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A Pilot Study on the Performance of Presepsin in Acute Appendicitis: A Prospective Case-Control Study

Akut Apandisitte Presepsin Performansı Üzerine Bir Pilot Çalışma: Prospektif Bir Vaka Kontrol Çalışması

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Abstract

Aim: Diagnostic biomarkers are needed for pediatric acute appendicitis (AA). We hypothesized that presepsin (soluble CD14 subtype), a biomarker for sepsis, can also be used in pediatric AA and aimed to investigate its diagnostic value in those patients.

Material and Method: This prospective case-control study was conducted on children admitted to the Pediatric Emergency Department with suspected acute appendicitis. Serum levels of interleukin-6, and presepsin were statistically analyzed for their diagnostic values.

Results: No remarkable demographic differences were present between the 41 cases and 47 controls. Clinical and routine laboratory findings were significantly positive for acute appendicitis in the cases compared to controls. ROC analysis indicated an AUC for presepsin as 0.999 (CI 95%: 0.890-0.993) and for interleukin-6 as 0.963 (CI 95%:0.949-1.000). The best cut-off point value for presepsin was at 739 pg/ml, corresponding to a sensitivity of 97.56% and a specificity of 100%. The best cut-off point value for interleukin-6 was at 19 pg/ml, corresponding to a sensitivity of 97.56% and a specificity of 90.32%.

Conclusions: Our study results indicate that presepsin can be considered a biomarker for diagnosing appendicitis in pediatric cases. Future studies might better include the combination with other biomarkers in pediatric cases.

Keywords: Pediatric acute appendicitis, Presepsin, Biomarker, Interleukin-6.

Öz

Amaç: Pediatrik akut apandisit (AA) için tanısal biyobelirteçlere ihtiyaç vardır. Sepsis için bir biyobelirteç olan presepsinin (çözünür CD14 alt tipi) pediatrik AA'da da kullanılabileceğini düşünerek bu hastalarda tanısal değerini araştırmayı amaçladık.

Gereç ve Yöntem: Bu prospektif vaka-kontrol çalışması, Çocuk Acil Servisi'ne akut apandisit şüphesiyle başvuran çocuklar üzerinde yapıldı. Serum interlökin-6 ve presepsin seviyeleri, tanısal değerleri için istatistiksel olarak analiz edildi.

Bulgular: 41 vaka ve 47 kontrol arasında anlamlı bir demografik farklılık yoktu. Olgularda kontrollere göre klinik ve rutin laboratuvar bulguları akut apandisit açısından anlamlı derecede pozitifti. ROC analizi, presepsin için 0.999 (CI %95: 0.890-0.993) ve interlökin-6 için 0.963 (CI %95:0.949-1.000) için bir AUC gösterdi. Presepsin için en iyi eşik noktası değeri 739 pg/ml olup, %97.56 duyarlılık ve %100 özgüllüğe sahipti. İnterlökin-6 için en iyi eşik noktası değeri 19 pg/ml idi, bu da %97.56'lık bir duyarlılığa ve %90.32'lik bir özgüllüğe sahipti.

Sonuç: Çalışma sonuçlarımız, pediatrik vakalarda apandisit teşhisi için presepsinin bir biyobelirteç olarak kabul edilebileceğini göstermektedir. Gelecekteki çalışmalar, pediatrik vakalarda diğer biyobelirteçlerle kombinasyonu daha iyi içerebilir.

Anahtar Kelimeler: Pediatrik akut apandisit, Presepsin, Biomarker, Interlökin-6

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INTRODUCTION

Acute appendicitis (AA), a common childhood surgical emergency, has a significant economic burden for the health system and morbidity for the patient, i.e., post-surgical infections, multiple hospital visits.[1] AA was responsible for 31.4% of all pediatric surgeries that contributed to the cumulative burden of the revisit-associated length of stay and costs.[2] A frequent presentation in the pediatric emergency department (ED), AA has challenges, especially due to delayed diagnosis.[3]

Abdominal ultrasonography (US) without radiation exposure risk has been the standard imaging study that provides diagnostic accuracy in pediatric cases; it has the disadvantage of being operator-dependent.[4] The scoring systems, like the Alvarado score (AS) and Pediatric Appendicitis Score (PAS), are integral to medical evaluation; however, their specificity and sensitivity spectrum vary widely.[5,6] The specificity of AS and PAS varies between 59%-72% and 50%-70%, respectively, while sensitivity varies between 76%-89% and 86%-93.8%, respectively.[7–9]

Difficulties in diagnosing AA have led to increased search for biomarkers for a timely and accurate diagnosis.[10] Considering its etiopathogenesis as a vicious cycle of an immune response, comprising of infection, obstruction, and inflammation, researchers focused on investigating the immuno-inflammatory system components, i.e., white blood cells, interleukins.[11–13]

Procalcitonin (PCT), known for its rapid response against bacterial infections, has been studied for its potential as a biomarker. The diagnostic accuracy of PCT was high in differentiating the clinical severity in children with AA.[14,15] The associations between appendicitis severity and single gene polymorphisms (SNPs) in cytokine genes, i.e., CD14, TLR4, IL-6, tumor necrosis factor (TNF) -alpha, and IL-1-beta, had been investigated.[16] On the other hand, the low specificity of CRP for AA was recently underlined, and its limited utility as a diagnostic biomarker was emphasized.[10,17] Plasma levels of IL-6, CRP, and PCT were significantly different in children with AA compared to children with non-AA causes of abdominal pain.[18] The overall performance of IL-6 has been reported to be superior to PCT, especially regarding cost, sensitivity, and prediction of perforation.[19]

The soluble subtype of CD14 (sCD14), named as presepsin (PSEP), had been identified as a new biomarker for sepsis in sixty-six patients, of whom 40% with gastrointestinal pathologies had appendicitis.[20] Afterward, PSEP has been consistently reported to be a biomarker for sepsis severity, prognosis, and mortality risk.[21,22] A meta-analysis indicated that the sensitivity and accuracy of PSEP were superior, while its specificity was inferior to PCT or CRP in pediatric sepsis.[23] In 2018, a Turkish study reported that PSEP levels were significantly higher in adult patients with AA compared to the controls.[24] Recently, another study pointed out the diagnostic value of PSEP to differentiate between complicated and uncomplicated AA.[25] In another study, no statistically significant difference were found in presepsin levels the acute and perforated appendicitis groups and they observed that serum presepsin levels were not elevated in paediatric appendicitis.[26]

Most literature on PSEP is about its relationship with sepsis; moreover, the number of studies on the diagnostic value of PSEP in AA is not only extremely limited but also has been conducted in adult patients. We hypothesized that if PSEP levels might differentiate children with and without AA, it would potentially aid in a diagnosis marker of AA. Therefore, we aimed to determine the PSEP levels in pediatric AA patients and investigate its performance as a diagnostic biomarker in literature. We want to suggest a biomarker that would promptly refer patients with suspected acute appendicitis to the surgeon and to formulate various diagnostic threshold values.

MATERIAL AND METHOD

Study Design and Patient Population

This prospective case-control study consisted of pediatric patients admitted to the Department of Pediatric Emergency in Ankara Training and Research Hospital, a tertiary teaching hospital in the capital of Turkey, with a suggestive diagnosis of acute appendicitis between August 2020 and August 2021. The parents of patients included in the study provided signed informed consent, and the institutional ethics board approved the study (date: 09.03.2020, number: E-20 338), which was designed in line with the Declaration of Helsinki.

The study inclusion criteria consisted of patient age between 4 and 18 years, abdominal pain that lasted for a maximum of three days, and right lower quadrant tenderness in physical examination suggestive of acute appendicitis. The patients diagnosed with inflammatory bowel disease, Familial Mediterranean Fever, and other infectious diseases (gastroenteritis, urinary tract enfection) were excluded from the study.

All patients were included in the study according to these criteria, and clinical scoring, laboratory findings and US results were evaluated. Patients with negative US but clinical suspicions were consulted with the surgeon and CT was requested from the required patients.

Laboratory tests and imaging studies were ordered, and pediatric surgery consultation was requested for all eligible patients admitted to the department of pediatric emergency.

Methodology

At initial presentation per institutional standard-of-care, urine samples and 2 ml. of venous blood from each patient was obtained for urinalysis, complete haemogram, including WBC, absolute count of neutrophils (Neu), sedimentation rate, PSEP, IL-6 and biochemical tests. The blood samples of the patients were taken at the time of the first application to the emergency department.

Presepsin was studied by ELISA method (Sun Red Biotechnology Company) and also IL-6 was studied by ELISA method (DIA source Immunoassays). The results of both parameters were obtained by reading on Biotek Instruments ELx800 microplatereader device. Hemogram (WBC) and CRP were performed on the Sysmex XN-1000 and Roche Cobas 6000 respectively. Serum samples were used for PSEP, IL-6 and CRP (BD Vacutainer SST II Advance Serum Separator Tube) and whole blood samples were used for hemogram analysis (BD Vacutainer EDTA Tube). For PSEP, intra-assay CV<8% (coefficient of variation), inter-assay CV<10%. For IL-6, intra-assay CV<4.3%, inter-assay CV<5.4%. Precision of CRP between August 2020 and August 2021 were CV 3.3% and 4.6% for levels 1 and 2 respectively. Serum levels of > 5 mg/L for CRP, >20 mm/h for sedimentation rate were considered as high in laboratory values.

The decision for surgery was made according to the clinical judgment of the consulting pediatric surgeon after a thorough evaluation of the physical signs, laboratory and imaging findings of patients. The case group in the study consisted of operated patients with a pathologically confirmed diagnosis of acute appendicitis.

The patients who were discharged by the surgeon from the pediatric emergency department were followed up by the pediatric surgery calling after 1-2 weeks.

Statistical Analyses

Statistical analyses were performed using the Jamovi Project 2.0 (2020) and JASP 0.14.1.0. The descriptive statistics with mean, median, standard deviation, frequency, minimum and maximum values were used to describe the categorical and numerical data. Quantitative data were assessed for normal distribution using the Shapiro-Wilk test, and comparisons between the groups were performed using the Student's t-test, while the Mann-Whitney U test was used for variables without normal distribution. Pearson's chi-square, Fisher-Freeman-Halton, and Fisherart exact tests analyzed the categorical variables with normal distribution. A p-value below 0.05 was considered statistically significant for all statistical tests.

RESULTS

The study was completed with 89 patients with a mean age of 12.9 and 12.1 years for the cases (n=41) and controls (n=47), respectively (p=0.269). The demographic data of 41 cases and 47 controls revealed that the distribution of gender between the study groups was not significantly different (p=0.999). The median presentation month to the Department of Pediatric Emergency was April in the cases and June in the controls, with a significant difference between the groups (p= 0.003). **Table 1** demonstrates the demographic and clinical data of cases and controls.

The medical history of the participants indicated a significantly longer duration of pain in the control group (median=2, min-max=1-3) compared to that of the cases (median=2, min-max: 1-2) (p<0.001). Only one patient in the control group had a complaint of dysuria, and no significant difference in this regard was observed between the groups (p=0.999). Rebound sign was found to be present in 32 cases (78%) and one control (2.1%) with a statistically significant difference (p<0.001).

The imaging studies revealed that the median size of the appendix was significantly larger (median=8 mm, min-max=3-14 mm.) in cases than in the controls (median=3 mm, min-max:1-6.5 mm.) (p<0.001). An appendix measurement larger than 4 mm on US was significantly more in cases (n=41, 100%) than in controls (n=16, 34%) (p<0.001). No statistically significant differences between the groups were present for the CT findings (p>0.05). CT was requested to 11 patients from the appendicitis group who were clinically suspected and 7 patients from the control group. The median PSEP value of 11 patients was found to be 1033.5 pg/ml, the median PSEP value of 7 patients was found to be 591.4 pg/ml and the difference was statistically significant (p<0.05).

The haemogram results showed significantly higher levels of WBC, Neu, and CRP in cases compared to controls (p<0.001). No statistically significant difference in the sedimentation rate was present between the study groups (p=0.966).

The PAS of the case group (median= 9, min-max=8-10) were significantly higher than those of the control group (median=6, min-max=1-12) (p<0.001). The cases had significantly higher ASs (median= 9, min-max=8-10) than the controls (median= 5, min-max=3-6) (p<0.001). Scoring was made by pediatric emergency care.

The biochemical tests did not result in any significant difference in PCT levels between the groups (p=0.504). The serum concentration of IL-6 was found significantly higher in cases (median= 64 pg/ml, min-max= 6-1327 pg/ml) than controls (median= 10 pg/ml, min-max= 2-43 pg/ml) (p<0.001). Moreover, the serum concentration of PSEP was significantly higher in cases (median= 948 pg/ml, min-max=739-2654 pg/ml) than controls (median= 584 pg/ml, min-max=300-767 pg/ml) (p<0.001).

The diagnostic values of PSEP, IL-6, CRP, WBC were further evaluated by constructing ROC curves, and the area under the curve (AUC) was estimated. We found an overall AUC for PSEP as 0.999 (CI 95%: 0.890-0.993) and for IL-6 as 0.963 (CI 95%:0.949-1.000). The best cut-off point value for PSEP was at 739 pg/ml, corresponding to a sensitivity of 97.56% and a specificity of 100%. On the other hand, the best cut-off point value for IL-6 was at 19 pg/ml, corresponding to a sensitivity of 97.56% and a specificity of 90.32% (**Table 2**).

Table 1. Demographic and clinical data of case group and control group.

	Study Groups		p-values
	Case group (n=41)	Control group (n=47)	
Gender‡			
Female	18 (43.9)	20 (42.6)	0.999***
Male	23 (56.1)	27 (57.4)	
AgeΩ	12.9 ± 3.3	12.1 ± 3.9	0.269*
Presentation month†	4.0.[1.0 – 12.0]	6.0.[1.0 – 12.0]	**0.003****
PAS †	9.0.[8.0 – 10.0]	5.0.[3.0 – 6.0]	**<0.001****
AS†	9.0.[8.0 – 10.0]	5.0.[3.0 – 6.0]	**<0.001****
AS‡			
0-4	0 (0.0)	22 (46.8)	**<0.001*****
5-7	0 (0.0)	25 (53.2)	
8-10	41 (100.0)	0 (0.0)	
Rebound sign‡			
Yes	32 (78.0)	1 (2.1)	**<0.001*****
No	9 (22.0)	46 (97.9)	
Signs in physical exam‡			
Yes	41 (100.0)	1 (2.1)	**<0.001*****
No	0 (0.0)	46 (97.9)	
Duration of pain†	2.0.[1.0 – 2.0]	2.0.[1.0 – 3.0]	**<0.001****
Dysuria‡			
Yes	0 (0.0)	1 (2.1)	0.999***
No	41 (100.0)	46 (97.9)	
WBC†(10^9/L)	15120.0.[11800.0 – 22200.0]	8870.0.[4260.0 – 13100.0]	**<0.001****
Neutrophil Ω	11942.7 ± 3374.2	4583.6 ± 1839.0	**<0.001***
CRP† (mg/L)	34.1.[1.2 – 238.8]	2.2.[0.1 – 14.3]	**<0.001****
PCT†(mcg/L)	0.1.[0.0 – 1.8]	0.0.[0.0 – 0.3]	0.504**
PSEP†	948.0.[739.0 – 2654.0]	584.0.[300.0 – 767.0]	**<0.001****
IL6 levels (pg/ml) †	64.0.[6.0 – 1327.0]	10.0.[2.0 – 43.0]	**<0.001****
Appendix swelling in US (mm) †	8.0.[3.0 – 14.0]	3.0.[1.0 – 6.5]	**<0.001****
Normal 0-3 mm	0 (0.0)	31 (66.0)	**<0.001*****
Suspected 4-7 mm	13 (31.7)	16 (34.0)	
Appendicitis 7 mm over	28 (68.3)	0 (0.0)	
Patients recommended CT			
Yes	11 (26.8)	7 (14.9)	0.263***
No	30 (73.2)	40 (85.1)	
Appendix swelling in CT (mm) †	10.0.[7.0 – 12.0]	-	-
Sedimentation rate (mm/h)†	9.0.[2.0 – 34.0]	8.0.[4.0 – 32.0]	0.966**

‡: n (%), †: median.[min-max], Ω: mean ± standard deviation, *. T-Test for Independent Samples, **. Mann-Whitney U test, ***. Pearson Chi-Square, Fisher's Exact test or Fisher Freeman Halton test, AA, acute appendicitis; AS, Alvarado score; CRP, C reactive protein; CT, computed tomography; PAS, Pediatric Appendicitis Score; PCT, procalcitonin; PSEP, presepsin; US, abdominal ultrasonography; WBC, white blood cell count.

Table 2. Diagnostic value of Interleukin-6, Presepsin, WBC and CRP.

	AUC	Sensitivity	Specificity	Cut Off	CI 95%	p-value
IL-6 (pg/ml)	0.963	97.56	90.32	>19	0.890- 0.993	<0.001
PSEP (pg/ml)	0.999	97.56	100	>739	0.949- 1.000	<0.001
WBC (10^9/L)	0.989	90.24	97.87	>12720	0.938- 1.000	<0.001
CRP (mg/L)	0.984	97.56	97.87	>12.1	0.931- 0.999	<0.001

CI: Confidence Interval, AUC: Area under curve, PSEP: Presepsin, WBC: White bllod cell, CRP: C-Reactive protein.

DISCUSSION

This, to the best of our knowledge, this study was aimed to determine the diagnostic value of presepsin in pediatric acute appendicitis. We found that serum PSEP levels were significantly higher in the cases than controls and determined that a 739 ng/ml cut-off value of PSEP had a 100% specificity and 97.56% sensitivity for an accurate diagnosis of AA.

As suggested in a recent review, the management in the ED would be improved, and the efficiency of AA diagnosis would be increased with a diagnostic tool developed with the biomarker technology.[10]

The elevated levels of CRP, WBC were consistently demonstrated to be a significant indicator for AA diagnosis. The researchers indicated that WBC and Neu had higher sensitivity early in the disease, while the sensitivity of CRP increased with the progression and reached its highest sensitivity at day four.[27,28] Recently, the conventional biomarkers, CRP, WBC, and Neu, were demonstrated to have inadequate characteristics to be used alone in diagnosing pediatric AA.[17] In the current study, consistent with the previous literature, the levels of WBC, CRP, and Neu in cases were significantly higher in the cases compared to controls

(p<0.001 for each variable).

Another biomarker suggested for AA diagnosis is PCT, which responds rapidly to severe and extensive bacterial infections. In our study, there was no significant difference in levels of PCT between the cases and controls (p:0.504). We interpret this result might be due to the lack of difference in the severity of the clinical picture among the participants in our study. A recent meta-analysis on pediatric AA supported our interpretation by indicating a better diagnostic accuracy of PCT in differentiating disease severity.[14]

In a prospective cohort study, Kakar et al. found that IL-6 had not only identified AA but also differentiated between the complicated and uncomplicated cases. The authors also speculated that slightly elevated levels of IL-6 in controls might potentially be due to the temporary inflammation of the renal, gastrointestinal, or respiratory epithelium.[29] The cut-off value for IL-6 to predict AA in adults was found to be 14 pg/ml with a sensitivity, specificity, and AUC of 84%, 79%, and 0.8, respectively.[15] In our study, we found that IL-6 levels were significantly higher in the cases (median= 64 pg/ml) compared to controls (median= 10 pg/ml) (p<0.001). The highest AUC of 0.992 with 100% specificity and 93.3% sensitivity at the cut-off value of >12.2 pg/ml was obtained for IL-6 for differentiating the non-surgical cause of abdominal pain group patients from AA patients in a study comparing WBC, CRP, and IL-6 as biomarkers.[29] Similar to the results of Sack et al., our ROC analysis revealed a cut-off value of >19 pg/ml with an AUC of 0.963 with 90.32% specificity and 97.56% sensitivity for IL-6 for differentiating AA cases from controls in our study with pediatric age patients.[30]

Although sepsis and AA are two distinct entities, there are important overlaps in their pathogenesis, especially in the response against microorganisms and the process of inflammation. Moreover, sepsis is the most critical fatal complication of AA. Therefore, it seems logical to consider that the concept of investigations for sepsis can theoretically be extended for AA. Based on the literature findings, there seems to be a two-way relationship between sCD14 and IL-6. IL-6 was found to stimulate the production of CD14 in hepatocytes[31], while sCD-14 was found to induce IL-6 mRNA expression.[32]

It is rational to think that a diagnostic biomarker would ideally maximize the clinical utility and minimize the procedural cost and analytical time. An assessment of sixty-two studies on AA biomarkers concerning the sensitivity, specificity, perforation prediction, cost, invasiveness, patient acceptability, result timing, and reproducibility indicated that IL-6 had the highest beneficial characteristics with disadvantages of a 168-hrs process time and expensive cost per test. Although the techniques used for measuring WBC, CRP, PCT, and IL-6 were determined to be convenient, the cost and time required for analysis were higher and longer for PCT and IL-6 than those for the WBC and CRP. Those factors were considered critical limitations of PCT and IL-6 analyses in routine clinical use.[33]

The promising evidence on the role of PSEP in sepsis and various inflammatory and infectious pathologies demonstrated its potential to indicate intestinal inflammation. In case of bacterial infection, plasma PSEP levels with a half-life of 4-5 hrs were shown to increase early (2 hrs) and peak after 3 hrs.[21,34] Ozer et al. found that the PSEP levels in adult AA patients were significantly higher than the controls, while no such significance for the PSEP in differentiating the non-perforated vs. perforated appendicitis was found (p:0.918).[24] PSEP has recently been reported to be an accurate biomarker for identifying septic neonates who had a higher risk of a rapid worsening of the clinical picture. The authors stated that the overall diagnostic accuracy of PSEP was better than PCT and CRP for stratification of septic neonates in the earlier course of the disease.[35] As the timely diagnosis of pediatric AA is of the essence, the swift pharmaco-kinetics of PSEP had been proposed to be superior to PCT with a half-life of 12-24 hrs and CRP, which peaks within the first 48 hrs of the inflammatory process. CRP and PCT had been known for their longer kinetics in bacterial infections.[21,34]

As an example, our study results indicated the potential of PSEP as a biomarker in pediatric AA. We found that the median PSEP level in AA cases (948 pg/ml) was significantly higher than that in the controls (584 pg/ml) (p<0.001). In a recent study conducted on adult AA patients, PSEP was a significant parameter in differentiating complicated and uncomplicated AA. The cut-off value for PSEP to differentiate the severity of the AA was >272 pg/ml with an AUC of 0.965 for the specificity of 98.77% and a sensitivity of 92.31%.[25] Our ROC analysis results showed that the cut-off value for PSEP in differentiating pediatric AA cases from controls was >739 pg/ml with an AUC of 0.999 for the specificity of 100% and a sensitivity of 97.56%. Currently, we cannot interpret and compare our results with the literature as PSEP has been researched as a biomarker for AA in only two previous studies, both conducted on adult patients. On the other hand, it is evident that the results of the present study, which yielded significantly high values of AUC, sensitivity, and specificity for PSEP in differentiating pediatric AA cases from controls, seem to be promising.

Caution should be taken to interpret the diagnostic potential of biomarkers in the context of clinical presentation and the findings from imaging studies for an absolute confirmation or exclusion of AA diagnosis.[10,18] The combination of the conventional triple inflammatory markers, WBC, Neu, and CRP, was found to have superior diagnostic value than their individual uses in a study of pediatric AA.[28] Measuring the combination of PCT and IL-6 in AA cases had been suggested to be more beneficial in reaching a clinical decision for ruling out AA and reducing the rate of negative laparotomies.[19] As previously suggested, we consider that the combination of clinical and laboratory data with PSEP levels in pediatric patients would further its value as a diagnostic biomarker.[10,18,19,28]

Our results could not be generalized, and caution should be taken to extrapolate our conclusions to other populations with pediatric patients. The most important strengths of the current study worth noting are the confirmation of the diagnosis of AA using pathology results.[11] However, the small sample size obtained from a single center and the lack of subgrouping patients were our main limitations. Furthermore, we could not evaluate the serum levels of PSEP matched to a consistent reference standard in the pediatric age group due to the unavailability of such standards. We only encountered a single study for reference ranges of PSEP in the pediatric age group; however, that study was conducted specifically on the term and preterm neonates.[36] Another limitation of the study could be considered for measuring PSEP levels only once at the time of initial admission, so we are not aware of any time-dependent trends in serum PSEP levels that might aid in further understanding its diagnostic value.

CONCLUSION

Our study results would be valuable as a reference for further research of PSEP as a diagnostic biomarker in pediatric AA in future studies. We also suggest that the search for an accurate biomarker for AA must include the cost-effectiveness and the appropriate time for that marker to appear in the body compartments of patients. Therefore, we suggest that further studies should be planned the diagnostic value of PSEP as a biomarker in combination with clinical and laboratory data with strong evidence of benefit in diagnosis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of ..... Ethics Committee (Date: 09.03.2020, Decision No: E-20-338).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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