Indian Academy of Pediatrics (IAP)

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

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UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

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Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

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A Novel Marker for Predicting Fulminant Myocarditis: Systemic Immune–Inflammation Index.

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BASED ON ARTICLE

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SUMMARY

Background: In myocarditis, searching for effective and appropriate prognostic biomarkers can help clinicians identify high-risk patients on time and make better medical decisions in clinical practice. The prognostic value of the systemic immune–inflammatory index (SII), an innovative biomarker of inflammation, in fulminant myocarditis in children has not been assessed. This study aims to (1) determine the effect of SII and other inflammatory markers on the prognosis of patients with myocarditis and (2) characterize other factors affecting adverse outcomes in myocarditis.

Methods: This retrospective study analyzed myocarditis subjects admitted to Pediatric Emergency Department between January 1, 2015, and October 1, 2021.

Results: The study enrolled 106 subjects (67% male, 12.5 years (IQR 6-16)). There were 16 cases (15%) of fulminant myocarditis (FM) and 90 cases (85%) of non-fulminant myocarditis (nFM). There was a significant difference in the white blood cell count, absolute neutrophil count, absolute lymphocyte count, Immature granulocytes, and SII index between FM and nFM. SII was calculated with the formula SII = (P × N)/L, where P, N, and L refer to peripheral platelet, neutrophil, and lymphocyte counts per liter, respectively. The optimal cut-off point for SII was 1378.0(× 109/L). In the FM group, the median SII was 1927 (1147.75–3610.25) and in the nFM group, it was 351 (251.75–531.25) ($p<0.001$). In FM estimation, AUC was 0.87 for WBC (95% CI 0.72–1.00, $p=0.002$), 0.94 for ANC (95% CI 0.85–1.00, $p=0.000$), and 0.92 for SII (95% CI 0.82–1.00, $p=0.000$). Spearman's correlation analysis showed a significant negative correlation between SII and LVEF ($r=0.576$, $p<0.001$). The highest AUC values were associated with ANC, SII, and WBC levels to predict FM.

Conclusion: SII, a readily available biomarker from routine blood parameters, allows early recognition of negative outcomes and can independently predict the prognosis of myocarditis in children.

COMMENTARY

The systemic immune-inflammatory index (SII) is an innovative biomarker of inflammation that combines lymphocyte, neutrophil and platelet count information and is a strong prognostic indicator of poor outcomes in some inflammatory diseases such as antineutrophil cytoplasmic antibody-associated vasculitis, Henoch-Schönlein purpura and neoplasia (lung cancer or hepatocellular carcinoma) represents. But it has not been tested previously for its prognostic value in fulminant myocarditis in children. In adults, the SII index was the predictor of mortality in patients with infective endocarditis, in cardiogenic shock patients, and for severe illness in acute pulmonary embolism. This index can also be used in combination with the other parameters in the early diagnosis of neonatal sepsis in congenital heart defects (1-2). In the study article, they used the SII for its prognostic value in FM in children. The criteria of myocarditis were defined as patients meeting signs and symptoms of acute cardiac dysfunction (e.g., dyspnea, exercise intolerance, syncope, chest pain with exertion, tachypnea, unexplained tachycardia, hepatomegaly, gallop rhythm), elevated troponin level, echo evidence of ventricular dysfunction without underlying structural heart defect, presence of prodromal disease (respiratory or gastrointestinal) within two weeks of symptom onset, ECG changes suggestive of acute myocardial injury or arrhythmia. The definition of the fulminant course of acute myocarditis was the presence of severe hemodynamic compromise requiring inotropic agents or ventricular assist devices such as an intraaortic balloon pump, left ventricular assist device, or extracorporeal membrane oxygenation, ECMO. The primary outcome in the study was the comparison of SII of FM and nFM patients. Secondary outcomes were the comparison of other inflammatory markers of both groups and the determination of other factors affecting the prognosis of myocarditis.

SII can be easily obtained by the routine blood test for complete blood count, the most commonly performed test in clinical practice. It is a non-invasive prognostic biomarker that is inexpensive, reliable, robust, reproducible, and practical. This marker was first identified by Hu et al. (3) proposed for hepatocellular carcinoma. It has shown a higher predictive value for prognosis in cancer than other inflammatory factors such as platelet-to-lymphocyte (PLR) and neutrophil-to-lymphocyte (NLR) ratios. In addition, it can comprehensively reflect the relationship of the host's immune and inflammatory status, and is also a more objective marker with better predictive reliability for prognosis. It is an index for predicting prognosis and outcome from various study data in children with sepsis, urinary tract infections, infections, cancer and metabolic syndrome in children with obesity (4-5).

In the study described above, the authors found that the AUC of the ANC (0.94) is higher than the SII (0.92), but the positive predictive value of the ANC (53.8) is lower than the SII (68.8). Easy to calculate, the SII Index helps to quickly identify high-risk patients and guide the best medical decisions in pediatric practice. The cut-off value of SII was 1378 for FM and shows a strong negative correlation with LVEF. In order to predict PICU admission, the optimal cut-off point of SII value was 798 with a likelihood ratio of 49.6. The AUC for PICU admission was 0.956 (95% CI=0.919–0.994, $p<0.001$). SII value 878 with likelihood ratio 19.3 is the best cut-off point for predicting the evolution of mechanical ventilator needs. In terms of predicting mechanical ventilator need, the AUC was 0.879 (95% CI=0.802-0.955, $p<0.001$). SII value 1003 was also the best cut-off point to predict the evolution of

inotrope need with likelihood ratio 51.5. The AUC for developing mechanical ventilator need is 0.953 (95% CI=0.911–0.995, p<0.001). Lastly, the SII was best able to predict mortality at 1818, with a likelihood ratio of 9.03. The AUC for estimating mortality was 0.909 (95% CI=0.853–0.964, p=0.040). In FM, 50% of cases had complications and 12.5% died, while in nFM, only 2.2% had complications and none died. The study also correlated electrocardiography, echocardiography, and cardiac enzymes with outcomes. As this was a brief commentary and focused on SII we have highlighted that in this manuscript.

In this research paper, the authors reported that troponin or pro-BNP levels alone are not predictive of FM. They found that the SII median value was 1594.00 (IQR 942.25–2411.75) in multisystem inflammatory syndrome in children, [MIS-C, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induced], and significantly higher than the other virus-related inflammatory response groups (p<0.001). The median SII values of MIS-C patients in the fulminant and non-fulminant groups were 1051 (701–3629.5) and 2081 (920–2652), respectively (p=0.602). SII has an optimal sensitivity of 81.25% in predicting the occurrence of severe patients with COVID-19, allowing for a sensible distribution of medical resources to reduce severe patient mortality for physicians (4). Usul et al. (5) found that the predictive ability in COVID-19 diagnosis is superior to that of NLR and PLR because of the marked difference in values in SARS-CoV-2 positive and negative individuals. In the present research paper, they emphasized that the SII index is easy to calculate, which helps to quickly identify high-risk patients and make the best medical decisions in pediatric practice. To the best of our knowledge, this is the first study focused on examining the association between SII and myocarditis in children.

Limitation

Nevertheless, this article has an important meaning even if it is a retrospective study, which is a single-center experience with limited number of cases of FM. This study lacked the assessment of inflammatory markers for mortality and the need for ECMO or pericardiocentesis.

Conclusion

In conclusion, the SII index has shown accuracy in describing the imbalance of immunity and inflammation in various diseases. The highest AUC values were associated with ANC, SII, and WBC levels to predict fulminant myocarditis. The high SII is a novel prognostic indicator to predict ICU admission, mechanical ventilation requirement, inotrope requirement, and mortality. Additionally, it allows early detection of negative outcomes and can independently predict the prognosis of myocarditis in children.

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