparse. Hence the objective of this study was to document LVDD in sepsis from a tertiary care rural hospital.

2. Material and Methods

This cross - sectional study was conducted in intensive care unit (ICU) of department of Medicine from a tertiary care teaching hospital from September 2016 to August 2018.140 consenting patients above 18 years of age and fulfilling the criteria for sepsis as mentioned in guidelines for sepsis were included in the study. The exclusion criteria were cases of chronic hypertension, myocardial, pericardial, valvular and coronary artery disease as also patients with cardiac dysrhythmias and 2D Echo showing regional wall motion abnormality (RWMA) or left ventricular ejection fraction (LVEF) less than 55% (normal EF more than 55%). All admitted patients were clinically assessed for sepsis by clinical and biochemical investigations. Appropriate cultures (from source of infection) and CBC, LFT, KFT, ABG and C - reactive protein (CRP) were sent.

Bedside 2D Echo [model Wipro GE Vivide SR - 460051WXE (15)] documented mitral inflow peak early diastolic filling (E Wave), mitral inflow late diastolic filling (A wave), septal e' and ratio of mitral inflow peak early diastolic filling to mitral inflow late diastolic filling (E/A), ratio of early diastolic mitral inflow to peak early mitral medial annular velocity (E/septal e') were calculated. The worst APACHE 2 (acute physiology and chronic health evaluation) scores within first 24 hours of ICU admission were noted.

Patients were examined in left lateral decubitus position for optimal acoustic window. Scan was performed to obtain 4 chamber, 2 chamber, parasternal long axis view, short axis and subcostal view.2D Echo and Doppler continous wave doppler (CW), pulse wave doppler (PW) and tissue doppler imaging (TDI) assessment was done. Observations and measurements of the 2D Echo measures were taken and recorded in standard proforma sheet. At the end of the study, all observations were subjected to standard statistical analysis and conclusions were drawn.

For diastolic function assessing LVDD, four chamber view was obtained and optimised.

Pulse Doppler sample volume was placed at mitral leaflet tips and spectral display was generated. E wave and A wave velocity was measured.

Tissue Doppler mode was then activated and Doppler sample volume placed at medial mitral annulus and spectral display was generated and septal e' velocity was measured.

Left ventricular diastolic dysfunction was assessed by using hemodynamic Doppler (E/A) and tissue Doppler (septal e') and patients were categorized as presence or absence of LVDD according to the ASE guidelines (2009). [28]

- Presence of LVDD was when E/A ratio was between 0.8 - 1.5cm/second and septal e' less than 8 cm/second. (mild or grade 1 LVDD: less than 0.8; moderate or grade I2 LVDD: 0.8 – 1.5; severe or grade 3 LVDD: more than 2)
- Absence of LVDD was determined if E/A ratio was more than 1 cm/second and septal e' was more than 8 cm/second.

For distinguishing E/A ratio normal from pseudonormal, E/A ratio to be normal should be more than 1 but less than 2 cm/second and when the patient is asked to do valsalva both the E and A values should decrease with no change in ratio. E/ septal e' should be less than 10 cm/second.

For E/A ratio to be pseudonormal, range should be between 0.8 to 1.5 cm/second and on valsalva E decreases more than A so the ratio decreases that is less than one. E/septal e' to be more than 15 cm/second.

Statistical analysis:
All Statistical analysis was done by using statistical package of social science (SPSS) 22.0 version and Graph Pad Prism 6.0 version.

The data was presented as mean for continuous variables or absolute number (%) for categorical variable unless otherwise specified.

A 'p' value <0.005 was considered statistically significant.

Correlation of all culture (from source of infection) and CRP with left ventricular diastolic dysfunction was compared by using Z test for differentiating between two means.

In all other tables, categorical data was compared using chi square test.

Cox Regression multivariate regression analysis was used for comparing independent predictors with outcome of the patients.
Receiver operating curve (ROC) was calculated by sensitivity and specificity.

3. Results

Of the 140 study participants, 94 were males with a mean age of 50.15 ± 16.37 years and had an equal distribution across all age groups. The mean value of mean arterial pressure (MAP) was 74.17±23.27 mmhg. Chronic kidney disease (CKD) and diabetes mellitus (DM) were common co - morbidities. The mean APACHE 2 score was 27 and all patients had deranged kidney function. The mean leukocyte count was high.

LVDD was documented in patients between 40 to 60 years showing a statistical significance.

The higher APACHE 2 score correlated with presence of LVDD showing statistical significance shown in [Table 1].

The following table shows that higher APACHE 2 scores and presence of LVDD was significantly related with in - hospital mortality shown in [Table 2].

The mean age of non survivors was 55 yrs and there were more males (80%) as compared to females. The statistically significant variables were MAP, high APACHE 2 score and tachycardia. There was no correlation with co - morbidities and CRP. However positive cultures, high leukocyte count and low platelet count were significant lab values in the non

- survivors. Presence of LVDD was seen in 86% of non - survivors

The Walds statistics and multivariatae analysis showed that MAP, positive cultures (from source of infection), APACHE 2 scores and septal e' were strong independent predictors of in - hospital mortality. As we know the hazard ratio is always a better and independent predictor as well as represents the instantaneous risk over the entire study while odds ratio represents the cumulative risk over the entire study period hence hazard ratio represents extremely less selection bias in comparison to odds ratio. In respect to the table above hazard ratio nearly equivalent to one indicates the difference between the groups is proportion that is equivalence contribution to death. The hazard ratio of culture 3.10 indicates three times risk of mortality independent of other co - variables in the study shown in [Table 3].

Table 1: Correlation of APACHE 2 score with LVDD (n = 140)

APACHE 2 Scoring points	No of patients	Left ventricular diastolic dysfunction	
		Present	Absent
0 to 4	0		
5 to 9	0		
10 to 14	1	1 (100%)	0 (0%)
15 to 19	13	4 (30.77%)	9 (69.23%)
20 to 24	44	18 (40.91%)	26 (59.09%)
25 to 29	52	36 (69.23%)	16 (30.77%)
30 to 34	26	21 (80.77%)	5 (19.23%)
35 to 100	4	3 (75%)	1 (25%)
Total	140	83 (59.29%)	57 (40.71%)
ϰ2 - value		18.73, p=0.0022, S, p<0.05	

(p value < 0.05)

Table 2: Correlation of outcome and APACHE 2 score and LVDD with in - hospital mortality (n=140)

APACHE - 2 Scoring points	No of patients	Actual Outcome			
		Survivor (n=104)		Non Survivor (n=36)	
		Left ventricular diastolic dysfunction present	Left ventricular diastolic dysfunction absent	Left ventricular diastolic dysfunction present	Left ventricular diastolic dysfunction absent
0 to 4	0				
5 to 9	0				
10 to 14	1	1 (0.96%)	0 (0%)	0 (0%)	0 (0%)
15 to 19	13	4 (3.85%)	9 (8.65%)	0 (0%)	0 (0%)
20 to 24	44	13 (12.50%)	25 (24.04%)	5 (13.89%)	1 (2.78%)
25 to 29	52	23 (22.12%)	14 (13.46%)	13 (36.11%)	2 (5.56%)
30 to 34	26	11 (10.58%)	3 (2.88%)	10 (27.78%)	2 (5.56%)
35 to 100	4	0 (0%)	1 (0.96%)	3 (8.33%)	0 (0%)
Total	140	52 (50%)	52 (50%)	31 (86.11%)	5 (13.89%)
ϰ2 - value		14.47, p=0.012, S, p<0.05		29.09, p=0.0001, S, p<0.05	

(p value < 0.05)

Table 3: Wald statistics and multivariate analysis for independent predictors of in - hospital mortality (n=140)

Parameters	B	S. E.	Wald	p - value	Hazard Ratio	Odd's Ratio	95% C. I. for EXP (B)	
							Lower	Upper
MAP	-0.037	0.011	12.357	0.0001, S	0.95 (0.941 - 0.986)	0.963	0.94	0.98
Culture (from source of infection)	1.115	0.514	4.699	0.030, S	3.10 (1.121 - 8.215)	3.05	1.11	8.36
APACHE 2 Score	0.159	0.061	6.799	0.009, S	1.18 (1.021 - 1.312)	1.173	1.04	1.32
Septal e'	-0.223	0.101	4.903	0.027, S	0.75 (0.61 - 0.965)	0.8	0.65	0.97
Outcome	-2.322	2.229	1.086					

(p value < 0.05)

4. Discussion

The mean age of patient was 50±16 years which was a younger population as compared to other studies where the mean age was between 60 to 70 years. [29, 30, 31]

The presence of LVDD in sepsis in both males and females was observed in patients above 40 years of age. The non - survivors had lower MAP and higher APACHE 2 scores which was similar to other studies. [30, 32, 33]

Presence of chronic kidney disease and diabetes were significant co - morbidities observed in the study population which was contrary to other studies. The presence of LVDD was seen in 86% of non - survivors.

Though LVDD is associated with age, hypertension, diabetes mellitus, the LVDD is still an important predictor of mortality than age and other co - morbidities in patients of sepsis.

High APACHE 2 scores correlated with presence of LVDD in sepsis patients.

Although the value of biomarkers like CRP is not statistically significant yet, it was included as a routine lab investigation. There are no gold standard biomarkers in sepsis, however procalcitonin and sTREM 1 as sepsis biomarkers are being used frequently. But, in resource poor settings their use should be discouraged.

The application of multivariate logistic analyses observed that mean arterial blood pressure, APACHE 2 score, septal e' and cultures taken from source of infection were strong independent predictors of in - hospital mortality.

Other studies observed ICU scores like sequential organ failure assessment (SOFA) scores and also E/e' as independent predictors of mortality. [29, 34]

In this study, none of the patients were old diagnosed cases of sepsis.

There is sufficient data of LVDD in sepsis and its impact on outcome from developed countries. However, there is insufficient evidence from middle and low income countries. [27, 35]

This study from low resource setting observed that to prognosticate mortality with simple measures like mean arterial pressure, blood cultures, septal e', E/septal e' which are accessible and inexpensive resources in the background of increasing burden of sepsis in developing countries.

5. Conclusion

In the absence of expensive biomarkers and other modalities that prognosticate in - hospital mortality in patient of sepsis. MAP, cultures, and LVDD can be valuable tools. The ability to put emphasis on easily accessible and measured parameters like mean arterial pressure, cultures, and measurement of septal e' and E/septal e' cannot be underestimated and hence should be included in the sepsis management protocol.

Conflict of Interest
Authors declare no conflict of interest.

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