Journal of Society Medicine
Research & Review Articles on Diseases
Journal of Society Medicine. 2023; 2(11)

Correlation of Fibrinogen Level with PELOD-2 Score As A Predictive Factor For Mortality in Pediatric Sepsis

Dia Tri Susanti[1], Gema Nazri Yanni[1], Johannes H. Saing[1], Erna Mutiara[2], Aridamuriany D. Lubis[1], Olga R. Siregar[1]

[1] *Department of Pediatrics, Faculty of Medicine, Universitas Sumatera Utara, Medan, North Sumatra, Indonesia*
[2] *Faculty of Public Health, Universitas Sumatera Utara, Indonesia*

***Corresponding Author**: Dia Tri Susanti, E-mail: diatri22@gmail.com

ARTICLE INFO

Article history:
Received
10 November 2023

Revised
28 November 2023

Accepted
30 November 2023

Manuscript ID:
JSOCMED-101123-211-5

Checked for Plagiarism: Yes

Language Editor:
Rebecca

Editor-Chief:
Prof. Aznan Lelo, PhD

Keywords

Fibrinogen, PELOD-2 score, Mortality

ABSTRACT

Introduction: Fibrinogen is a prognostic biomarker in septic children, lower fibrinogen levels are closely related to higher risk of death. Organ dysfunction was diagnosed based on PELOD-2 score. The aim of this study was to determine the corelation between fibrinogen levels and PELOD-2 score as a predictor of mortality in pediatric patient with sepsis treated in the PICU and HCU at H. Adam Malik General Hospital.

Method: A cross-sectional study of pediatric patients with sepsis treated in the PICU and HCU H. Adam Malik General Hospital, Medan. Correlation of fibrinogen levels with PELOD-2 scores was seen on day I and day III of treatment in patient aged 1 month to 18 years with a hospital stay of at least 72 hours and were analyzed using the Spearman test and the relationship between fibrinogen and mortality was analyzed using the Mann-Whitney test.

Results: 50 subjects were recruited in this study, fibrinogen levels had no correlation with PELOD-2 score day I (p = 0,074, r = -0,225) and with PELOD-2 score days III (p = 0,110, r = -0,229) and with mortality (p = 0,160).

Conclusion: Fibrinogen levels were not correlate with PELOD-2 score as a predictive factor for mortality in septic children.

How to cite: Susanti DT, Yanni GN, Saing JH, Mutiara E, Lubis AD, Siregar OR. Correlation Of Fibrinogen Level With PELOD-2 Score As A Predictive Factor For Mortality In Pediatric Sepsis. *Journal of Society Medicine*. 2023; 2(11): 384-391. **DOI: https://doi.org/10.47353/jsocmed.v2i11.106**

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by immune dysregulation in response to infection.[1] It contributes to 19% of all global deaths, with the highest age-specific incidence occurring in children under 5 years old. Among all hospital visits, 0.7% are cases of sepsis in children, with an incidence of 2.8% in hospitalized patients in the United States. Epidemiological studies using clinical data have found that sepsis occurs in up to 8% of all pediatric intensive care unit (PICU) admissions, resulting in 1 out of 4 deaths in the PICU. Study conducted by Yanni GN et al. at Haji Adam Malik General Hospital from May 2018 to October 2018, 43 sepsis cases were identified out of 83 patients admitted to the PICU, with a mortality rate of 25%.[2,3] This corresponds with data obtained from the PICU at RS Cipto Mangunkusumo, which reported a mortality rate of 54% among 502 pediatric sepsis patients.[4]

The diagnosis of sepsis is established based on the presence of signs of infection, which include predisposing factors for infection, signs or evidence of an ongoing infection, inflammatory response, and signs of organ dysfunction or failure. Organ dysfunction is assessed using the PELOD-2 score. Sepsis is diagnosed when the score is equal to or greater than 11 (or ⩾7).[1]

Coagulation disorders in sepsis can range from coagulation activation that is only detectable by sensitive markers to disseminated intravascular coagulation (DIC), which incidences in severe sepsis varies between

14% and 32% and is associated with increased mortality in sepsis. In cases of DIC, fibrinogen plays a role as an acute-phase protein and serves as a marker with high specificity (82%) but has low sensitivity (66.67%).[5,6] Fibrinogen is a valuable prognostic biomarker in pediatric sepsis. A fibrinogen level lower than 2 g/L upon admission to the PICU is closely associated with a higher risk of mortality in pediatric sepsis. Recent reports indicate that fibrinogen levels less than 200 mg/dl are associated with a sharp increase in mortality in adult patients with severe sepsis.[7,8] Pudjiadi et al. conducted a study in the pediatric ward of Cipto Mangunkusumo Hospital to determine the incidence of DIC in pneumonia patients, which showed that 19.6% of the patients experienced a decrease in fibrinogen levels.[9]

Study by Azfar et al. on patients diagnosed with severe sepsis or septic shock showed that APACHE II > 20 (P = 0.001), fibrinogen < 2 (P = 0.019), and D-dimer > 1 (P = 0.06) were independent predictors of mortality in severe sepsis or septic shock. Plasma levels of Fibrin (fibrinogen) degradation products (FDPs) increase in relation to disseminated intravascular coagulation (DIC) and fibrinolysis.[10] This contradicted the findings of Sharma et al., in which they stated that plasma fibrinogen (P < 0.01) was higher in patients compared to controls, with a 6% decrease and 8% increase in patients suspected of sepsis and normal levels in all controls.[11]

In general, study on mortality in pediatric sepsis has often been associated with the PELOD-2 score. Previous studies have indicated a relationship between fibrinogen levels and mortality in children with sepsis. However, there hasn't been much study on the correlation between fibrinogen and the PELOD-2 score as a predictive factor for mortality in children with sepsis.

METHOD

This is an analytical observational study with a prospective cohort design aimed at assessing the relationship between fibrinogen levels and the PELOD-2 score in children with sepsis as a predictive factor for mortality in the Pediatric Intensive Care Unit (PICU) and High Care Unit (HCU) at Haji Adam Malik General Hospital. The study was conducted from July 2021 to June 2022. Target population included children aged 1 month to 18 years with sepsis. The study's sample consists of a subset of the accessible population that meets the inclusion and exclusion criteria and was obtained through consecutive sampling, with a total of 50 participants.

The inclusion criteria encompass all patients aged 1 month to ⩽18 years diagnosed with sepsis in the PICU and HCU at Adam Malik Hospital, with a minimum treatment duration of 72 hours (hospitalization for ⩾3 days). Exclusion criteria include pediatric patients with underlying hematological conditions, or children diagnosed with congenital or hereditary disorders and malignancies who died within less than 24 hours. This study was conducted with the approval from the Health Research Ethics Committee of the University of North Sumatra and H. Adam Malik General Hospital in Medan.

The collected data is then processed and analyzed with the assistance of computer software. Univariate analysis is conducted to describe the basic demographic characteristics of the research subjects, results of supporting examinations, and scoring. Categorical data is presented in the form of frequency distributions, tables, or graphs. Numerical data is presented as means and standard deviations for normally distributed data, and as medians for data that are not normally distributed.

Bivariate analysis is conducted to assess the relationship between fibrinogen levels and the PELOD-2 score, analyzed using the Spearman correlation test. The relationship between fibrinogen and mortality is assessed using the Mann-Whitney test if the data is not normally distributed. The significance level used is p < 0.05, and the significance level and confidence interval used are p < 0.05 and 95%. Additionally, the study involves determining a cut-off point and calculating the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of fibrinogen as a diagnostic test for mortality in children with sepsis.

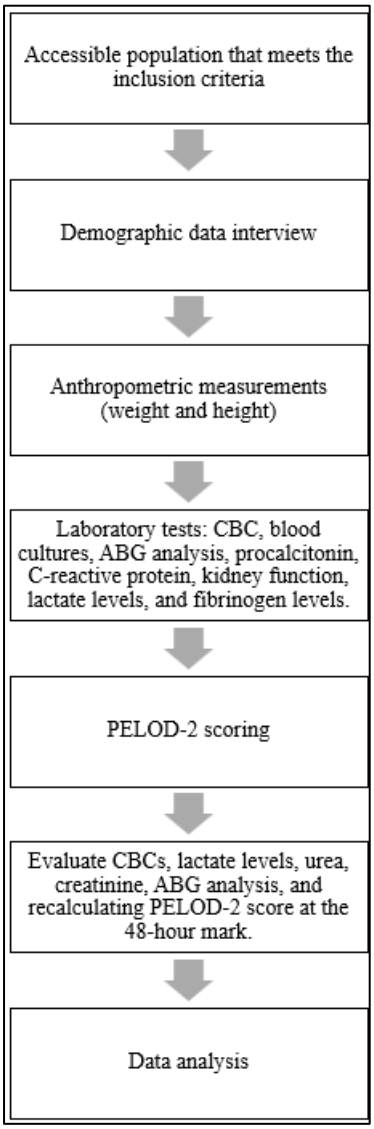

Figure 1. Study procedure flow chart

RESULT

This study involves 50 pediatric patients with sepsis who were admitted and treated in the PICU and HCU at H. Adam Malik General Hospital and met the inclusion criteria. Table 1 presents the demographic characteristics of the research subjects. The majority of the pediatric subjects are male, with a total of 33 individuals (66%).

The most common age groups are children under 1 year and those aged 12-18 years, each comprising 14 individuals (28%). The median body weight and height of the subjects are 17.45 (ranging from 3.1 to 62) kg and 109.5 (ranging from 49 to 170) cm, respectively. Based on the nutritional status assessment, most of the subjects are classified as having poor or good nutrition, with 19 individuals in each category (38%). This is followed by 10 individuals (20%) with very poor nutrition and 2 individuals (6%) with excess nutrition. Based on their underlying diseases, the majority of the subjects experienced central nervous system infections, with 15 individuals (30%), followed by respiratory diseases with 13 individuals (26%), and post-operative cases with 7 individuals (14%). Out of the subjects, 45 individuals (90%) had positive culture results. There were 32 individuals (64%) among the pediatric subjects who did not survive, while 18 individuals (36%) survived. The fibrinogen levels for the research subjects had a median value (range) of 190.5 (37.3-900). The PELOD-2 score on day 1 had a median value (range) of 10.5 (5-16), and the PELOD-2 score on day 3 had a median value (range) of 10 (4-14).

Table 1. Demographic characteristic of pediatric patients with sepsis

Demographic characteristic	n = 50
Gender, n (%)	
Male	33 (66)
Female	17 (34)
Age, n (%)	
< 1 years	14 (28)
1 – 5 years	10 (20)
6 – 11 years	12 (24)
12 – 18 years	14 (28)
Weight, kg	
Median (Min – Max)	17,45 (3,1-62)
Height, cm	
Median (Min – Max)	109,5 (49-170)
Nutritional status, n (%)	
Very poor	10 (20)
Poor	19 (38)
Good	19 (38)
Excess	2 (4)
Underlying disease, n (%)	
Renal disease	5 (10)
Infection	4 (8)
CNS Infection	15 (30)
Heart disease	6 (12)
Post-operative	7 (14)
Respiratory disease	13 (26)
Blood culture, n (%)	
Positive	45 (90)
Negative	2 (4)
No specimen	3 (6)
Outcome, n (%)	
Death	32 (64)
Survived	18 (36)
Clinical hemmorhages	16 (32)
Fibrinogen, mg/dL	
Median (Min – Max)	190,5 (37,3-900)
PELOD-2 score Day 1	
Median (Min – Max)	10,5 (5 – 16)
PELOD-2 score Day 3	
Median (Min – Max)	10 (4-14)

Tabel 2 provides analysis results of relationship between fibrinogen level and PELOD-2 score Day 1 dan Day 3. By using the Spearman correlation test, it was shown that there was no significant relationship found between fibrinogen and the PELOD-2 score on the first and third days ($p > 0.05$).

Table 2. Correlation between Fibrinogen and PELOD-2 score day 1 and day 3

	Fibrinogen	
	p*	r
PELOD-2 score Day 1	0,074	-0,225
PELOD-2 score Day 3	0,110	-0,229

*Spearman

Tabel 3 provides analysis results of relationship between fibrinogen and mortality of pediatric patients with sepsis. The median fibrinogen levels in pediatric subjects who did not survive were 160 mg/dl (ranging from 37.3 to 842 mg/dl), while in children who survived, the median fibrinogen levels were lower, specifically, 221 mg/dl (ranging from 100 to 900 mg/dl). Using the Mann-Whitney test, it is indicated that there is no significant relationship between fibrinogen levels and mortality in pediatric sepsis patients ($p = 0.160$).

Table 3. Relationship between Fibrinogen and Mortality of pediatric patients with sepsis

	Death	Survive	p
Fibrinogen			
Median (Min-Max)	160 (37,3-842)	221 (100-900)	0,160

*Mann-Whiney

Analysis results using the ROC curve (Figure 2) revealed an AUC (Area Under the Curve) of 37.9% for fibrinogen in predicting mortality in pediatric sepsis patients treated in the PICU and HCU at Haji Adam Malik General Hospital, with a p-value of 0.160 and a 95% confidence interval of 22.4-53.5%. This indicates that fibrinogen cannot be used to predict mortality in children with sepsis.

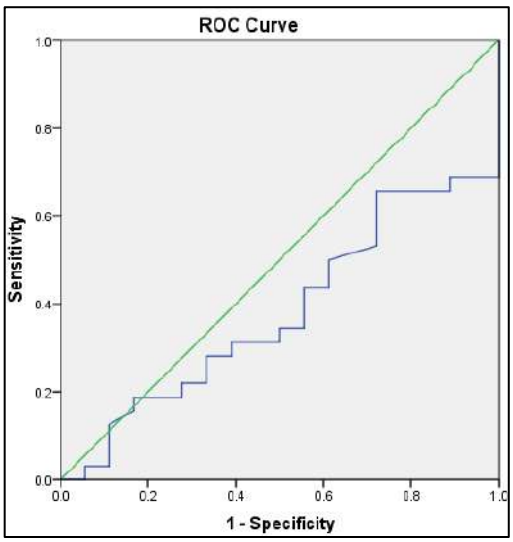

Figure 2. ROC Curve of Fibrinogen against Mortality in Children with Sepsis

Based on the line graph in Figure 3, the cut-off value for fibrinogen in this study to predict mortality in children with sepsis treated in the PICU and HCU is 198. Table 4 displays accuracy values, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy, for fibrinogen in predicting mortality in children with sepsis treated in the PICU and HCU at Haji Adam Malik General Hospital.

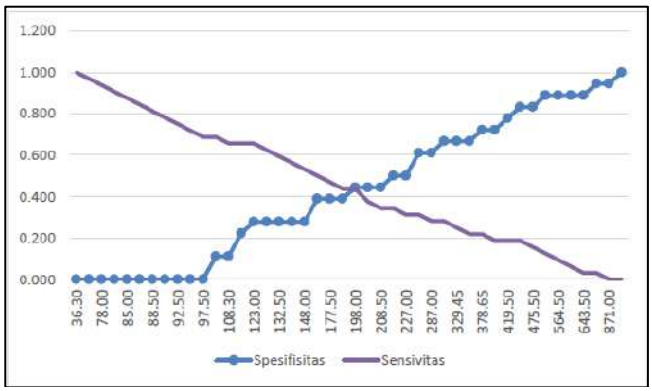

Figure 3. Line Graph of Sensitivity and Specificity of Fibrinogen against Mortality in Children with Sepsis

The likelihood of mortality in children with sepsis with fibrinogen levels below the cutoff point is presented with a relative risk (RR) value as indicated in Table 5, which is 1.28 (95% CI 0.84-1.96). This means that in children with sepsis with fibrinogen levels equal to or less than 198 mg/dL, the likelihood of mortality is 1.28 times higher compared to those with fibrinogen levels above 198 mg/dL. The confidence interval (CI) provides a range within which the true relative risk is likely to fall with a certain level of confidence.

The sensitivity of fibrinogen in predicting mortality is 56%, with specificity of 55%, the positive predictive value (PPV) is 69%, the negative predictive value (NPV) is 41%, and the accuracy is 56%. These

values provide insights into the diagnostic performance of fibrinogen in predicting mortality in children with sepsis.

Table 4. Diagnostic Test of Fibrinogen in Predicting Mortality in Children with Sepsis

	Mortality		Sensitivity	Specifisity	PPV	NPV	Accuracy
	Yes	No					
Fibrinogen							
≤ 198	18	8	56%	55%	69%	41%	56%
>198	14	10					

Table 5. Relationship Between Fibrinogen Levels and Mortality in Children with Sepsis

	Mortality		RR	95% CI
	Yes	No		
Fibrinogen				
≤ 198	18	8	1,28	0.84 – 1,96
>198	14	10		

DISCUSSION

Fibrinogen, also known as a positive acute-phase protein, increases in response to systemic inflammation, tissue injury, and various types of cancer.[12] In a study conducted by Omiya K et al., they found that the mean plasma fibrinogen and fibrinogen synthesis rate increased in sepsis patients compared to non-sepsis patients. This is consistent with the findings of this study, which observed a median fibrinogen level of 190.5 (ranging from 37.3 to 900), which is higher than the cut-off value from previous research. This increase may be attributed to the heightened synthesis of fibrinogen as a positive acute-phase protein in response to sepsis.[13] In this study, higher fibrinogen levels were observed in patients who survived compared to those who passed away. This finding is consistent with the research conducted by Sharma A. et al., which found that plasma fibrinogen increased in 16% of patients and decreased in 6% of patients.[11]

Spearman's correlation test results showed that no significant relationship was found ($p = 0.074$) with correlation values of -0.225 for the PELOD-2 score on day 1 ($p = 0.110$) and -0.229 for the PELOD-2 score on day 3, it indicates that there is no significant correlation between fibrinogen levels and the PELOD-2 score as a predictive factor for mortality in pediatric sepsis. Up to this point, there has been no research that has conducted a correlation test between fibrinogen levels and the PELOD-2 score to predict mortality in children with sepsis. However, there is a study that examined the correlation between fibrinogen levels and lactate levels in children with sepsis. From that study, it was found that fibrinogen levels correlated with lactate levels. In the non-survivor group, fibrinogen levels were lower ($p < 0.001$) compared to the survivor group, and lactate levels were higher in the non-survivor group compared to the survivor group ($p < 0.001$).[9]

Coagulopathy is associated with organ failure and mortality.[8] In this study, it was found that there is no relationship between fibrinogen and mortality ($p = 0.160$), with a cut-off of ⩽198 mg/dL having a sensitivity of 56%, specificity of 55%, positive predictive value (NPP) of 69%, negative predictive value (NPN) of 41%, and an accuracy of 56%. This corresponds with the study conducted by Wada et al., which found that 47% of the total 560 patients had fibrinogen levels >200 mg/dL, and only 24% had fibrinogen levels <100 mg/dL.[14] This can be attributed to the fact that fibrinogen is not a sensitive marker for the diagnosis of DIC (Disseminated Intravascular Coagulation) and its levels often increase in patients with sepsis. Fibrinogen is an acute-phase reactant and can increase during the early phase of sepsis.[11,14]

In 2016, the Indonesian Pediatric Society (IPS) released a consensus on the diagnosis and management of pediatric sepsis. This consensus is based on Sepsis-3 and recommends an organ dysfunction assessment system using the Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score. A cut-off score of ⩾11 is established as the criterion for predicting life-threatening organ dysfunction. A study at RS Cipto Mangunkusumo found a PELOD-2 score of ⩾10 as a predictor of life-threatening organ dysfunction in sepsis

patients. This differs from a multicenter study in Europe, which identified a PELOD-2 score of ⩾8 as the cut-off point.[15]

This is the first study to compare fibrinogen levels with mortality and the PELOD-2 score at Haji Adam Malik General Hospital. No similar study has been conducted at Haji Adam Malik General Hospital before. The limitations of this study include a study design that only compares data at a single time point. The sample size in this study is relatively small, which can affect the statistical analysis. Additionally, all samples were considered to have entered the PICU and HCU for the first time without considering their prior history of PICU and HCU care at other hospitals or their medical history before admission to the PICU and HCU.

CONCLUSION

Based on the results of the study regarding the correlation of fibrinogen levels with the PELOD-2 score in children with sepsis as a predictive factor for mortality, it can be concluded that there is no correlation between fibrinogen and the PELOD-2 score on day 1 ($p = 0.074$, $r = -0.225$) and day 3 ($p = 0.110$, $r = -0.229$), and there is no relationship between fibrinogen and mortality in pediatric sepsis ($p = 0.160$). Therefore, further study is needed to assess the correlation of fibrinogen levels with the PELOD-2 score with a larger sample size and additional study to assess other risk factors that may increase the risk of mortality in children with sepsis.

DECLARATIONS

Ethics approval and consent to participate. Permission for this study was obtained from the Ethics Committee of Universitas Sumatera Utara and Haji Adam Malik General Hospital.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

FUNDING

This research has received no external funding

COMPETING INTERESTS

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

ACKNOWLEDGMENTS

None

REFERENCE

1 Hadinegoro SRS, Chairulfa tah A, Latief A, Pudjiadi AH, Malisie RF, Alam A. Konsensus: Diagnosis dan tatalaksana sepsis pada anak. Jakarta: Ikatan Dokter Anak Indonesia. 2016: 1-6.

2 Cruz AT, Lane RD, Balamuth F, Aronson PL, Ashby DW, Neuman MI, dkk. Updates on pediatric sepsis. J Am Coll Emerg Physicians Open. 2020: 1-3.

3 Yanni GN, Saragih RAC. Platelet profile as prognostic factor in critically ill children. Open Access Maced J Med Sci. 2020; 966-8.

4 Priyatiningsih DR, Latief A, Pudjiadi AH. Karakteristik sepsis di pediatric intensive care unit RSUPN dr. Cipto Mangunkusumo. Jakarta: Fakultas Kedokteran Universitas Indonesia; 2016
5 Levi M, De Jonge E, Poll T. Rationale for restoration of physiological anticoagulant pathways in patients with sepsis and disseminated intravascular coagulation. Crit Care Med. 2001; 29: 90-4.
6 Levi M, Schultz M, Poll T. Disseminated intravascular coagulation in infectious disease. Semin Thromb Hemost. 2010; 36: 367-77.
7 Tang X, Shao L, Dou J, Zhou Y, Chen M, Cui Y, dkk. Fibrinogen as a predictor in pediatric patients with sepsis: A Database Study. Mediators Inflamm. 2020: 1-9.
8 Matsubara T, Yamakawa K, Umemura Y, Gando S, Ogura H, Shiraishi A, dkk. Significance of plasma fibrinogen level and antithrombin activity in sepsis: A multicenter cohor study using a cubic spline model. Thromb Res. 2019; 181: 17-23.
9 Pudjiadi MT, Said M, Mangunatmadja I, Satari HI, Wulandari HF, Andriastuti M. Angka Kejadian koagulasi intravaskular diseminata pada pneumonia. Sari Pediatri. 2012; 14: 52 -6.
10 Azfar M, Khan M, Khurshid M. Fibrinogen at admission is an independent predictor of mortality in severe sepsis and septic shock. Crit Care. 2014; S2-S182.
11 Sharma A, Sikka M, Gomber S, Sharma S. Plasma fibrinogen and d-dimer in children with sepsis: A Single-centre Experience. Iran J Pathol. 2018; 13: 272-5.
12 Huisman E, Crighton G. Pediatric fibrinogen part I- pitfalls in fibrinogen evaluation and use of fibrinogen replacement products in children. Frontiers in pediatric. 2021; 9: 1-10.
13 Omiya K, Sato H, Sato T, Wykes L, Hong M, Hatzakorzian R. Albumin and fbrinogen kinetics in sepsis: a prospective observational study. Omiya et al. Critical Care. 2021; 25: 1-6.
14 Wada H, Mori Y, Okabayashi K, Gabazza EC, Kushiya F, Watanabe M, dkk. High plasma fibrinogen level is associated with poor clinical outcome in DIC patients. Am J Hematol. 2003; 7: 1-7.
15 Simanjuntak Y, Saputra I, Triratna S, Bakri A, Iriani Y. Validation of PELOD-2 score as a predictor of life-threatening organ dysfunction in pediatric sepsis. Paediatr Indones. 2020; 60 (5): 227-32.