Cardiac Dysfunction and Serum Ferritin Level as Early Prognostic Markers in Children with Sepsis.

Nagwa Mohamed Sabry Abdelsalam Mahmoud (dr_nagwa163@yahoo.com)
Minia University Faculty of Medicine
https://orcid.org/0000-0002-2221-710X

Ahlam M. Ismail
Minia University Faculty of Medicine

Moustafa Ahmed El Sayed Ahmed Abu Elela
Minia University Faculty of Medicine

Islam nashaat roshdy Ahmed
Minia University Faculty of Medicine

Research

Keywords: Cardiac Dysfunction, Serum Ferritin Level, Children with Sepsis, Prognostic Markers

DOI: https://doi.org/10.21203/rs.3.rs-126216/v1

License: © This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Objective: This study aimed to evaluate the association of Cardiac dysfunction assessed by Echocardiogram study, ferritin, c-reactive protein, and leukocyte count with unfavorable outcomes in pediatric sepsis within the pediatric intensive care unit.

Methods: A prospective cohort study was carried out from September 2019 to April 2020, with 40 patients admitted to a pediatric intensive care unit (PICU) at Minia University Children and Maternal hospital, aged between 28 days and 15 years. Inclusion criteria were patients diagnosed with sepsis, need for mechanical ventilation for quite 48h, and vasoactive drugs. Serum levels of C-reactive protein, ferritin, and leukocyte count were collected within 24 h of admission (D1), and 72 h (D3) after admission to PICU. Patients underwent echocardiography study to figure out the ejection fraction of the ventricle on D1 and D3. The outcomes measured through length of stay at hospital and at the pediatric intensive care unit, mechanical ventilation (MV) duration, free hours of VM, duration of use of inotropic agents, maximum inotropic score, and mortality.

Results: Patients with elevated ferritin levels on D1 had less ventilator-free time and higher maximum inotropic score. Patients with cardiac dysfunction by echocardiogram on D1 had longer hospital stay pediatric intensive care unit, stay longer duration of mechanical ventilation higher maximum inotropic score, and fewer ventilator-free hours

Conclusion: Cardiac dysfunction by echocardiography study and serum ferritin value was significantly related to unfavorable outcomes in pediatric patients requiring admission to PICU with sepsis.

Introduction

Sepsis remains a crucial explanation for morbidity and mortality within the pediatric intensive care unit (PICU) environment. Definitions for sepsis and organ dysfunction for children have been developed by the International Consensus Conference on Pediatric Sepsis

Systemic inflammatory response syndrome — The systemic inflammatory response syndrome (SIRS) is present when a child has an abnormality of temperature (fever or hypothermia) or age-specific abnormality of the white blood cell count and one among the followings: tachycardia, bradycardia, respiratory distress, or pulmonary condition requiring mechanical ventilation. SIRS within the presence of suspected or proven infection constitutes sepsis. Clinical manifestations typically progress along a continuum of severity from sepsis to severe sepsis, septic shock, and multiple organs failure [1]. [2].

Finding tools which will anticipate or monitor unfavorable evolution in sepsis can contribute to the development of care in these critically-ill patients.

Thus, several biological markers have recently been studied as tools to gauge disease progression in bacterial infections, sepsis, and septic shock.(3–8)
Among the biomarkers, the foremost often utilized in the authors’ setting are leukocyte count, c-reactive protein (CRP), procalcitonin, and ferritin levels (4,6–8).

Inflammatory biomarkers, such as C-reactive protein and procalcitonin, may be useful in select cases, (9,10). For example, For example, procalcitonin and C-reactive protein (CRP) could also be useful in identifying the presence of significant bacterial infection in infants and young children who present to an emergency department with emergency department with fever and no apparent source of infection. They may also be useful in predicting bacterial infection in patients with fever and neutropenia (11,12) In addition, C-reactive protein may guide safe de-escalation of antibiotics for patients who clinically improve in the absence of an identifiable source of infection (15). However, there are limited studies in pediatrics correlating serum levels with unfavorable outcomes.

In pediatric sepsis, myocardial dysfunction is one of the foremost causes of clinical deterioration. (16) Myocardial dysfunction could even be present in up to 50% of cases of severe sepsis or septic shock, causing systolic or diastolic ventricular dysfunction and contributing to shock and mortality. (17) The echocardiogram is already utilized in the management of patients with septic shock during volumetric resuscitation and to settle on the simplest vasoactive drug. (18,19) It’s speculated that evaluations obtained by echocardiographic assessment are often used as markers of sepsis evolution. Additionally, few studies have associated these measures with unfavorable outcomes in pediatric sepsis. (20)

**Patients And Methods**

This prospective cohort study included 40 patients; they were recruited during the period from September 2019 to April 2020 at Minia University Children and Maternal hospital, department of pediatrics, pediatric intensive care unit. This study was approved by ethical committee, faculty of drugs, El- Minia University. A written consent was obtained from each parent to agree to participate within the study. Protect the participant’s confidentiality, avoiding using deceptive practice. Giving participants the proper to withdraw from our research. We declared no conflict of interest with respect of the study. Demographic and clinical data of patients included within the study were collected and analyzed.

All patients hospitalized during the abovementioned period who required mechanical ventilation (MV) for quite 48 h using cardiovascular support and who had clinical diagnosis or suspicion of sepsis were included. Exclusion criteria were: congenital heart disease, presence of confirmed or suspected endocrine disease, diagnosis of congenital or acquired immunosuppression, severe liver impairment. Sepsis was defined because the presence of two or more of subsequent four criteria: tachycardia, tachypnea, temperature change, leukocytosis, or leukopenia for age within the presence of confirmed or suspected infection based on 2001 SCCM/ ACCP/ ATS/ eSCiM/ SiS Consensus Conference (24).

The organic dysfunctions were classified consistent with Goldstein et al. (21) The presence of two or more organic dysfunctions was considered as multiple-organ dysfunction syndrome. All patients within the study had their serum levels of CRP, ferritin, and leukocyte counts assessed at study entry 24 h (D1),
and 72 h (D3) after admission. The sample was stratified consistent with CRP values (greater than 6 mg/L), ferritin (≥ 250 ng/mL) (22), and leukocyte count (15,000/ L) for association with outcomes.

On D1 and D3, all patients underwent transthoracic echocardiography to work out left ventricular ejection fraction (EF). The EF represents the ejected volume, in percentage, of the left ventricular end-diastolic volume, i.e., what proportion blood is ejected into the aorta at systole. (23)

Assessment of cardiac dysfunction: done by transthoracic echocardiography to work out left ventricular ejection fraction on day of admission D1 & D3. The device used is logic v2 GE echo with 3 and 6 MHz transducer. All assessments were performed using an equivalent device and by an equivalent pediatric cardiologist with experience within the Pediatric Cardiology Service of the Hospital.

Technique: Bedside echo cardiogram is usually used for assessing ventricular measurements and function. The left ventricle's systolic function is tested qualitatively on "eye-balling" visual inspection and quantitatively by evaluating circumferential fraction shortening or Simpson's planimetry determining the fraction of the ejection. The assessment of left ventricular diastolic activity is predicated largely on the examination of the mitral valve and pulmonary venous Doppler tracings or Doppler tissue. Measurement of Cardiac Dimensions: The ventricular axis are often measured using M-mode, which is measured using the leading-edge technique. The left ventricular M-mode trace is collected from the parastern long-axis (PLAX) or parastern short-axis (PSAX) vision, the cursor in M-mode should be positioned at the level of the posterior mitral valve leaflet perpendicular to the interventricular septum and posterior wall.

Evaluation of Left Ventricular Systolic Function was done using Qualitative Assessment: An experienced non-echo cardiographer can perform visual inspection to assess left ventricular function, and Quantitative Assessment: the foremost widely used parameters for determining systolic left ventricular function are fraction shortage and ejection fraction. The FS is obtained from M-mode tracings or 2D imaging within the long parasternal axis view at the ideas of the bicuspid valve leaflets or within the short parasternal view at the papillary muscle level. The left ventricular end-diastolic dimension (LVEDD) is estimated at the top of the T-wave, the R-wave of the cardiac cycle and therefore the left ventricular end-systolic dimension (LVESD) is calculated using the subsequent equation: FS (%) = LVEDD – LVESD / LVEDD × 100. The EF may be a measurement, expressed as a percentage, of what proportion blood the ventricle pumps out with each contraction, calculated using the subsequent equation: EF (%) = LVEDV – LVESV / LVEDV × 100. (23)

The left ventricular shortening fraction was also measured, using an equivalent formula, altogether patients. The results obtained were overlapping; therefore, it had been decided to use only the EF within the statistical analyses.

The following outcomes were evaluated: length of hospital stay (days), length of stay within the PICU (day’s time of total MV (hours), time without MV (hours), total time of inotropic use, maximum inotropic score, and mortality.
For the maximum inotropic score, the absolute best value, obtained on any day of the study, was calculated through a summation obtained from the formula: dose of dopamine + dobutamine + (epinephrine × 100) + (noradrenaline × 100) + (milrinone × 10). All of them were expressed in mcg/kg/min. (25) The Pediatric Index of Mortality 2 (PIM2) was calculated on the first day of the PICU, according to the routine of this service. (26) A PIM2 value of 6% was chosen because the cutoff point for severity, because it’s that the upper limit of historical mortality during this service.

The analysis of the data was administered using the IBM SPSS 20.0 statistical package software and MedCalc version 12.2.1.0 (MedCalc Software, Ostend, Belgium). Data were expressed as median, interquartile range (IQR), mean ± standard deviation (SD) for quantitative measures additionally to both number and percentage for categorized data. The normality of data was assessed using Kolmogorov-Smirnov test. Mann Whitney test was used for comparison between independent groups and Wilcoxon test for dependent groups for non-parametric data. The Chi-square test or Fisher’s exact test were used to compare categorical variables.

Receiver operating characteristic (ROC) curve was computed and therefore the area under the ROC curve was used to evaluate the ability of serum ferritin and ejection faction to predict occurrence of mortality. The optimum cutoff was defined because the value that maximized the area under the ROC curve. Spearman correlation was used to describe the association between two variables. Multiple binary logistic regressions were used to create a predictive model. A P-value of 0.05 or less was considered significant.

Results

There were 150 hospitalizations during the above-mentioned study period and, of these, 40 patients were eligible for the study. Socio-demographic characters of the studied cases, as presented in Table 1 shows the percentage of the females was (60%), males were (40%), eighty-five percent (85%) of cases was between 1 month and 2 years and 15% was between 2-6years, 65% of cases were from rural areas, with weight had mean ± SD (9.1 ± 4.4), and length/height had mean ± SD (75.9 ± 17.7). positive consanguinity was found in 30% of cases, As shown in Table (2), Serum Ferritin level among studied cases at day of admission (D1) and day 3, most cases show increased serum ferritin level above normal range and significantly decreased between day 3 and day of admission D1 (p < 0.001) also as shown in the same table Ejection faction at day of admission D1 and day 3 among studied cases, there is a statistically significant increase between day 3 and day of admission D1 as regard to Ejection faction (p = 0.001). in our study, there was a statistically significant difference between patients with cardiac dysfunction (EF < 55%) and those without cardiac dysfunction (EF ≥ 55%) as regard to serum Ferritin level (ferritin level increased in pediatric patients with cardiac dysfunction) (table 3).

In our study, the Outcome of studied cases, shows that the number of nonsurvivors was 24 and their percentage was 60%, while the number of survivors was 16 and their percentage was 40%, in our study, the Median value of serum Ferritin level is significantly higher among non-survivors than survivors.
pediatric patients with sepsis ($p = 0.021$). Our results also show that the Median value of Ejection fraction is significantly lower among non-survivors than survivors septic pediatric patients ($p = < 0.001$) as presented in Table (4).

Table (5) shows the relation between cardiac dysfunction at day of admission D1 and outcome among studied cases. This table shows that the number of non-survivors was 18 and their percentage was 94.7% and the number of survivors was 1 and their percentage was 5.3% among studied cases with cardiac dysfunction, while the number of non-survivors was 6 and their percentage was 28.6% and the number of survivors was 15 and their percentage was 71.4% among studied cases without cardiac dysfunction.

Table (6) shows that serum ferritin level has a sensitivity of 62.5% and specificity of 81.2% in prediction of mortality with ($p$ value = 0.002) with cut-off point $> 550$, while ejection fraction has sensitivity of 83.3% and specificity of 87.5% in prediction of mortality with ($p$ value = $< 0.001$) with cut-off point $\leq 56$%. Also as shown in the same, serum ferritin level had a sensitivity of 68.4% and specificity of 66.7% in prediction of cardiac dysfunction with ($p$ value = 0.016) with cut-off point $> 510$.

Final Table (7) shows Univariate and multivariable binary logistic regression analysis for predictors of mortality. This table clarify that factors found to be significantly associated with mortality by univariate analysis were entered the multivariable model to detect the significant predictors of mortality. Cardiac dysfunction and serum ferritin were found to be predictors of mortality. Patients with cardiac dysfunction were more likely to die than patients without cardiac dysfunction ($p = 0.035$). The increase in serum ferritin by 10 units was associated with a 10% increase in the odds of child to die (AOR = 1.01, 95% CI = 1.0–1.02).

**Discussion**

Sepsis is an important cause of mortality and morbidity in the pediatric intensive care unit, early identification and therapeutic interventions is the cornerstone in the outcome of sepsis, early recognition of sepsis is not always straightforward and clinical signs at presentation can be misleading due to frequent comorbidities or variable demographic characteristics. (27)

Cardiac dysfunction is one of the main causes of clinical deterioration in pediatric patients (16), the echocardiogram is already used in the management of patients with septic shock during volumetric resuscitation and to choose the best vasoactive drug (18), evaluations obtained by echocardiographic assessment can be used as markers of sepsis, few studies have associated these measures with unfavorable outcomes in pediatric sepsis (20).

Our study aimed to verify the association between serum ferritin levels and cardiac dysfunction with unfavorable outcomes in pediatric sepsis.

This present study was conducted on 40 infants and children suffering from sepsis of different causes admitted in the pediatric intensive care unit at Minia University Children and Maternal hospital,
department of pediatrics. 85% of cases were between 1 month and 2 years, they were 24 females (60%) and 16 males (40%).

Ferritin was the most prominent inflammatory marker in our study. It is an iron-storing protein, responsible for releasing it in a controlled way. In inflammatory processes, a great production of ferritin occurs, inducing a decrease in serum iron, believed to decrease the availability of iron to microorganisms. For this reason, ferritin in critically ill pediatric patients may be increased, and it is associated with severity in some illnesses (7).

C-reactive protein is an acute-phase reactant; it rises within six hours of the onset of inflammation and may raise to 10,000 folds with a peak at 48 hours, and disappears equally rapidly after the destructive process has stopped. CRP is not only useful in detecting the presence of an inflammatory disease but is also useful in following its progress and effectiveness of treatment. In particular serial measurements of CRP are very useful, for instance when one has to decide about the duration of antibiotic therapy in infection (28).

The diagnoses of the studied cases were three main categories: pneumonia (50%), central nervous system (CNS) infection (30%), and gastroenteritis (20%). The etiology of increase the risk of pneumonia may include environmental factors, genetic susceptibility, and ethnic causes (29). In this respect (Weiss et al., 2014) carried a study on the global epidemiology of pediatric sepsis and found that the most frequent site of infection was the respiratory system with pneumonia (40%). (30)

This present study showed that there was a highly statistically significant difference between a day of admission D1 and third day as regard to C-reactive protein with median value of CRP was higher on the day of admission 48 mg/L (24–104) compared to third day that was 24 mg/L (12–48) with P-value < 0.001.

Our study showed that there was a highly statistically significant difference between a day of admission D1 and third day as regard to serum ferritin level with median value of Ferritin level was higher on the day of admission 522 ng/ml (395–652) compared to third day that was 400 ng/ml (335.5–562) with P-value < 0.001.

In the current study, we found that the median value of Ferritin level was significantly higher among nonsurvivors septic cases 565 ng/ml (453.5-769.5) than survivors septic cases 456.5 ng/ml (347.5–539) with p-value = 0.021. This result agrees with (Bennett et al., 2011) (35) who found that very high serum ferritin levels are associated with high mortality in pediatric intensive care patients.

Our current study showed that cardiac dysfunction (EF < 55%) was present among 47.5% of the studied cases. This finding of cardiac dysfunction in sepsis (low Ejection fraction) of 47.5% of cases is higher than studies published by (Raj et al., 2014) (16) 37% of cases ;( Pulido et al., 2012) (33) 27% of cases; and (Furian et al., 2012) (34) 33% of cases.
The current study showed that the median value of Ejection fraction% was significantly lower among non-survivors 44% (36.5–55.5) than survivors with sepsis 60% (58.5–65.5) with P-value < 0.001.

This comes in agreement with (Elgazzar et al., 2018) (32) whose study carried out on 50 pediatric patients admitted to the pediatric intensive care unit (PICU) of Menoufia University Hospital with septic shock and found decreased EF% was higher among died than improved septic cases.

The present study showed that the number of cases died with cardiac dysfunction (18 patients 94.7%) was higher than that with no cardiac dysfunction (6 patients 28.6%) with p-value < 0.001.

In our study, we found that the median value of serum Ferritin level was significantly higher among cases with cardiac dysfunction than cases without cardiac dysfunction. In this respect (Tonial et al., 2017) (31) found that the mean value of serum Ferritin level was significantly higher among cases with cardiac dysfunction than those without cardiac dysfunction.

In our study, we found a statistically significant difference between cases with cardiac dysfunction and those without cardiac dysfunction as regard to duration of mechanical ventilation (hr) with p-value < 0.001, duration of inotropes (hr) with p-value 0.002, and maximum inotropic score with P-value < 0.001 while there was no statistically significant difference between cases with cardiac dysfunction and those without cardiac dysfunction as regard to duration of PICU admission (days) with P-value 0.713.

(Garcia et al., 2007) (6) found a statistically significant difference between cases with cardiac dysfunction and those without cardiac dysfunction as regards to duration of mechanical ventilation (hr) with P-value = 0.011, duration of PICU admission (days) with P-value = 0.02, and maximum inotropic score with P-value = 0.001. while there was no statistically significant difference between cases with cardiac dysfunction and those without cardiac dysfunction as regards to duration of inotropes (hr) with P-value = 0.231.

The receiver operating characteristics area under the curve (ROC-AUC) value of ferritin level > 550 ng/ml as cut point was 0.741 has a sensitivity of 62.5% and specificity of 81.2%. in prediction of mortality among studied patients.

Factors found to be significantly associated with mortality by univariable analysis were entered the multivariable model to detect the significant predictors of mortality, cardiac dysfunction, and serum ferritin were found to be predictors of mortality. Patients with cardiac dysfunction were more likely to die than patients without cardiac dysfunction (p = 0.035), the increase in serum ferritin by 10 units was associated with a 10% increase in the odds of child to die (AOR = 1.01, 95% CI = 1.0–1.02).

(Garica et al., 2007) (6) found ferritin level > 500 ng/ml is associated with a higher mortality rate with P-value 0.02.

Conclusion
cardiac dysfunction by echocardiogram (EF < 55%) on D1 and serum ferritin values (≥ 300 ng/mL) on DO, obtained in pediatric patients with sepsis admitted to the PICU, were significantly associated with unfavorable outcomes.

Study Limitations

Some limitations of this study should be indicated. The first is related to EF measurement by echocardiogram, which is a professional-dependent assessment. This method was chosen, despite its limitations, because it is available in most PICU services in Minia university hospital. The second is the lack of other biomarkers already studied in pediatric sepsis. It was decided to study the ones that are easily obtained and most commonly used in our PICU. Finally, the number of patients was a limitation. The authors studied an expressive group of very severe patients, in whom the inclusion and exclusion criteria were strict. The sample, while producing significant differences in results, had a low statistical power.

References

1. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005; 6:2.

2. Davis AL, Carcillo JA, Aneja RK, et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Crit Care Med 2017; 45:1061.

3. Teng Chung T, Hinds CJ. Treatment with GH and IGF-1 in critical illness. Crit Care Clin. 2006; 22:29-40.

4. Vila Pérez D, Jordan I, Esteban E, García-Soler P, Murga V, Bonil V, et al. Prognostic factors in pediatric sepsis study, from the Spanish Society of Pediatric Intensive Care. Pediatr Infect Dis J. 2014; 33:152-7.

5. Van Leeuwen HJ, Heezius EC, Dallinga GM, van Strijp JA, Verhoef J, van Kessel KP. Lipoprotein metabolism in patients with severe sepsis. Crit Care Med. 2003; 31:1359-66.

6. Garcia PC, Longhi F, Branco RG, Piva JP, Lacks D, Tasker RC. Ferritin levels in children with severe sepsis and septic shock. Acta Paediatr. 2007; 96:1829-31.

7. Demirkol D, Yildizdas D, Bayrakci B, Karapinar B, Kendirli T, Koroglu TF, et al. Hyperferritinemia in the critically ill child with secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction syndrome/macroage activation syndrome: what is the treatment? Crit Care. 2012; 16:52.

8. Raschke RA, Garcia-Orr R. Hemophagocytic lymphohistiocytosis-sis: a potentially underrecognized association with systemic inflammatory response syndrome, severe sepsis, and septic shock in adults. Chest. 2011; 140:933-8.
9. Marshall JC, Reinhart K, International Sepsis Forum. Biomarkers of sepsis. Crit Care Med 2009; 37:2290.

10. Kaplan JM, Wong HR. Biomarker discovery and development in pediatric critical care medicine. Pediatr Crit Care Med 2011; 12:165.

11. Luaces-Cubells C, Mintegi S, García-García JJ, et al. Procalcitonin to detect invasive bacterial infection in non-toxic-appearing infants with fever without apparent source in the emergency department. Pediatr Infect Dis J 2012; 31:645.

12. Maniaci V, Dauber A, Weiss S, et al. Procalcitonin in young febrile infants for the detection of serious bacterial infections. Pediatrics 2008; 122:701.

13. Hatzistilianou M, Rekliti A, Athanassiadou F, Catriu D. Procalcitonin as an early marker of bacterial infection in neutropenic febrile children with acute lymphoblastic leukemia. Inflamm Res 2010; 59:339.

14. Juutilainen A, Hämäläinen S, Pulkki K, et al. Biomarkers for bacteremia and severe sepsis in hematological patients with neutropenic fever: multivariate logistic regression analysis and factor analysis. Leuk Lymphoma 2011; 52:2349.

15. Downes KJ, Weiss SL, Gerber JS, et al. A Pragmatic Biomarker-Driven Algorithm to Guide Antibiotic Use in the Pediatric Intensive Care Unit: The Optimizing Antibiotic Strategies in Sepsis (OASIS) Study. J Pediatric Infect Dis Soc 2017; 6:134.

16. Raj S, Killinger JS, Gonzalez JA, Lopez L. Myocardial dysfunction in pediatric septic shock. J Pediatr. 2014;164: 72-7.

17. Smeding L, Plötz FB, Groeneveld AB, Kneyber MC. Structural changes of the heart during severe sepsis or septic shock. Shock. 2012; 37:449-56.

18. Deep A, Goonasekera CD, Wang Y, Brierley J. Evolution of haemodynamics and outcome of fluid-refractory septic shock in children. Intensive Care Med. 2013;39: 1602-9.

19. Ranjit S, Kissoon N. Bedside echocardiography is useful in assessing children with fluid and inotrope resistant septic shock. Indian J Crit Care Med. 2013; 17:224-30.

20. Carmona F, Manso PH, Silveira VS, Cunha FQ, de Castro M, Car- iotti AP. Inflammation, myocardial dysfunction, and mortality in children with septic shock: an observational study. Pediatr Cardiol. 2014; 35:463-70.

21. Goldstein B, Giroir B, Randolph A. International consensus conference on pediatric sepsis. International pediatric sep- sis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6: 2-8.

22. Laks D [Thesis] Ferritina como marcador de resposta infla- matória sistêmica de crianças criticamente doentes. Porto Alegre (RS): Programa de Pós-Graduação em Medicina/Pediatria e Saúde da Criança; Pontifícia Universidade Católica do Rio Grande do Sul; 2010.

23. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pel- lika PA. Recommendations for chamber quantification. Eur J Echocardiogr. 2006; 7:79-108.
24. Singer, M., Deutschman, C. S., Seymour, C. W., et al., (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA, 315(8): 801–810.

25. Brierley J, Carcillo JA, Choong K, Cornell T, Decaen A, Deymann A, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med. 2009; 37:666-88.

26. Slater A, Shann F, Pearson G, Paediatric Index of Mortality (PIM) Study Group. PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med. 2003;29: 278-85.

27. El-Shafiea MS, Khaled M. and Taema A. (2017): Role of presepsin compared to C-reactive protein in sepsis diagnosis and prognostication. The Egyptian Journal of Critical Care Medicine.

28. Lobo SM (2012). Sequential C-reactive protein measurements in patients with serious infections: does it help? Crit.Care.16(3):130.

29. El-Kinany HA, Mahfouz AA and Abd El-Fattah LE (2018). Impact of pre-pediatric ICU management on prognosis of sepsis and septic shock at Alexandria University Children's Hospital. Alex J Pediatr [serial online] [cited 2018 Dec 24]; 31: 14-21.

30. Weiss SL, Fitzgerald JC, Balamuth F, et al., (2014). Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis. Crit Care Med. 42:2409–2417.

31. Tontial CT, Garcia PCR, Schweitzer LC, et al., (2017). Cardiac dysfunction and ferritin as early markers of severity in pediatric sepsis. J Pediatr (Rio J). 93(3):301-307.

32. Elgazzar BA, Hassan FM, Khattab AA, et al., (2018). E/A ratio and troponin I level as measures of mortality in patients with shock in pediatric intensive care units. Menoufia Med J [serial online] [cited 2018 Dec 27]; 31: 677-80.

33. Pulido JN, Afessa B, Masaki M, et al., (2012). Clinical spectrum, frequency, and significance of myocardial dysfunction in severe sepsis and septic shock. Mayo ClinProc.87: 620-628.

34. furian T, Aguiar C, Prado K, et al., (2012). Ventricular dysfunction and dilation in severe sepsis and septic shock: relation to endothelial function and mortality. J Crit Care. 27, 319.e9- e15

35. Bennett, T. D., Hayward, K. N., Farris, R. W. D. et al., (2011). Very high serum ferritin levels are associated with increased mortality and critical care in pediatric patients. Pediatric Critical Care Medicine, 12(6), e233– e236.

Tables
Table 1
Demographic, clinical and laboratory data for studied patients at presentation

| Parameter                          | Total Patients (n=40) |
|------------------------------------|-----------------------|
| **Demographic data**               | No & %                |
| **Age (months)**                   |                       |
| Range                              |                       |
| 1 month – 2 years                 | 34 (85%)              |
| 2 – 6 years                        | 6 (15%)               |
| **Sex**                            |                       |
| Male                               | 16 (40.0%)            |
| Female                             | 24 (60.0%)            |
| **Residence**                      |                       |
| Rural                              | 26 (65%)              |
| Urban                              | 14 (35%)              |
| **Weight (kg)**                    |                       |
| Range                              | 3.5-23                |
| Mean± SD                           | 9.1±4.4               |
| **Length/Height (cm)**             |                       |
| Range                              | 55-120                |
| Mean± SD                           | 75.9±17.7             |
| **Consanguinity**                  |                       |
| +ve                                | 12 (30%)              |
| -ve                                | 28 (70%)              |
| **Family history of similar condition** |                   |
| +ve                                | 9 (22.5%)             |
| -ve                                | 31 (77.5%)            |
| **Diagnosis prior to PICU admission** |                 |
| Pneumonia                          | 20 (50.0%)            |
| CNS infection                      | 12 (30.0%)            |
| Viral encephalitis                 | 11 (27.5%)            |
| Gastro-enteritis                   | 8 (20.0%)             |
| Meningococcemia                    | 1 (2.5%)              |
| **Laboratory tests**               | Range | Median | Mean± SD |
| Hemoglobin (g/dl)                  | 8-10  | 9      | 9±1.5    |
| Total leucocyte count (x109/L)     | 9.5-23.5 | 15.5 | 16.8±9.3 |
|                          | D1                  | D3                  | Wilcoxon test | p value |
|--------------------------|---------------------|---------------------|---------------|---------|
| Ferritin (ng/ml)         | Median (IQR)        | 522 (395–652)       | 400 (335.5–562) | -3.677  | < 0.001* |
|                          | Mean ± SD           | 554.4 ± 223.3       | 447.8 ± 183.8  |         |         |
| EF%                      | Median (IQR)        | 55 (41.5–60)        | 60 (55-68.5)   | -3.417  | 0.001*  |
|                          | Median ± SD         | 52.28 ± 11.2        | 59.65 ± 9.64   |         |         |

This table shows that most cases show increased serum ferritin level above normal range and significantly decreased between day 3 and day of admission D1 (p < 0.001). Also shows that there is statistically significant increase between day 3 and day of admission D1 as regard to Ejection fraction (p = 0.001).
Table 3

Relation between Serum Ferritin level and cardiac dysfunction (EF %) at day of admission D1 among studied cases.

|                     | With cardiac dysfunction EF < 55% (n = 19) | Without cardiac dysfunction EF ≥ 55% (n = 21) | ZMWU test | p value |
|---------------------|-------------------------------------------|---------------------------------------------|-----------|---------|
| Ferritin            |                                           |                                             |           |         |
| Median (IQR)        | 568 (457–754)                             | 463 (365–568)                              |           |         |
| Mean ± SD           | 625.6 ± 214.3                             | 490 ± 216.2                                | -2.181    | 0.029*  |

ZMWU → Z value of Mann Whitney U test

The table shows that there was statistically significant difference between pediatric patients with cardiac dysfunction (EF < 55%) and those without cardiac dysfunction (EF ≥ 55%) as regard to serum Ferritin level (ferritin level decreased in pediatric patients without cardiac dysfunction).

Table 4

Outcome regarding serum ferritin level and Ejection fraction% among studied cases.

| Outcome                  | Non survivors (n = 24) (60.0%) | survivors (n = 16) (40.0%) | ZMWU | p value |
|--------------------------|---------------------------------|-----------------------------|------|---------|
| Ferritin                 |                                 |                             |      |         |
| Median (IQR)             | 565 (453.5–769.5)               | 456.5 (347.5–530)           | -2.306 | 0.021*  |
| Mean ± SD                | 630.7 ± 244.2                   | 440 ± 122.4                 |      |         |
| Range                    | (254–1150)                      | (240–650)                   |      |         |
| EF%                      |                                 |                             |      |         |
| Median (IQR)             | 44 (36.5–55.5)                  | 60 (58.5–65.5)              | -4.106 | < 0.001*|
| Mean ± SD                | 46.17 ± 10.82                   | 61.44 ± 5.3                 |      |         |
| Range                    | (33–70)                         | (50–72)                     |      |         |

This table shows that Median value of serum Ferritin level is significantly higher among non-survivors than survivors septic pediatric patients (p = 0.021).

This table also shows that Median value of Ejection fraction is significantly lower among non-survivors than survivors septic pediatric patients (p = < 0.001).
Table 5

relation between cardiac dysfunction at day of admission D1 and outcome among studied cases

|                  | With cardiac dysfunction EF < 55% (n = 19) | Without cardiac dysfunction EF ≥ 55% (n = 21) | χ² | p value | OR (95% CI) |
|------------------|----------------------------------------|------------------------------------------|----|---------|-------------|
| Outcome          |                                        |                                          | 18.195 | < 0.001* | 45.5 (4.9-416.5) |
| Non-survivors    | 18 (94.7%)                             | 6 (28.6%)                                |     |         |             |
| Survivors        | 1 (5.3%)                               | 15 (71.4%)                               |     |         |             |

This table shows that the number of non-survivors was 18 and their percentage was 94.7% and the number of survivors was 1 and their percentage was 5.3% among studied cases with cardiac dysfunction, while the number of non-survivors was 6 and their percentage was 28.6% and the number of survivors was 15 and their percentage was 71.4% among studied cases without cardiac dysfunction.

Table 6

serum ferritin level EF% and as predictive value of mortality among the studied cases.

|           | Cut-off | AUC  | P value     | Sensitivity | Specificity | PPV   | NPV  |
|-----------|---------|------|-------------|-------------|------------|-------|------|
| Ferritin  | > 550   | 0.741| 0.002*      | 62.5%       | 81.2%      | 83.3% | 59.1%|
| EF%       | ≤ 56    | 0.887| < 0.001*    | 83.3%       | 87.5%      | 90.9% | 77.8%|

This table shows that serum ferritin level has sensitivity of 62.5% and specificity of 81.2% in prediction of mortality with (p value = 0.002) with cut-off point > 550, while ejection fraction has sensitivity of 83.3% and specificity of 87.5% in prediction of mortality with (p value = < 0.001) with cut-off point ≤ 56%.
Table 7
Univariate and multivariable binary logistic regression analysis for predictors of mortality

| Predictors              | Mortality                                                                 |
|-------------------------|---------------------------------------------------------------------------|
|                         | Crude OR (95% CI) | p value | Adjusted OR (95% CI) | p value |
| EF                      |                                                                                   |
| No cardiac dysfunction  | 1.00 (Reference) | 1.00 (Reference) |                                                                  |
| Cardiac dysfunction     | 45. (4.86–416.5) | 0.001 | 63.22 (1.35–2963) | 0.035* |
| Serum Ferritin          | 1.01 (1.00-1.02) | 0.005 | 1.01 (1.00-1.02) | 0.038* |
| Duration of MV (hr)     | 1.03 (1.01–1.04) | 0.002 | 1.00 (0.96–1.04) | 0.874 |
| Duration of inotropes (hr) | 1.03 (1.01–1.05) | 0.008 | 0.99 (0.95–1.03) | 0.538 |
| Max. inotropic score    | 1.03 (1.01–1.06) | 0.004 | 1.00 (0.95–1.05) | 0.924 |

N.B. Dependent variable mortality, OR odds ratio, CI confidence interval

R2 = 0.758

This table shows that factors found to be significantly associated with mortality by univariate analysis were entered the multivariable model to detect the significant predictors of mortality. Cardiac dysfunction and serum ferritin were found to be predictors of mortality. Patients with cardiac dysfunction were more likely to die than patients without cardiac dysfunction (p = 0.035). The increase in serum ferritin by 10 unit was associated with 10% increase in the odds of child to die (AOR = 1.01, 95% CI = 1.0–1.02).

Figures
Figure 1

Receiver operating characteristic (ROC) curve displaying the diagnostic accuracy of serum ferritin to predict the mortality in the studied cases. This figure shows that serum ferritin level has sensitivity of 62.5% and specificity of 81.2% in prediction of mortality with (p value=0.002) with cut-off point >550.
Figure 2

Receiver operating characteristic (ROC) curve displaying the diagnostic accuracy of EF% to predict the mortality in the studied cases. This figure shows that ejection fraction has sensitivity of 83.3% and specificity of 87.5% in prediction of mortality with (p value=<0.001) with cut-off point ≤56%.
Figure 3

Receiver operating characteristic (ROC) curve displaying the diagnostic accuracy of serum ferritin to predict the occurrence of cardiac dysfunction in the studied cases. This figure shows that serum ferritin level had sensitivity of 68.4% and specificity of 66.7% in prediction of cardiac dysfunction with (p value=0.016) with cut-off point>510.