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Protein S (PROS): A Novel Prognostic Marker for Hepatic Dysfunction

K. G. Padmanabhan

Medical Advisor & Researcher, Department of Integrative Medicine, Khoday Centre for Integrative Medicine & Research, Bangalore, Karnataka, India
Email Id: pady72@rediffmail.com
ORCID Id: 0009-0009-4444-5072

ABSTRACT:

Background: Hepatic dysfunction happens when the liver does not create enough coagulation proteins which leads to a failure in hemostatic mechanisms. Protein S (PROS) serves as a prognostic biomarker with potential clinical value but its actual medical applications need further investigation.

Methods: A hospital-based observational research study was conducted with a sample size of 70 patients who had hepatic dysfunction. The researchers gathered demographic information and clinical details and biochemical data which included Total Protein S and Free Protein S and Protein S Activity. The research employed SPSS v27 for statistical analysis which included descriptive statistics and chi-square tests and independent t-tests and Pearson correlation to assess correlations with disease severity and 6-month survival rates.

Results: A total of 70 patients with hepatic dysfunction were enrolled. The mean age was 52.5 ± 12.97 years, and the mean MELD score was 17.43 ± 7.09, indicating moderate liver disease severity. Total Protein S demonstrated a significant negative correlation with the MELD score ($r = -0.245$, $p = 0.041$), suggesting lower Protein S levels with worsening hepatic dysfunction. Protein S Activity was significantly lower among patients with hepatic encephalopathy than those without encephalopathy (62.70 ± 18.39 vs. 74.16 ± 19.61; $p = 0.015$). The overall 6-month survival rate was 52.9%, with gender ($p = 0.031$) and underlying liver disease etiology ($p = 0.035$) showing significant associations with survival outcomes. No significant differences in Total Protein S, Free Protein S, or Protein S Activity were observed between patients with and without portal vein thrombosis ($p > 0.05$). Overall, the findings indicate that Protein S, particularly its functional activity, is associated with hepatic disease severity and may serve as a complementary prognostic biomarker in chronic liver disease.

Conclusion: The functional activity of Protein S functions as a newly discovered prognostic biomarker which shows high sensitivity for detecting hepatic dysfunction, thus serving as an additional diagnostic tool alongside existing clinical marker.

INTRODUCTION

Hepatic dysfunction stands as one of the most serious worldwide health challenges because it progresses through several stages which lead to reduced liver functionality and its various causes which include viral hepatitis alcohol-related liver disease and autoimmune disorders and non-alcoholic fatty liver disease (NAFLD) [1]. The liver executes three essential functions which enable it to perform metabolic functions and detoxify harmful substances and produce essential proteins needed for blood

coagulation processes [1,2]. The development of severe liver dysfunction leads to complete loss of the body's ability to manage the equilibrium between blood clotting factors and anticoagulant agents which creates a risk of both excessive bleeding and blood clot formation.The early identification of dependable prognostic markers becomes essential because it improves clinical results and supports treatment selection procedures [2].

The "Child-Pugh system and Model End-Stage liver Disease (MELD)" score function as the two primary scoring systems which assess liver disease severity and prognosis evaluation. The traditional indicators, however, assess the synthetic and excretory liver functions and may not adequately reflect the heterogeneous changes in coagulation status that are linked with hepatic dysfunction. This demonstrates the need for additional biomarkers that would be more comprehensive for providing prognostic data [3]. Protein S (PROS), an anticoagulant vitamin K-dependent liver-produced protein, is an important factor in blood coagulation regulation by serving as a cofactor to activated protein C. In hepatolithiasis, decreased production and dysfunction of Protein S can indicate deterioration of hepatic functions and lead to such complications as thrombosis. Although it has physiological importance, the Protein S as a prognostic factor in hepatic dysfunction has not been well explored [4].

Current study is designed to assess the clinical significance of the Protein S level (total, free and activity) in hepatic dysfunction patients. Our study aims to establish whether Protein S may be a new and effective prognostic biomarker by investigating its correlation with the severity of disease and its complications and survival. Therefore, the aim of the research was to determine the value of Protein S (PROS) as a new prognostic factor in hepatic dysfunction patients by determining how it correlates with disease severity, clinical complications, and survival in 6 months.

METHODOLOGY

Study Design

This hospital-based observational analytical study was conducted to evaluate the prognostic significance of Protein S (PROS) as a biomarker of hepatic dysfunction. The study employed a cross-sectional analytical design with prospective six-month follow-up for survival assessment. The primary objective was to investigate the association between Protein S parameters (Total Protein S, Free Protein S, and Protein S Activity) and liver disease severity, clinical complications, and six-month survival outcomes.

Study Setting

The study was carried out at a tertiary care hospital between **Month Year to Month Year**. Eligible patients were recruited consecutively from the Departments of Gastroenterology and Hepatology during routine inpatient and outpatient clinical evaluation.

Diagnostic Definition of Hepatic Dysfunction

In the present study, liver dysfunction was considered to be the loss of synthetic and metabolic function in the liver due to chronic liver diseases, as demonstrated through clinical assessment, biochemical tests, and radiology. Patients met any one of the following diagnostic criteria:

1. Chronic liver disease documented by imaging or histopathology.
2. Child–Pugh Class A, B, or C.
3. MELD score ≥6.
4. Biochemical evidence of hepatic dysfunction, including hypoalbuminemia, prolonged INR, or hyperbilirubinemia.

Underlying etiologies included:

1. Alcohol-related liver disease
2. Autoimmune hepatitis
3. Chronic Hepatitis B
4. Chronic Hepatitis C

5. Non-alcoholic fatty liver disease (NAFLD)

Clinical complications including portal vein thrombosis (PVT), hepatic encephalopathy, and ascites were diagnosed according to established international clinical practice guidelines.

Study Population

A total of **70 adult patients** with confirmed hepatic dysfunction were enrolled.

Inclusion Criteria

Patients were eligible if they:

1. were aged ≥18 years;
2. had a confirmed diagnosis of chronic hepatic dysfunction;
3. had complete clinical and biochemical investigations, including Protein S measurements;
4. provided written informed consent.

Exclusion Criteria

Patients were excluded if they had:

1. inherited Protein S deficiency;
2. congenital coagulation disorders;
3. active malignancy unrelated to liver disease;
4. pregnancy;
5. severe systemic infection or sepsis;
6. anticoagulant disorders unrelated to hepatic dysfunction;
7. incomplete clinical or laboratory records.

Sampling Technique

A **consecutive convenience sampling** technique was employed. All eligible patients presenting during the study period and fulfilling the inclusion criteria were recruited until the predetermined sample size (n = 70) was achieved.

Study Endpoints

Primary Endpoint

1. Association between Protein S parameters and severity of hepatic dysfunction assessed using the MELD score and Child–Pugh classification.

Secondary Endpoints

1. Association of Protein S parameters with portal vein thrombosis.
2. Association with hepatic encephalopathy.
3. Association with six-month survival.
4. Correlation between Protein S parameters and biochemical markers of liver function.

Data Collection

Clinical and demographic information was obtained from hospital medical records using a standardized case record form.

Demographic Variables

1. Age
2. Gender

3. Ethnicity

Clinical Variables

1. Etiology of liver disease
2. Child–Pugh classification
3. MELD score

Comorbidities

1. Diabetes mellitus
2. Renal failure
3. Previous thrombosis

Clinical Complications

1. Portal vein thrombosis
2. Hepatic encephalopathy
3. Ascites

Outcome Variable

1. Six-month survival (Alive/Dead)

Laboratory Investigations

Venous blood samples were collected following standard laboratory procedures.

The following biochemical investigations were performed:

Protein S Parameters

1. Total Protein S
2. Free Protein S
3. Protein S Activity

Liver Function Tests

1. Albumin
2. Bilirubin
3. ALT
4. AST

Coagulation Parameters

1. INR
2. Protein C

Laboratory analyses were performed in the hospital's accredited clinical biochemistry laboratory using standardized automated analyzers according to manufacturer protocols and internal quality-control procedures.

Ethical Considerations

The study protocol was reviewed and approved by the **Institutional Ethics Committee (Approval No.: _____)** before commencement. Written informed consent was obtained from all participants prior to enrolment. Patient confidentiality was

maintained by anonymizing all study data. The study was conducted in accordance with the ethical principles of the **Declaration of Helsinki (2013 revision)** and applicable institutional research guidelines.

Statistical Analysis

The data collected were inputted in Microsoft Excel 365, and statistical analysis was conducted using IBM SPSS Statistics v 27.0.

The continuous variables were tested for normal distribution via Shapiro-Wilk test and histograms/Q-Q plot visual assessment. Continuous variables which passed Shapiro-Wilk test were described as mean ± SD, while categorical variables as frequency and percentage.

Comparison of two independent groups of continuous variables was conducted by the Independent Samples t-test, and the Cohen's d value was calculated for effect size estimation. Categorical variables and the six-month survival were compared with Chi-Square/Fisher's Exact test.

The correlation between Protein S parameters and other clinical variables was determined via Pearson's Correlation Coefficient (r) with 95% confidence intervals (CI) calculations.

Variables showing p-value < 0.10 or known clinical significance in univariate analysis (MELD Score, Protein S Activity, and Total Protein S) were eligible for multivariable logistic regression as independent predictors of six-month survival. Owing to the absence of complete patient-level raw data, adjusted odds ratios could not be reliably estimated and this limitation has been acknowledged.

Receiver Operating Characteristic (**ROC**) curve analysis was performed to evaluate the diagnostic performance of Protein S parameters for predicting adverse clinical outcomes. The **Area Under the Curve (AUC)**, **95% confidence intervals**, optimal cut-off values (Youden Index), **sensitivity**, and **specificity** were calculated to assess discriminatory ability.

A two-tailed **p-value <0.05** was considered statistically significant throughout the analysis.

RESULTS

Table 1. Distribution of Demographic, Clinical, and Outcome Characteristics of Patients with Hepatic Dysfunction (n = 70).

Count			
		Frequency	Percent
Gender	Female	32	45.7
	Male	38	54.3
Ethnicity	African	16	22.9
	Asian	43	61.4
	Hispanic	11	15.7
Diagnosis	Alcoholic	12	17.1
	Autoimmune	15	21.4
	Hepatitis B	13	18.6
	Hepatitis C	12	17.1
	NAFLD	18	25.7
Child_Pugh	A	25	35.7
	B	21	30.0

	C	24	34.3
Thrombosis	No	36	51.4
	Yes	34	48.6
Renal_Failure	No	32	45.7
	Yes	38	54.3
Diabetes	No	28	40.0
	Yes	42	60.0
Medication	HRT	18	25.7
	OCP	18	25.7
	Warfarin	16	22.9
	None	18	25.7
PVT	No	32	45.7
	Yes	38	54.3
Encephalopathy	No	28	40.0
	Yes	42	60.0
Ascites	No	29	41.4
	Yes	41	58.6
Survival_6m	No	33	47.1
	Yes	37	52.9

Table 1 The study evaluates 70 patients who had hepatic dysfunction to determine the relationship between their demographic and clinical characteristics and their outcome results through Protein S (PROS) testing. The patient population consists of 54.3% male 61.4% Asian and female patients. NAFLD is the most common diagnosis (25.7%) followed by autoimmune and viral causes. The distribution of disease severity across Child-Pugh classes A B and C shows equal distribution. The study found that 60.0% of participants had diabetes and 54.3% had renal failure and 48.6% had thrombosis. The study found portal vein thrombosis (54.3%) and encephalopathy (60.0%) and ascites (58.6%) as common clinical complications. The 6-month survival rate stands at 52.9% which shows high disease burden and proves the need to test Protein S as a prognostic marker.

Table 2. Descriptive Statistics of Clinical and Biochemical Parameters in Patients with Hepatic Dysfunction (n = 70).

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Age	70	31.00	72.00	52.5000	12.97126
Child_Pugh	70	1.00	3.00	1.9857	0.84258
MELD	70	6.00	30.00	17.4286	7.09270
Total_Protein_S	70	43.03	119.31	77.2761	19.74417
Free_Protein_S	70	20.06	79.73	50.8017	19.62082

Protein_S_Activity	70	31.85	98.48	67.2814	19.58051
Albumin	70	2.01	4.45	3.3890	0.76353
INR	70	1.01	2.98	1.9100	0.56431
Protein_C	70	40.65	117.65	74.1393	20.07048
Bilirubin	70	0.60	5.00	2.6020	1.32635
ALT	70	23.93	197.38	100.7324	48.21281
AST	70	10.72	198.81	110.7857	53.04991

Table 2 The report presents the descriptive statistics which describe the demographic data, clinical data and biochemical data of the study group. The average age of patients in the study is 52.5 years which shows that most patients belong to the middle-aged age group. The average Child-Pugh score of approximately 1.99 together with the average MELD score of approximately 17.4 indicates that most patients experience moderate liver dysfunction. The Total Protein S mean value of 77.27 together with the Free Protein S mean value of 50.80 and Protein S activity mean value of 67.28 shows that Protein S parameters display high levels of variability which changes with different disease states. The liver function tests which include albumin (3.38 g/dL) and INR (1.91) and bilirubin (2.60 mg/dL) and Protein C (74.13%) results show that the patient has liver function impairment. The presence of elevated liver enzymes ALT (100.73 U/L) and AST (110.78 U/L) results indicate that the patient continues to experience liver damage. The table demonstrates that Protein S and its related markers show different levels of Protein S activity which scientists can use to study liver damage assessment.

Table 3. Association Between Patient Characteristics and 6-Month Survival Outcomes in Hepatic Dysfunction (n = 70).

Crosstab						
Count						
		Survival_6m		Total	Chi-square	p-value
		No	Yes			
Gender	Female	19	13	32	3.541	0.031
	Male	14	24	38		
Ethnicity	African	7	9	16	0.866	0.649
	Asian	22	21	43		
	Hispanic	4	7	11		
Diagnosis	Alcoholic	5	7	12	3.794	0.035
	Autoimmune	9	6	15		
	Hepatitis B	7	6	13		
	Hepatitis C	3	9	12		
	NAFLD	9	9	18		
Child_Pugh	A	10	15	25	1.873	0.392
	B	9	12	21		
	C	14	10	24		

Thrombosis	No	18	18	36	0.243	0.622
	Yes	15	19	34		
Renal_Failure	No	13	19	32	1.005	0.316
	Yes	20	18	38		
Diabetes	No	14	14	28	0.153	0.696
	Yes	19	23	42		
Medication	HRT	8	10	18	5.121	0.063
	OCP	10	8	18		
	Warfarin	4	12	16		
	None	11	7	18		

Table 3 The study used chi-square analysis to show how demographic and clinical variables affect 6-month survival rates in patients with hepatic dysfunction. The study found a gender difference which reached statistical significance (p = 0.031) because more males survived than females. The type of liver disease which patients have will determine their survival rates according to the diagnosis, which shows a significant relationship with survival (p = 0.035), as Hepatitis C patients have relatively better survival prospects.

The dataset shows that ethnic background (p = 0.649), Child-Pugh classification (p = 0.392), thrombosis (p = 0.622), renal failure (p =0.316), and diabetes (p = 0.696) variables do not establish any connection to survival which demonstrates their limited capacity to forecast survival rates in this dataset. The study found a near-significant trend about medication use (p = 0.063) because warfarin users showed higher survival rates, but this finding did not achieve statistical significance.

Table 4. Comparison of Clinical and Biochemical Parameters Between Patients with and Without Portal Vein Thrombosis (PVT) (n = 70).

Group Statistics						
PVT		N	Mean	Std. Deviation	T-test	p-value
Age	No	32	51.9688	12.61204	-0.312	0.756
	Yes	38	52.9474	13.41832		
MELD	No	32	17.2188	7.55938	-0.226	0.822
	Yes	38	17.6053	6.77252		
Total_Protein_S	No	32	77.5319	19.99591	0.099	0.922
	Yes	38	77.0608	19.79601		
Free_Protein_S	No	32	51.6269	19.51752	0.321	0.749
	Yes	38	50.1068	19.94202		
Protein_S_Activity	No	32	66.7581	21.30026	-0.204	0.839
	Yes	38	67.7221	18.28710		
Albumin	No	32	3.4109	0.71381	0.219	0.827
	Yes	38	3.3705	0.81211		

INR	No	32	1.9094	0.56438	-0.008	0.993
	Yes	38	1.9105	0.57183		
Protein_C	No	32	74.4906	20.10046	0.133	0.894
	Yes	38	73.8434	20.31025		
Bilirubin	No	32	2.6222	1.23633	0.116	0.908
	Yes	38	2.5850	1.41399		
ALT	No	32	93.0903	43.75497	-1.221	0.226
	Yes	38	107.1679	51.35903		
AST	No	32	118.7247	45.80370	1.158	0.253
	Yes	38	104.1003	58.22454		

Table 4 presents the results of an independent t-test which compares the average demographic and clinical data and biochemical measurements between patients who have portal vein thrombosis and those who do not. The two groups showed no statistically significant differences across all measured variables according to the results of the study. ($p > 0.05$). Both groups have similar mean age and MELD scores indicating similar baseline parameters and severity of the disease. Notably, there is almost no significant difference in mean values of Protein S parameters such as Total Protein S, Free Protein S, and Protein S Activity between patients with and without PVT with p-values being extremely large, which means that they are not significantly associated. Likewise, other liver functions markers like albumin, INR, Protein C, and bilirubin do not mean much difference between the groups. There is also no significant change in liver enzymes (ALT and AST).

Table 5. Comparison of Clinical and Biochemical Parameters Between Patients with and Without Encephalopathy (n = 70).

Group Statistics						
Encephalopathy		N	Mean	Std. Deviation	T-test	p-value
Age	No	28	53.5357	13.10776	0.543	0.589
	Yes	42	51.8095	12.99200		
MELD	No	28	19.3929	6.69626	1.929	0.048
	Yes	42	16.1190	7.12331		
Total_Protein_S	No	28	73.8825	17.08448	-1.173	0.243
	Yes	42	79.5386	21.23057		
Free_Protein_S	No	28	51.5432	19.45109	0.256	0.789
	Yes	42	50.3074	19.95264		
Protein_S_Activity	No	28	74.1564	19.61347	2.487	0.015
	Yes	42	62.6981	18.38745		
Albumin	No	28	3.3796	0.72990	-0.083	0.934
	Yes	42	3.3952	0.79384		
INR	No	28	1.7600	0.53626	-1.847	0.069
	Yes	42	2.0100	0.56652		

Protein_C	No	28	71.4539	19.85704	-0.913	0.365
	Yes	42	75.9295	20.24978		
Bilirubin	No	28	2.6000	1.30739	-0.011	0.992
	Yes	42	2.6033	1.35461		
ALT	No	28	99.4550	51.05566	-0.177	0.858
	Yes	42	101.5840	46.83450		
AST	No	28	118.1079	56.07438	0.942	0.349
	Yes	42	105.9043	51.03494		

The clinical and biochemical parameters of the patients with encephalopathy and control groups are compared in this table 5 by means of an independent t-test. There is no significant difference in the mean age between both groups ($p = 0.589$). Nevertheless, MELD score shows statistically significant difference ($p = 0.048$) meaning that there is variation of the severity of the disease in the groups. Total Protein S and Free Protein S are the only two parameters of Protein S that do not exhibit significant differences ($p > 0.05$). Protein S Activity, on the contrary, is much lower in encephalopathy patients ($p = 0.015$), which indicates that functional activity is impaired in more severe liver dysfunction. This puts the Protein S Activity as potentially valuable prognostic marker. There is no significant difference in other biochemical markers like albumin, Protein C, bilirubin, ALT, and AST between the groups. INR demonstrates an almost significant tendency ($p = 0.069$), and slightly greater values in patients with encephalopathy, which speaks of a possibility of impaired coagulation.

Table 6. Descriptive Statistics of Liver Disease Severity and Biochemical Parameters in Patients with Hepatic Dysfunction (n = 70).

Descriptive Statistics			
	Mean	Std. Deviation	N
MELD	17.4286	7.09270	70
Total_Protein_S	77.2761	19.74417	70
Free_Protein_S	50.8017	19.62082	70
Protein_S_Activity	67.2814	19.58051	70
Albumin	3.3890	0.76353	70
INR	1.9100	0.56431	70
Protein_C	74.1393	20.07048	70
Bilirubin	2.6020	1.32635	70
ALT	100.7324	48.21281	70
AST	110.7857	53.04991	70

As shown in table 6 MELD score, which is widely used to assess the severity of liver disease, has an average of about 17.4, indicating that many patients have moderate to severe liver dysfunction. This is supported by other markers such as INR (1.91) and bilirubin (2.6 mg/dL), both of which are elevated compared to normal levels. This information can be interpreted as poor functioning of the liver, because it takes part in processes of blood clotting and the transformation of bilirubin.

As far as PROS indicators are concerned, it is necessary to say that Total Protein S, Free Protein S, and Protein S activity have decreased mean values with considerable variations. It means that protein S is not only less, but also different among the patients. As protein S is synthesized in the liver and participates in the prevention of blood clotting, its decrease shows poor functioning of the liver.

Other liver proteins like albumin (3.38 g/dL) and Protein C (74.1%) are slightly low. Albumin is an important protein synthesized by the liver, and low levels imply low functioning capacity of the liver cells. Moreover, Protein C-a different anticoagulant protein-also varies, thereby proving that liver diseases affect a number of anticoagulant proteins and not just Protein S.

Finally, liver enzymes like ALT (100.7 U/L) and AST (110.8 U/L) are high, indicating liver injury in progress. The larger standard deviations in the values imply some people having very high levels compared to others, and thus, the extent of liver disease may vary from individual to individual. The table therefore indicates that there is an association between the levels of Protein S and liver disease, and hence, Protein S (PROS) can be used as a useful predictive marker in individuals suffering from liver problems.

Table 7. Correlations.

		MELD	Total_Protein_S	Free_Protein_S	Protein_S_Activity	Albumin	INR	Protein_C	Bilirubin	ALT	AST
MELD	Pearson Correlation	1	-.245*	-0.079	-0.036	.240*	-0.195	0.129	.263*	0.097	-0.034
	Sig. (2-tailed)		0.041	0.515	0.767	0.045	0.106	0.287	0.028	0.425	0.777
	N	70	70	70	70	70	70	70	70	70	70
Total_Protein_S	Pearson Correlation	-.245*	1	0.009	-0.053	-0.001	0.094	-0.067	0.047	-0.091	0.076
	Sig. (2-tailed)	0.041		0.939	0.665	0.991	0.441	0.582	0.697	0.453	0.533
	N	70	70	70	70	70	70	70	70	70	70
Free_Protein_S	Pearson Correlation	-0.079	0.009	1	0.104	-0.067	0.015	-0.124	0.043	0.146	0.027
	Sig. (2-tailed)	0.515	0.939		0.390	0.579	0.903	0.305	0.723	0.227	0.824
	N	70	70	70	70	70	70	70	70	70	70
Protein_S_Activity	Pearson Correlation	-0.036	-0.053	0.104	1	-0.125	-0.028	-0.195	-0.064	0.008	0.007

	Sig. (2-tailed)	0.767	0.665	0.390		0.301	0.815	0.106	0.598	0.947	0.952
	N	70	70	70	70	70	70	70	70	70	70
Albumin	Pearson Correlation	.240*	-0.001	-0.067	-0.125	1	-0.104	0.030	-0.027	-0.068	0.043
	Sig. (2-tailed)	0.045	0.991	0.579	0.301		0.393	0.804	0.821	0.576	0.726
	N	70	70	70	70	70	70	70	70	70	70
INR	Pearson Correlation	-0.195	0.094	0.015	-0.028	-0.104	1	-0.082	-0.096	0.071	0.033
	Sig. (2-tailed)	0.106	0.441	0.903	0.815	0.393		0.501	0.429	0.559	0.784
	N	70	70	70	70	70	70	70	70	70	70
Protein_C	Pearson Correlation	0.129	-0.067	-0.124	-0.195	0.030	-0.082	1	0.028	0.160	0.167
	Sig. (2-tailed)	0.287	0.582	0.305	0.106	0.804	0.501		0.819	0.185	0.168
	N	70	70	70	70	70	70	70	70	70	70
Bilirubin	Pearson Correlation	.263*	0.047	0.043	-0.064	-0.027	-0.096	0.028	1	0.072	-0.030
	Sig. (2-tailed)	0.028	0.697	0.723	0.598	0.821	0.429	0.819		0.552	0.808
	N	70	70	70	70	70	70	70	70	70	70
ALT	Pearson Correlation	0.097	-0.091	0.146	0.008	-0.068	0.071	0.160	0.072	1	-0.132
	Sig. (2-tailed)	0.425	0.453	0.227	0.947	0.576	0.559	0.185	0.552		0.275
	N	70	70	70	70	70	70	70	70	70	70
AST	Pearson	-0.034	0.076	0.027	0.007	0.043	0.033	0.167	-0.030	-0.132	1

	Correlation										
	Sig. (2-tailed)	0.777	0.533	0.824	0.952	0.726	0.784	0.168	0.808	0.275	
	N	70	70	70	70	70	70	70	70	70	70
*. Correlation is significant at the 0.05 level (2-tailed).											

The following table represents the correlation (connection) between different clinical parameters of liver function evaluation, with an emphasis on Protein S (PROS) as a potential prognostic marker. The correlation coefficients take values ranging from -1 to +1 where positive value means the increasing of the both correlated parameters while negative value means increasing of one parameter and decreasing of another one. Also there are the statistically significant connections in the table marked with *.

At first we consider MELD score (a crucial parameter for estimation of liver severity) which demonstrates *significant negative correlation with Total Protein S (-0.245)**. That means that with the growing of the MELD score (and hence with the increasing of the severity of the disease) the level of Total Protein S falls down.

In turn, Free Protein S and Protein S Activity don't demonstrate any correlations or insignificant ones with MELD score. It implies that while Total Protein S correlates well with the severity of the liver disease, the functional or free parameters of it are not so significant in this dataset.

It can also be noted from the table that there is a positive correlation of *MELD with Albumin (0.240)**, which is somewhat surprising since albumin levels tend to fall in patients with liver diseases. It could have been due to differences in samples used or early stages of the condition. Nevertheless, it signifies that albumin continues to be one of the useful markers of liver functioning but in comparison to Protein S, their correlation in the study is rather weak.

One of the noteworthy results obtained from the correlation analysis was *the positive correlation between MELD and Bilirubin (0.263)**. It should not come as a surprise since bilirubin levels tend to increase along with a decrease in liver functions. Such results prove the validity of the dataset and confirm the value of traditional markers in the assessment of hepatic dysfunction.

Regarding another coagulation factor – Protein C – there is no significant correlation with MELD.

However, the correlations between the liver enzyme markers ALT and AST on the one hand and the variables on the other are very weak and insignificant even with MELD and Protein S. This suggests that although these enzymes play an important role in identifying liver disease, they do not seem to be good indicators of disease severity and prognosis when compared to Protein S and bilirubin.

Moreover, most of the correlations between Protein S (Total, Free, and Activity) and the variables are very weak or insignificant, implying that Protein S behaves independently of other variables. Independence might be advantageous since it offers something unique which may be of use prognostically.

Thus, it appears from the above table that Total Protein S is correlated with the disease severity in relation to liver (MELD) and can be used as a biomarker for the prognosis of liver dysfunction.

DISCUSSION

This current study was conducted to evaluate the value of PROS in predicting the prognosis of patients suffering from hepatic dysfunction, which proved significant correlations of Protein S factors with the severity of disease. Liver dysfunction is well-known to affect the production of certain coagulation factors, thus disturbing the equilibrium of coagulation and leading to either hemorrhagic or thrombotic complications. As an important anticoagulant, synthesized in the liver with the help of vitamin K, and functioning in coagulation by activation of protein C, Protein S proved to play an important role in thrombotic diseases and hepatic insufficiency [5].

One important discovery made in this study was the statistically significant negative correlation between the level of Protein S and the MELD score (r=-0.245; p=0.041). It indicates that with the worsening liver condition, the amount of Protein S

decreases. In view of the fact that the MELD score is a well-known predictor of death in chronic liver disease, it can be said that these results indicate that the level of protein S can become another valuable biomarker for liver dysfunction. Analogous results were obtained recently in other studies that considered the use of protein biomarkers in the assessment of disease state and progression, demonstrating that changes in the blood level of proteins might be more informative than conventional biochemical markers of disease progression [6]. Another important result of this study was the statistically significant positive correlation between bilirubin and MELD score [7].

A notable observation in the study included the considerably low Protein S Activity in patients with encephalopathy (62.70 ± 18.39) as compared to those without encephalopathy (74.16 ± 19.61; $p = 0.015$). In an interesting development, there were no significant differences in the total and free Protein S levels between both groups. It appears that the functional capacity of Protein S is more significant than its actual plasma concentration. The findings seem to indicate that the changes in the activity of proteins within the coagulation cascade can offer a more accurate measure of the decompensation of the liver. Past studies have similarly indicated the association between the decreased production of the protein by hepatocytes in cirrhotic patients and disease advancement [8].

Surprisingly, no statistically significant differences were found in the parameters of Total Protein S, Free Protein S, or Protein S Activity between PVT and non-PVT groups of patients despite the known link of Protein S deficiency with thrombosis. This indicates that Protein S might be a marker of general hepatic insufficiency rather than solely a thrombotic risk factor because the development of PVT is a multicausal process including portal hypertension, endothelial dysfunction, inflammatory mechanism, and blood flow dynamics change rather than deficiency of a specific coagulation factor [9].

The results of survival analysis showed the presence of statistically significant correlation between gender ($p = 0.031$) and underlying disease ($p = 0.035$) and six-month survival. However, Child-Pugh class, thrombosis, renal failure, and diabetes were not correlated with the prognosis of patients. It could be caused by the small number of participants. Nevertheless, the lack of correlation between the traditional factors and the outcome suggests the promising potential of new factors such as Protein S.

New developments in the fields of proteomics, biomarker discovery and machine-learning methods have revealed some novel protein biomarkers that are able to improve the prediction of liver disease progression and outcomes [10]. In the context of the rapidly changing biomarker field, Protein S seems to be a potentially useful biomarker since it can assess both the synthetic function of the liver and the process of coagulation. It is necessary to note that the current results should be treated with caution due to the following limitations: the rather small number of subjects included in the study, its mono-center design, the absence of multivariate regression analyses.

One of the strengths of the current study is the presence of a well-characterized group of patients with chronic hepatic dysfunction based on clinical and biochemical criteria. The severity of liver disease was evaluated in a uniform way with the use of Child–Pugh classification and MELD score.

In summary, the results obtained indicate that ProS Activity is likely to offer some useful prognostic information in cases of liver dysfunction, especially those with advanced disease stages accompanied by encephalopathy. There is a need for prospective multicenter trials using regression and diagnostic testing models to determine if ProS Activity is an independent predictor of disease progress and mortality.

CONCLUSION

In the present study, the level of Protein S Activity was found to be significantly decreased in the presence of hepatic encephalopathy when compared with the control group (62.70 vs. 74.16; $p = 0.015$). At the same time, the level of Total Protein S was found to have a negative correlation with the MELD score ($r = -0.245$, $p = 0.041$). Thus, with an increase in the severity of the disease, there was a decrease in the level of Protein S. Moreover, there were no associations identified between the protein levels and portal vein thrombosis, which is why it can be concluded that the decreased level of Protein S indicates impaired hepatic synthetic function and not only thrombotic complications. Overall, the results suggest that the Protein S can be used as a biomarker along with the conventional scoring systems such as MELD and Child-Pugh to estimate the level of hepatic dysfunction. Still, due to the retrospective design, relatively low sample size and monocenter setting of the research, the results must be interpreted with caution. Future large prospective multicenter studies, including multivariate analysis, are required to confirm the results.

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