International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2024; 7(3): 230-234
Received: 04-05-2024
Accepted: 11-06-2024

Dr. Mahadevan Selvaraj
Civil Hospital Campus, B.J. Medical College, Haripura, Asarwa, Ahmedabad, Gujarat, India

Dr. Sanjay Vinayak Dhotre
Civil Hospital Campus, B.J. Medical College, Haripura, Asarwa, Ahmedabad, Gujarat, India

Dr. Bhavesh Faldu
Civil Hospital Campus, B.J. Medical College, Haripura, Asarwa, Ahmedabad, Gujarat, India

Dr. Shah Priyanka Vinodkumar
Civil Hospital Campus, B.J. Medical College, Haripura, Asarwa, Ahmedabad, Gujarat, India

Dr. Bansri B Patel
Civil Hospital Campus, B.J. Medical College, Haripura, Asarwa, Ahmedabad, Gujarat, India

Dr. Hansa Goswami
Civil Hospital Campus, B.J. Medical College, Haripura, Asarwa, Ahmedabad, Gujarat, India

Corresponding Author:
Dr. Mahadevan Selvaraj
Civil Hospital Campus, B.J. Medical College, Haripura, Asarwa, Ahmedabad, Gujarat, India

Correlation between CRP and APTT in critically ILL children with sepsis

Dr. Mahadevan Selvaraj, Dr. Sanjay Vinayak Dhotre, Dr. Bhavesh Faldu, Dr. Shah Priyanka Vinodkumar, Dr. Bansri B Patel and Dr. Hansa Goswami

DOI: https://doi.org/10.33545/pathol.2024.v7.i3d.605

Abstract
Background: Sepsis is associated with a deflection of inflammatory and coagulative parameters, since some clotting factors are known to be involved in the host's defence against infection and inflammation. These parameters could play a crucial role in the course of sepsis and be used as prognostic markers in critically ill children.
Objectives: The present study aims at studying the Correlation between inflammatory marker C-reactive protein and Coagulatory parameter aPTT.
Materials and Methods: A total of 300 critically ill pediatric patients diagnosed with sepsis were retrospectively analysed to find out the correlation between C-reactive protein (CRP) and activated partial prothrombin time (APTT) during a time period of six months from 1st July 2023 to 30th June 2024.
Results: Logistic regression analysis revealed C-reactive protein and activated partial thromboplastin time (aPTT) to be predictors for survival ($p = 0.04$ and $p = 0.002$ respectively).
An aPTT prolongation is associated with higher mortality compared to survivors whose aPTT is not prolonged.
Conclusion: Non-overshooting aPTT is associated with a higher survival rate in pediatric patients with diagnosed sepsis and whenever there is prolonged aPTT patients are having DIC, septic shock and other clinical comorbidities which increases the mortality.

Keywords: Sepsis, C-reactive protein, aPTT, pediatric

Introduction
Although the number of deaths caused by sepsis has drastically decreased in the last couple of decades [1], sepsis remains one of the main causes of mortality in infants and toddlers worldwide [1-3]. Sepsis in children peaks in the neonatal period and symptoms may be nonspecific in those patients [4], while older children may show hyperthermia, tachycardia, tachypnoea, hypotension and disorders in hemostasis up to the clinical picture of disseminated intravascular coagulation (DIC).
Sepsis is initially characterized by excessive production of pro-inflammatory cytokines, leukocyte activation and tissue damage, followed by release of anti-inflammatory cytokines, leukocyte deactivation and immunosuppression [5]. In the later phase of sepsis, compensatory release of anti-inflammatory molecules is thought to mediate a state of immunosuppression associated with significant impairment of immune cell function (immunoparalysis) [6]. The systemic inflammation during sepsis is observed by measuring leukocytes, procalcitonin, C-reactive protein and others. Leukocyte count is part of the definition associated with the progression of sepsis [7].
Data confirm that procalcitonin, which specifically increases in bacterial processes [8], is suitable as a diagnostic parameter in many cases in adults due to its high specificity [9, 10]. However, limited data are available for use in pediatric patients [11].
C-reactive protein reflects the inflammatory process and is widely used in clinical routine. Many studies have described an interrelation between an elevated C-reactive protein level and sepsis [12-15]. Thus, in clinical routine, daily C-reactive protein measurements might be used to assess the efficacy of treatment [16]. C-reactive protein can also be with few exceptions, such as antithrombin or platelets, the role of coagulation parameters in sepsis is

largely ignored. New diagnostic, prognostic and therapeutic strategies can be deduced by observing coagulating laboratory data and, where appropriate, modifying them in the event of excessive activation or dysregulation of the system [27, 28]. An increase in the pro-coagulatory parameters to high level is seen rather negatively in the inflammatory process because of their pro-thrombotic potential [29], although elevation of the pro-coagulatory parameters might be beneficial during sepsis due to their role in host defence. Therefore, it is worthwhile to examine the behaviour and influence of coagulation parameters in combination with the typical inflammatory parameters during sepsis.

Methods

This retrospective analysis comprises clinical data and routine laboratory parameters from 300 pediatric patients at the Pediatric Intensive Care Unit (PICU) of B.J. Medical College Hospital, Ahmedabad, Gujarat.

Inclusion of patients

All medical files of patients </= to 12 years of age who were treated at the pediatric intensive care unit (PICU) between 1st July 2023 to 30th June 2024, with the diagnosis of sepsis or systemic infection were reviewed. A total of 300 patients met the sepsis criteria of Goldstein [1]. There was no need to obtain oral and written informed consent from the study participants since the data were processed anonymously.

Data collection

Collected data includes demographic variables age, sex and the diagnosed underlying disease that triggered hospitalization. Septic shock was defined as the need for vasoactive drug to maintain blood pressure in the normal range during the septic episode [1]. The C-reactive protein level was used to objectify the progression of sepsis, because it is an established parameter of sepsis [12-16] and is used in our clinic in children of all ages. The coagulatory parameter a PTT was also noted for those patients.

Statistical analysis

All statistical assessments were two sided, and a significance level of 5% was used. The hypothesis of a normal distribution was not reasonable for most of the continuous variables (Shapiro–Wilk normality test). The Wilcoxon rank sum test and Fisher's exact test were applied to assess differences between survivors and non-survivors. We present continuous data as medians (25th–75th percentile) and binary variables as no./total no. (%). We show effect size and precision with estimated median differences between survivors and non-survivors for continuous data and odds ratios (OR) for binary variables, with 95% Confidence Interval (CI).

Results

Patient characteristics

In total, 300 patients met the eligibility criteria for study inclusion and final analysis. Of those septic children, 106(35.4%) did not survive while in hospital. Of the critically ill children, 43.8% suffered from sepsis and 56.2% from severe sepsis. Septic shock was reported in 96/300 (32%) children, of whom 42/96 (43.7%) died. Patients' baseline characteristics stratified for survival and non-survival are presented in Table 1.

Table 1: Number of Patients Survived

Sr.no		No. of cases
1	No. of patients survived	194(64.7%)
2	No. of patients expired	106(35.3%)
	Total	300

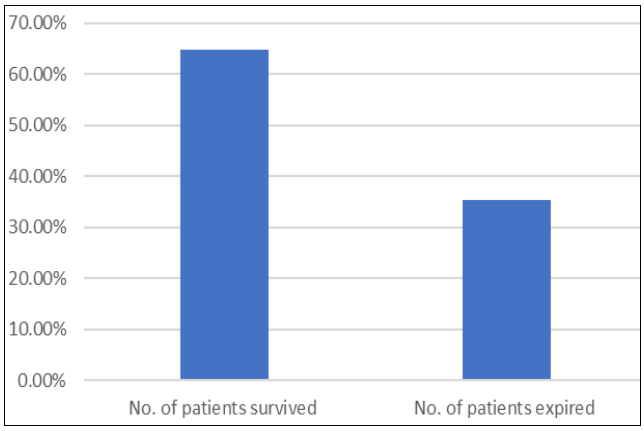

Fig 1: Number of Patients Survived

Table 2: Number of Patients Sepsis and Septic shock

Sr.no		No. of cases
1	No. of patients with sepsis	43.80% (132)
2	No. of patients septic shock	56.20% (168)
	Total	300

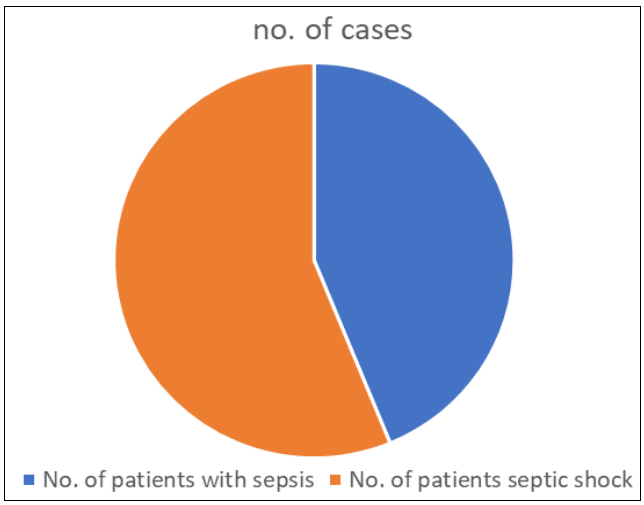

Fig 2: Number of Patients Sepsis and Septic shock

The most commonly affected organ systems resulting in ICU admission were the respiratory system in 66/300 (22%) and the central nervous system in 56/300(18.6%) children.
In total 300 patients 78% (204/300) patients have abnormal C-reactive protein values (>1mg/dl) and 60% (180/300) patients have abnormal aPTT values(>35seconds).
Out of 300 patients 20% (60/300) of patients not survived when aPTT is >35seconds (p=0.003, significant).

Table 3: Analysis of C-reactive protein:

Sr.no		No. of cases
1	No. of patients with abnormal C-reactive protein	78% (204)
2	No. of patients with normal C-reactive protein	22% (96)
	Total	300

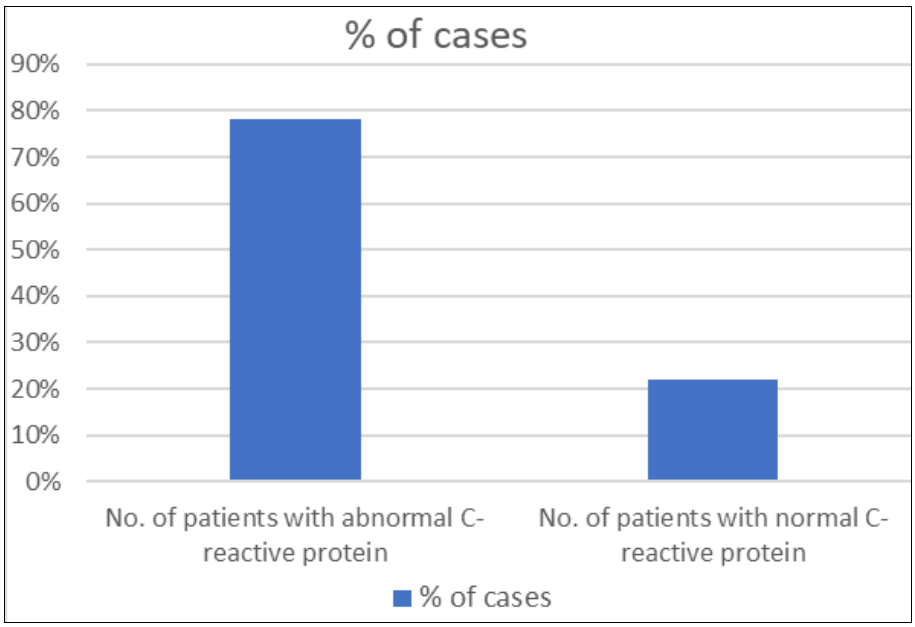

Fig 3: Analysis of C-reactive protein:

Table 4: Analysis of Activated partial thromboplastin time(aPTT):

Sr.no		
1	No. of patients with abnormal aPTT	60% (180)
2	No. of patients with Normal aPTT	40% (120)
	Total	300

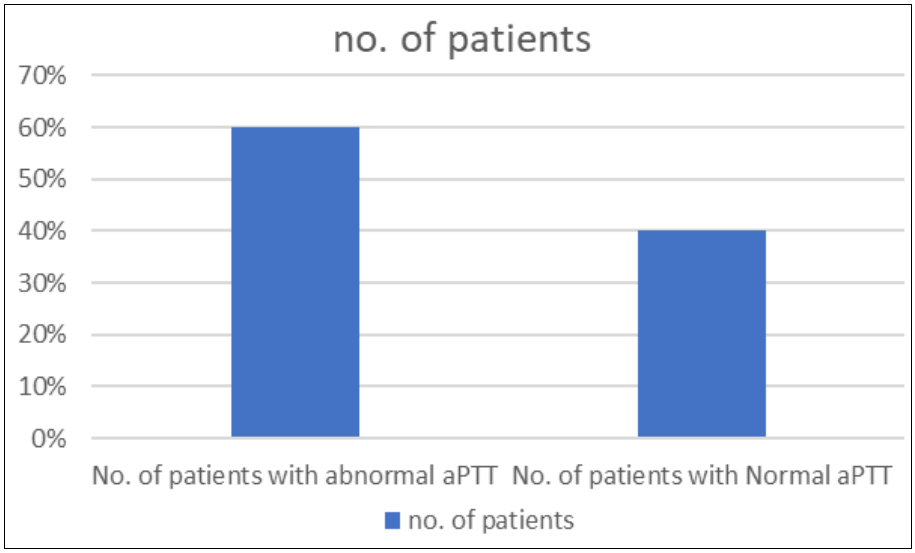

Fig 4: Analysis of Activated partial thromboplastin time(aPTT)

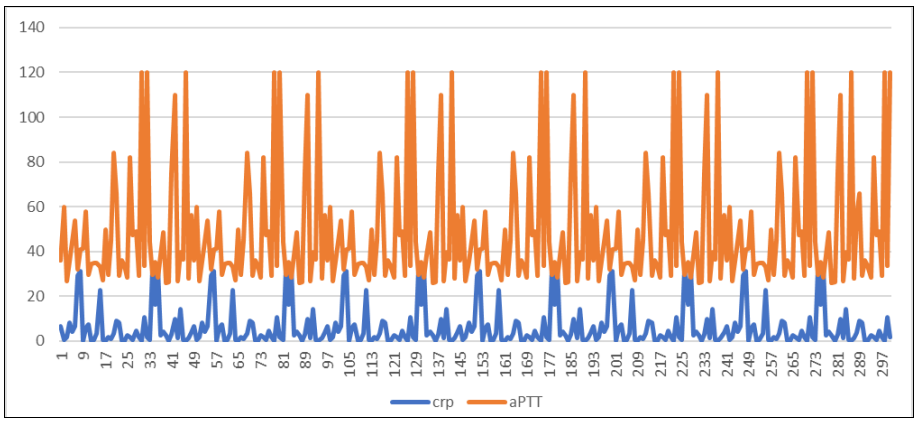

Fig 5: Correlation between C-reactive protein Activated partial thromboplastin time(aPTT)

Discussion

In this study, we investigated the impact of routinely measured coagulation and inflammation parameters on in-hospital survival in pediatric patients diagnosed with sepsis. The main result is that C-reactive protein at its peak level does not significantly differ between survivors
and non-survivors, whereas aPTT prolongation is associated with higher mortality. Several studies claim that C-reactive protein is of prognostic value in sepsis [12-15]. However, in our study focusing on mortality, C-reactive protein levels did not allow any differentiation between survivors and non-survivors. Most likely, in children as well as in adults with diagnosed sepsis C-reactive protein levels are highly elevated without predicting final outcome. Among the variables routinely measured while a prolongation of aPTT increases the risk. In this context of high levels of pro-thrombotic factors, the fear of a hypercoagulatory state during sepsis is present and justified, since this could contribute to the development of thrombosis. Coagulation parameter essential for the prediction of mortality in septic children in our study was aPTT. Prolongation leads to poorer outcome. A long aPTT might reflect the most severe cases of sepsis due to consumption of coagulation factors or high dose heparin therapy, but may also be caused by a factor XII deficiency. In septic patients, factor XII deficiency can be protective via attenuation of the factor XII-dependent bradykinin generation, complement activation and further contact pathway activation. The literature reports a mortality rate of 20–30% in the presence of septic shock [32], which increases to 52% in the case of additional MODS.

Our study is comparable with study conducted by “Christian Niederwanger and Mirjam Bachler” [33] in which prolonged aPTT is associated with increased mortality when there is elevated C-reactive protein in critically ill children with sepsis. The limitations of our study have to be mentioned.

Conclusion

The link between inflammation and coagulation plays a crucial role in children with sepsis. C-reactive protein does not allow discrimination between survivors and non-survivors. In contrast, prolonged aPTT is associated with lower survival, which might reflect therapy-related measures needed due to disease severity.

Acknowledgement

"We thank Dr. Dharti Ramani(colleague) and Dr. Vrushti Patel for their support and Dr. Saloni Parikh (colleague) for her expertise and guidance, which contributed to the success of this publication."

Conflict of Interest

Not available

Financial Support

Not available

References

1. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6(1):28.
2. Randolph AG, McCulloh RJ. Pediatric sepsis: important considerations for diagnosing and managing severe infections in infants, children, and adolescents. Virulence. 2014;5(1):179-189.
3. Hartman ME, Linde-Zwirble WT, Angus DC, Watson RS. Trends in the epidemiology of pediatric severe sepsis. Pediatr Crit Care Med. 2013;14(7):686-693.
4. Sokou R, Giallouros G, Konstantinidi A, Pantavou K, Nikolopoulos G, Bonovas S, *et al*. Thromboelastometry for diagnosis of neonatal sepsis-associated coagulopathy: an observational study. Eur J Pediatr. 2018;177(3):355-362.
5. van der Poll T, van Deventer SJ. Cytokines and anticytokines in the pathogenesis of sepsis. Infect Dis Clin North Am. 1999;13(2):413-426.
6. Reddy RC, Chen GH, Tekchandani PK, Standiford TJ. Sepsis-induced immunosuppression. Immunol Res. 2001;24(3):273-287.
7. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, *et al*. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med. 2003;31(4):1250-1256.
8. Schneider HG, Lam QT. Procalcitonin for the clinical laboratory: a review. Pathology. 2007;39(4):383-390.
9. Castelli GP, Pognani C, Meisner M, Stuani A, Bellomi D, Sgarbi L. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. Crit Care. 2004;8(4)
10. Clec’h C, Ferriere F, Karoubi P, Fosse JP, Cupa M, Hoang P, *et al*. Diagnostic and prognostic value of procalcitonin in patients with septic shock. Crit Care Med. 2004;32(5):1166-1169.
11. Chiesa C, Natale F, Pascone R, Osborn JF, Pacifico L, Bonci E, *et al*. C-reactive protein and procalcitonin: reference intervals for preterm and term newborns during the early neonatal period. Clin Chim Acta. 2011;412(11):1053-1059.
12. Schentag JJ, O’Keeffe D, Marmion M, Wels PB. C-reactive protein as an indicator of infection relapse in patients with abdominal sepsis. Arch Surg. 1984;119(3):300-304.
13. Maury CP. Monitoring the acute phase response: comparison of tumour necrosis factor (cachectin) and C-reactive protein responses in inflammatory and infectious diseases. J Clin Pathol. 1989;42(10):1078-1082.
14. Povoa P, Almeida E, Moreira P, Fernandes A, Mealha R, Aragao A, *et al*. C-reactive protein as an indicator of sepsis. Intensive Care Med. 1998;24(10):1052-1056.
15. Presterl E, Staudinger T, Pettermann M, Lassnigg A, Burgmann H, Winkler S, *et al*. Cytokine profile and correlation to the APACHE III and MPM II scores in patients with sepsis. Am J Respir Crit Care Med. 1997;156(3 Pt 1):825-832.
16. Yentis SM, Soni N, Sheldon J. C-reactive protein as an indicator of resolution of sepsis in the intensive care unit. Intensive Care Med. 1995;21(7):602-605.
17. Pinilla JC, Hayes P, Laverty W, Arnold C, Laxdal V. The C-reactive protein to prealbumin ratio correlates with the severity of multiple organ dysfunction. Surgery. 1998;124(4):799-805 (discussion 806).
18. Waydhas C, Nast-Kolb D, Trupka A, Zettl R, Kick M, Wiesholler J, *et al*. Posttraumatic inflammatory response, secondary operations, and late multiple organ failure. J Trauma. 1996;40(4):624-630 (discussion 630-1).
19. Ikei S, Ogawa M, Yamaguchi Y. Blood concentrations of polymorphonuclear leucocyte elastase and

interleukin-6 are indicators for the occurrence of multiple organ failures at the early stage of acute pancreatitis. J Gastroenterol Hepatol. 1998;13(12):1274-1283.
20. de Beaux AC, Goldie AS, Ross JA, Carter DC, Fearon KC. Serum concentrations of inflammatory mediators related to organ failure in patients with acute pancreatitis. Br J Surg. 1996;83(3):349-353.
21. Rau B, Steinbach G, Baumgart K, Gansauge F, Grunert A, Beger HG. Serum amyloid A versus C-reactive protein in acute pancreatitis: clinical value of an alternative acute-phase reactant. Crit Care Med. 2000;28(3):736-742.
22. Levi M, van der Poll T. Inflammation and coagulation. Crit Care Med. 2010;38(2 Suppl)
23. van der Poll T, Levi M. Crosstalk between inflammation and coagulation: the lessons of sepsis. Curr Vasc Pharmacol. 2012;10(5):632-638.
24. Berends ET, Kuipers A, Ravesloot MM, Urbanus RT, Rooijakkers SH. Bacteria under stress by complement and coagulation. FEMS Microbiol Rev. 2014;38(6):1146-1171.
25. Pahlman LI, Morgelin M, Kasetty G, Olin AI, Schmidtchen A, Herwald H. Antimicrobial activity of fibrinogen and fibrinogen-derived peptides—a novel link between coagulation and innate immunity. Thromb Haemost. 2013;109(5):930-9.
26. Senior RM, Skogen WF, Griffin GL, Wilner GD. Effects of fibrinogen derivatives upon the inflammatory response. Studies with human fibrinopeptide B. J Clin Invest. 1986;77(3):1014-1019.
27. Lauterbach R, Pawlik D, Radziszewska R, Wozniak J, Rytlewski K. Plasma antithrombin III and protein C levels in early recognition of late-onset sepsis in newborns. Eur J Pediatr. 2006;165(9):585-589.
28. Semeraro F, Colucci M, Caironi P, Masson S, Ammollo CT, Teli R, *et al*. Platelet drop and fibrinolytic shutdown in patients with sepsis. Crit Care Med. 2018;46(3)
29. Esmon CT. The interactions between inflammation and coagulation. Br J Haematol. 2005;131(4):417-430.
30. Akaike H. A new look at the statistical model identification. IEEE Trans Autom Control. 1974;19(6):716-723.
31. Ersoy B, Nehir H, Altinoz S, Yilmaz O, Dundar PE, Aydogan A. Prognostic value of initial antithrombin levels in neonatal sepsis. Indian Pediatr. 2007;44(8):581-584.
32. Wilkinson JD, Pollack MM, Ruttimann UE, Glass NL, Yeh TS. Outcome of pediatric patients with multiple organ system failure. Crit Care Med. 1986;14(4):271-274.
33. Niederwanger C, Bachler M, Hell T, *et al*. Inflammatory and coagulatory parameters linked to survival in critically ill children with sepsis. Ann Intensive Care. 2018;8:111. Available from: https://doi.org/10.1186/s13613-018-0457-8

How to Cite This Article
Selvaraj M, Dhotre SV, Faldu B, Vinodkumar SP, Patel BB, Goswami H. Correlation between CRP and APTT in critically ILL children with sepsis. International Journal of Clinical and Diagnostic Pathology. 2024;7(3):230-234.