ORIGINAL ARTICLE

Evaluation of Soluble CD25 as a Marker in Chronic Liver Diseases in Children

[1]Shaimaa A. Mohammed, [2]Osamaa E. Botrous, [2]Mahmoud Hodeib, [3]Mostafa S. Sheemy*
[1]Beni-Suef Specialized Hospital
[2]Department of Pediatrics, Faculty of medicine Beni-Suef University
[3]Department of Medical Microbiology & Immunology, Faculty of Medicine, Beni-suef University

Key words:
Soluble CD25, immunological marker, chronic Liver disease, Liver fibrosis, Interleukin-2 receptor

Corresponding Author:
Mostafa Saleh Sheemy MD
Medical Microbiology and Immunology Department
Faculty of Medicine, Beni-Suef University- Egypt
Tel.: 002-01005678424
E-mail:
dr.m.sheemy@gmail.com

ABSTRACT

Background*: Based on the crucial pathogenic role of inflammation for the progress of hepatic disorders, we hypothesized that the soluble interleukin-2 receptor (sIL-2R, also known as s CD25) would be a sign of inflammatory cell activation and disease severity in people with chronic liver diseases (CLD).* ***Objectives****: Our study aimed to evaluate soluble CD25 as a possible indicator of immune cell activation in CLD and acute liver diseases in a group of pediatric Egyptian patients.* ***Methodology****: This study was a case control study that included 120 children presented with liver disease aged 2 month-15 years and 60 unrelated healthy controls. The patients were recruited from Pediatric Hepatology Clinic, Beni- Suef University. All children were subjected to history taking, full clinical examination, laboratory tests (CBC, GGT, ALP, AST, ALT, serum albumin, PT, PC, PTT, INR and Soluble CD25 level).* ***Results****: Children with chronic liver disease with fibrosis had serum sIL-2R levels that were considerably lower (19.16±12.33 ng/ml) than children with acute liver disease (27.65±14.19 ng/ml) (p=0.036) and controls (29.23±13.20 ng/ml) (p=0.008). Children with chronic liver disease without fibrosis had a mean CD25 level of (23.33±16.31 ng/ml), which was not statistically different from other groups (p=0.655).* ***Conclusions****: further research is needed to clarify the role of sCD25 as an immunological marker to predict the occurrence of liver fibrosis in pediatric hepatic disorders and to differentiate between acute & chronic hepatic disorders.*

INTRODUCTION

Pediatric liver diseases comprise a wide variety of disorders, including infections, developmental abnormalities, genetic, and metabolic disorders that ultimately result in progressive alterations in structure of liver and may end in cirrhosis and its consequences. Children's liver problems are distinct from adult cases and involve many subgroups of acute and chronic illnesses.[1]

Children's chronic liver diseases (CLD) are a serious public health concern that cause significant morbidity and mortality. Although the actual prevalence of pediatric CLD is unknown, it has been reported that CLD causes roughly 15,000 children to be hospitalized each year in the United States. CLD in children is a precursor to liver disease in adults.[2]

The basis for the diagnosis of CLD is still thought to be the histopathological analysis of a liver biopsy. Recently, non-invasive approaches for the evaluation of CLD, such as transient liver elastography and biomarkers that could aid in the evaluation of liver fibrosis, have been suggested. However, there is still a pressing need for a biomarker that detects the presence of CLD at a better capacity.[2]

Since its discovery in 1985 the soluble interleukin-2 receptor (sIL-2R, sCD25) has become a clinically valuable tool for several diseases. It is regarded as a disease activity marker in sarcoidosis, but elevated serum concentrations have also been seen in other autoimmune conditions such rheumatoid arthritis and systemic lupus erythematosus. Additionally, sIL-2R is increased in several neoplastic diseases.[3]

Although many leukocytes release the interleukin-2 receptor (IL-2R, CD25), interleukin-2 is principally released by activated T-helper cells. Although active T lymphocytes and regulatory T cells release significant quantities of IL-2R, a component of the IL-2 receptor, it is generally known that activated B cells, monocytes, eosinophil, granulocytes, and natural killer cells (NK cells) also release CD25,[4]

The soluble counterpart of the IL-2 receptor appears to be created by proteolytic cleavage of IL-2Rα, and the release of sIL-2R into the circulation has been reported to be proportionate to its membrane-bound expression. This is thought to be the primary factor that sIL2-R is able to reliably predict disease activity in inflammatory illnesses.[5]

Since chronic inflammation is thought to be the leading factor of hepatic disorder progression, the tight

relationship of sIL-2R with inflammatory processes makes it potentially helpful as a marker in CLDs. There is a noticeable increase in sIL-2R in liver disorders, according to numerous studies focusing into sIL-2R in CLD.[6,7]

It is necessary to conduct additional research to assess sIL-2R concentrations prospectively as a promising marker for the progress of liver fibrosis and to clarify the potential functional role of sIL-2R in this process.[8] In order to assess the possible relevance of soluble CD25 as a marker in CLD and acute liver disorders in a sample of pediatric Egyptian patients, the current study investigated soluble CD25.

METHODOLOGY

The current case control study included 120 pediatric patients proved to have liver affection by clinical examination and hepatic function testing, enrolled from the pediatric outpatient clinic at Beni-Suef University Hospital. The cases involved; 60 patients suffering from acute liver diseases, 30 patients suffering from chronic liver diseases without fibrosis and 30 patients had chronic liver diseases with fibrosis. Sixty apparently healthy control subjects were randomly selected and included after obtaining an informed consent from all patients' guardians and approved by Beni-Suef University Faculty of Medicine Ethical Committee (Approval No.: FMBSUREC/09022020/ Mohammed).

All children have undergone a full history taking, clinical examination and abdominal ultrasonography to check the liver, spleen, and existence of ascites.

Laboratory investigations:

About 10 ml of venous blood were taken under complete aseptic conditions. Two ml of the blood sample were collected on sodium citrate to determine the prothrombin time and concentration, 2.0 ml of blood were taken on K-EDTA for complete blood picture (CBC) and remaining 6.0 ml was allowed to clot and centrifuged at 3000 rpm for 5 minutes. The sera were divided into two screw capped cryotubes, one for the determination of liver function testing and the other was stored at -70°C to be used for measuring serum soluble CD25 level by a double antibody sandwich enzyme-linked immunosorbent assay (ELISA) (Sun Red, China).[7]

Statistical methods:

Statistical tests were done using IBM SPSS® Statistics version 26 (IBM® Corp., Armonk, NY, USA). Quantitative data were presented as mean and standard deviation, while qualitative (Categorical) data were presented as frequencies and percentages. *ANOVA test* with Tukey post hoc test were used to compare multiple different variables. *Chi-square test* was employed to examine the association between categorical variables. The Spearman correlation coefficient was applied to find significant correlations between non-linear quantitative data. *Receiver operating characteristic (ROC) curve analysis* was used to evaluate the accuracy, sensitivity and specificity of CD25. The significance level was set at $p < 0.05$.

RESULTS

The current study included 120 pediatric patients proved to have liver affection by clinical examination and hepatic function testing, were enrolled from the pediatric outpatient clinic at Beni-Suef University Hospital. Sixty patients were diagnosed with acute liver illnesses, 30 with chronic liver illnesses without fibrosis, and 30 with chronic liver illnesses with fibrosis. Sixty apparently healthy control subjects were randomly selected and included.

The studied groups were balanced as regards the gender, while the age was significantly different (p-value = 0.039*), the mean age was (5.64 ± 3. 46 SD) in acute liver group, (7.04 ± 5.32 SD) in chronic liver without fibrosis group, (8.13 ± 3.54 SD) in chronic liver with fibrosis group, (6.52 ± 3.02 SD) in control group (Table 1).

Table 1: Comparison between the subgroups and control according to demographic data.

Demographic Data	Acute liver disease (n=60)	Chronic liver disease (n=60)		Control group (n=60)	P
		Without fibrosis (n=30)	With fibrosis (n=30)		
Sex					
Female	31 (51.7%)	16 (53.3%)	14 (46.7%)	30 (50.0%)	**0.958**
Male	29 (48.3%)	14 (46.7%)	16 (53.3%)	30 (50.0%)	
Age (years)					
Mean ± SD.	5.64 ± 3.46	7.04 ± 5.32	8.13 ± 3.54	6.52 ± 3.02	**0.039***
Range (Min. – Max.)	25.0 – 11.0	0.12 – 14.0	2.0 – 14.0	1.0 – 12.0	

p: p value for comparing between **the subgroups** and **control**
*: Statistically significant at $p \leq 0.05$

Table (2) shows the panel of diseases in the studied groups. *In the* acute liver disease group (Hepatitis A infection, Sepsis, Autoimmune hepatitis and Wilson's disease represented 70%, 20%, 6% and 4% respectively), in the chronic liver disease without fibrosis group (Autoimmune hepatitis, Cholestasis and Glycogen storage disease represented 50%, 43% and 7% respectively), while, in the chronic liver diseases with fibrosis group (Hemochromatosis, Progressive familial cholestasis, Bile acid synthetic disorder, Budd Chiari syndrome and Neonatal giant hepatitis represented 80%, 7%, 7%, 3% and 3% respectively).

Table 2: Panel of diseases in the studied groups:

Group	Diseases	Number	Percentage	Total No. (%)
Acute liver disease (n=60)	Hepatitis A infection	42	70 %	60 (100%)
	Sepsis	12	20 %	
	Autoimmune hepatitis	4	6 %	
	Wilson's disease	2	4 %	
Chronic liver disease without fibrosis (n=30)	Autoimmune hepatitis	15	50 %	30 (100%)
	Cholestasis	13	43 %	
	Glycogen storage disease	2	7 %	
Chronic liver disease with fibrosis (n=30)	Hemochromatosis	24	80 %	30 (100%)
	Progressive familial cholestasis	2	7 %	
	Bile acid synthetic disorder	2	7 %	
	Budd Chiari syndrome	1	3 %	
	Neonatal giant hepatitis	1	3 %	
Control (n=60)	Healthy	60	100 %	60 (100%)

Table (3) shows that there was a high statistical significant difference between subgroups and control regarding Hemoglobin, PT, PC, international normalized ratio (INR), AST, ALT, Alkaline Phosphatase (ALP), Bilirubin, albumin and GGT, similarly, shows that there was significant difference between subgroups and control regarding WBCs and platelet count.

Table 3: Comparison between the subgroups and controls according to routine laboratory investigations:

	Acute liver disease (n=60)	Chronic liver disease (n=60)		Control group (n=60)	P
		Without fibrosis (n=30)	With fibrosis (n=30)		
	Mean ± SD.	**Mean ± SD.**	**Mean ± SD.**	**Mean ± SD.**	
Hb	10.46 ± 1.77	10.78 ± 1.42	6.65 ± 0.48	11.66 ± 1.10	**<0.001***
Platelets	290.35 ± 83.64	316.0 ± 84.05	350.63 ± 116.59	315.40 ± 83.38	**0.003***
WBCs	8358.83± 6053.31	6895.07±2573.30	5913.33±1553.48	6464.15±8046.25	**0.033***
ALT	1148.45±785.35	395.10 ± 321.74	29.50 ± 6.84	26.17 ± 6.80	**<0.001***
AST	975.67 ± 664.73	339.93 ± 254.50	24.10 ± 6.71	26.23 ± 5.64	**<0.001***
Bilirubin	3.67 ± 2.24	7.58 ± 6.85	0.60 ± 0.21	0.50 ± 0.18	**<0.001***
Albumin	3.29 ± 0.67	2.79 ± 0.50	3.50 ± 0.31	3.67 ± 0.27	**<0.001***
PT	14.43 ± 3.60	17.52 ± 2.56	12.40 ± 0.80	12.35 ± 0.72	**<0.001***
PC	72.15 ± 19.48	52.69 ± 9.64	83.17 ± 6.59	90.13 ± 6.54	**<0.001***
INR	1.45 ± 0.75	1.93 ± 0.48	1.0 ± 0.01	1.01 ± 0.01	**<0.001***
GGT	65.18 ± 32.54	198.17 ± 213.37	28.60 ± 6.41	28.92 ± 6.50	**<0.001***
ALP	138.62 ± 70.33	453.0 ± 583.90	68.53 ± 9.88	64.83 ± 9.09	**<0.001***

WBCs = white blood cells, **ALT**= alanine amino transferase, **AST**= aspartate amino transferase, **PT** = prothrombin time, **PC** = prothrombin concentration, **INR** = international normalized ratio, **GGT** = gamma glutamate transferase, **ALP** = alkaline phosphatase,
p: p value for comparing between **the subgroups** and **control**
*: Statistically significant at **p ≤ 0.05**

The mean sCD25 level was 27.65±14.19, 23.33±16.31, 19.16±12.33 and 29.23±13.20 ng/ml in acute liver disease, and chronic liver disease without fibrosis, chronic liver disease with fibrosis and control groups respectively. There was a statistically significant difference between groups as determined by one-way ANOVA *(F=4.11, P=0.008)*. A Tukey post hoc test revealed that CD25 level was significantly lower among children with chronic liver disease with fibrosis compared to children with acute liver disease (p=0.036) and controls (p=0.008). While there was no statistically significant difference between the mean level of CD 25 among children with chronic liver disease without fibrosis and other groups (p=0.655) (Table 4 and Figure 1).

Table 4: Distribution of CD25 in different groups and controls:

Participants	Soluble CD25 level (ng/ml)		95% Confidence Interval for Mean		*P value Within groups*	*P value between groups*
	Mean±SD	Range	Lower Bound	Upper Bound		
Children with acute liver disease, n=60	27.65±14.19	10.0-56.2	23.99	31.32	0.036* a	0.008*d
Children with chronic liver disease without fibrosis, n=30	23.33±16.31	6.9-56.4	17.24	29.42	0.655 b	
Children with chronic liver disease with fibrosis, n=30	19.16±12.33	5.3-52.0	14.55	23.76	---	
Controls, n=60	29.23±13.20	13.3-54.9	25.81	32.64	0.008*c	

* : Statistically significant at $p \leq 0.05$
a. Difference between acute & chronic with fibrosis
b. Difference between chronic without fibrosis & chronic with fibrosis
c. Difference between chronic with fibrosis &control group.
d. Difference between all groups.

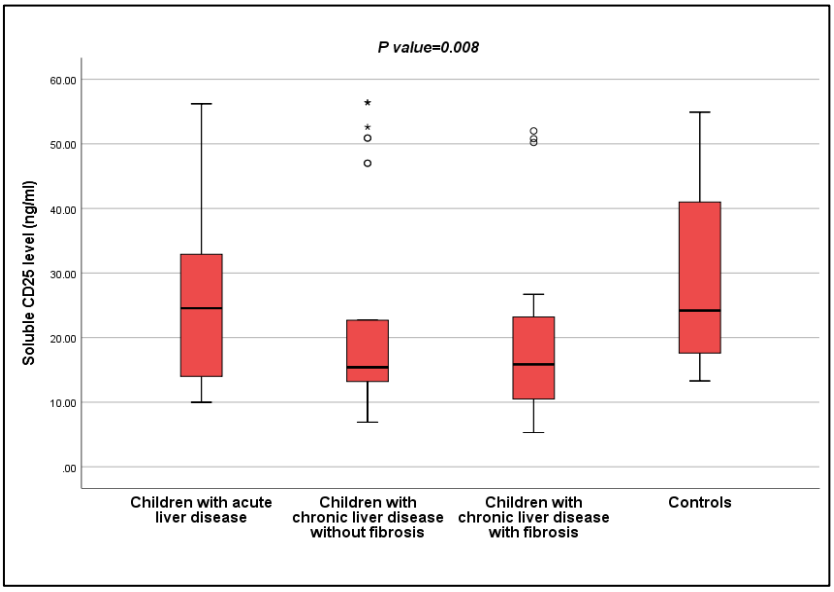

Fig. 1: The relation between values of sCD25 in the study groups

Correlation analysis between sCD25 and other parameters among the studied groups are shown in table (5). There was a statistically significant direct correlation between the levels of s CD25 and levels of Hemoglobin, ALT, AST, bilirubin and GGT (P= 0.004, 0.001, 0.011, 0.018 and 0.042 respectively) and there is statistically significant inverse correlation between the levels of s CD25 and duration of the disease (p=0.016), but all these direct and inverse correlations are weak ($r_s < 0.3$) (Table 5).

Table 5: Correlation between CD25 and clinical and laboratory parameters in all patients (n=120)

	CD25		
	r_s	P	Sig.
Age (years)	-0.109	0.237	**NS**
Duration	-0.220*	0.016*	**S**
Weight (kg)	-0.082	0.374	**NS**
Height (cm)	-0.073	0.428	**NS**
BMI (kg/m^2)	0.093	0.314	**NS**
Hemoglobin	0.261*	0.004*	**S**
Platelet	0.016	0.862	**NS**
WBCs	0.112	0.211	**NS**
ALT	0.298*	0.001*	**S**
AST	0.233*	0.011*	**S**
Bilirubin	0.217*	0.018*	**S**
Albumin	0.027	0.770	**NS**
PT	0.091	0.322	**NS**
PC	-0.079	0.392	**NS**
INR	0.117	0.202	**NS**
GGT	0.186*	0.042*	**S**
ALP	0.131	0.153	**NS**

r_s: Spearman coefficient
*: Statistically significant at $p \leq 0.05$
WBCs = white blood cells, **ALT**= alanine amino transferase, **AST**= aspartate amino transferase, **PT** = prothrombin time, **PC** = prothrombin concentration, **INR** = international normalized ratio, **GGT** = gamma glutamate transferase, **ALP** = alkaline phosphatase

Based on the ROC curve for serum sCD25 (Figure 2), area under the curve (AUC) was 0.664 at a cutoff value of 12.35 ng/mL (p-value was 0.007) with a sensitivity of 87.8% and a specificity of 43.3%. The Positive predictive value was 0.82 and the negative predictive value was 0.54.

Cutoff value	*p* value	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under curve
12.35	0.007	87.8%	43.3%	0.82	0.54	0.664

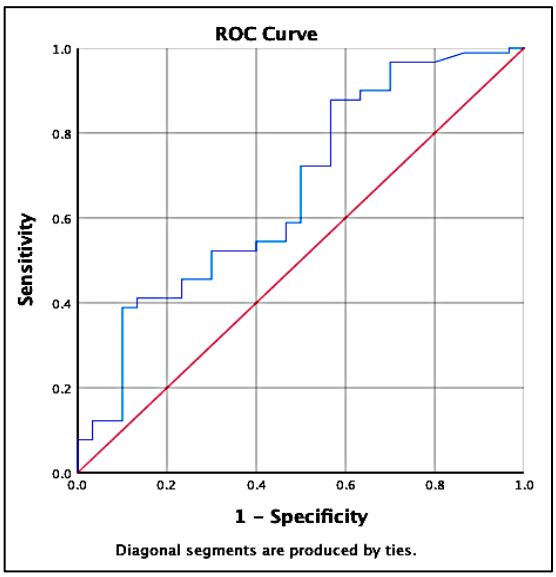

Fig. 2: Receiver operator characteristic (ROC) curve for sCD25

DISCUSSION

The current study examined the relation between s CD25 and hepatic disease in children (acute and chronic) in an attempt to find a reliable measurable predictor biomarker. Our study was a case control study conducted at Beni Suef University hospital, included 120 children (60 with acute and 60 with chronic liver disease) aged 2month-15 years and 60 unrelated healthy controls.

Our study found that the studied groups were balanced as regards the gender, there was high significant difference between groups to age (p-value = 0.039), and this result differs from the findings of Wagrees et al.[9] at Suez Canal University hospital. The studied populations were mostly males representing 70% in all studied groups; there was insignificant difference between groups to age or sex, The mean age was 58.4 ± 5.6 years in HCC group while was 50.4 ± 9.7 and 57.1 ± 12.3 years in cirrhotic and healthy controls respectively (p= 0.51).

Our study included pediatric patients with a variety of liver disorders that differed between the groups. In the acute liver disease group (Hepatitis A infection, Sepsis, Autoimmune hepatitis and Wilson's disease), in the chronic liver disease without fibrosis group (Autoimmune hepatitis, Cholestasis and Glycogen storage disease), while, in the chronic liver diseases with fibrosis group (Hemochromatosis, Progressive familial cholestasis, Bile acid synthetic disorder, Budd Chiari syndrome and Neonatal giant hepatitis), these panels of diseases differ from the other studies conducted to evaluate sCD25 in hepatic diseases; Hepatocellular Carcinoma in Chronic Hepatitis C patients, primary biliary cirrhosis and hepatic bile canaliculus.[9-11] This variation in the types of liver disorders could be attributed to differences in age categories and research populations. Also, these studies mostly focused on selected etiologies.

Our study showed high statistically positive difference among the groups to bilirubin, albumin, INR, and alkaline phosphatase ($p<0.001$), these results agree with Garcia et al.[7] findings for bilirubin ($p = 0.025$), alkaline phosphatase ($p = 0.037$), albumin ($r = -0.496$, $p<0.001$) and INR ($r = 0.349$, $p = 0.003$).

In this work there was statistically significant direct association between the sCD25 levels and ALT, AST, total bilirubin, direct bilirubin, prothrombin time but not correlated to albumin, INR. Barak et al.[10] had found a similar finding that soluble CD25 is negatively correlated to albumin. Moreover, Wagrees et al.[9] showed that there was statistically significant direct association between s CD25 levels and ALT, AST, total bilirubin, direct bilirubin, prothrombin time and this concurs with our study.

We found significantly lower mean values of sIL-2R in patients suffering from chronic liver disease with fibrosis than acute and healthy controls ($p=0.036$, 0.008 respectively) which contradicts the findings of Garcia et al.[7] who found that there were statistically significant higher mean values of sIL-2R within liver cirrhosis group than in control group. Additionally, Wagrees et al.[9] found a highly significant rise in sIL-2R levels in patients with cirrhotic liver and hepatocellular carcinoma in comparison to normal controls, ($p=0.001$). No difference was found in sIL-2R levels in HCC patients compared to liver cirrhosis patients ($p=0.862$). Similar results were obtained by a study done by Barak et al.[10] conducted on 84 patients with primary biliary cirrhosis (PBC) and 41 control subjects. They found that sIL-2R levels in PBC sera were substantially higher (1527 – 106, range 211–4023 pg/ml) compared to normal controls (566– 29, range 216–901 pg/ml; $P < 0.001$).

Furthermore, the current findings contradict the findings of Seidler et al. [12] who found that CLD patients had significantly higher blood sCD25 concentrations than 41 healthy controls (median 444 kU/L, range 14-1193 vs. median 818 kU/L, range 39-3976). Only patients with established liver cirrhosis had higher levels of sCD25 (median 374 kU/L, range 204-1795 vs. median 907 kU/L, range 39-3975), but there was no difference between noncirrhotic patients and controls. Patients who had severe or decompensated cirrhosis, classified as Child B and C, showed significantly higher sCD25 levels than patients without cirrhosis or with mild cirrhosis (median 600kU/L, range 39-3976, vs. median 1101 kU/L, range 317-3395).

In the current study, we observed a high statistically significant variation among subgroups and controls in terms of sCD25 level, which coincides with Stoop et al.[13] study on 50 patients who are chronically infected with hepatitis B virus (HBV), 23 healthy controls, and 9 individuals with resolved HBV infection, which found an increased percentage of T regulatory CD4+ CD25+ cells in chronic HBV as compared to controls.

The reasons for these discrepancies in results are not clear, though it may be related to differences in methodology used, in the study population, in the selection of subjects, study group, cause of liver illnesses and sample size.

However, one important limitation of these researches is that they concentrated on specific etiologies, primarily viral-related liver disorders or primary biliary cirrhosis. As a result, it was unclear if sCD25 could be used to assess inflammatory responses in progressing CLD and to what degree sCD25 could reflect activation of diverse leukocyte subpopulations in CLD.[14]

A possible explanation for our unexpected results is that, while sIL-2R levels are frequently being tested in diagnostic settings, this molecule's probable function remains controversial. This may be due in part to the IL-2-IL-2R pathway's paradoxical role in immune activation and self-tolerance.[15]

Another explanation is that higher levels of sCD25 in malignant diseases signify T-cell stimulation, indicating that an anti-tumor immune response is going on. This is true only if sIL-2R is predominantly secreted by effector T cells. But the scenario would be the opposite if the sCD25 is produced from T regulatory cells, which could result in inhibition of T-cell response (tolerance).[16, 17]

In our study correlation analyses between sCD25 and other parameters among the studied groups showed statistically significant positive relation between the concentrations of s CD25 and levels of Hemoglobin, ALT, AST, bilirubin and GGT ($P= 0.004$, 0.001, 0.011, 0.018 and 0.042 respectively) and there was a statistically significant negative relation between the concentrations of s CD25 and duration of the disease ($p=0.016$), these results agree with Wagrees et al.[9] who revealed a statistically significant direct correlation between the concentrations of s CD25 and levels of ALT, AST, total bilirubin, direct bilirubin, prothrombin time ($p<0.001$) and there was statistically significant

negative relation between the concentrations of sCD25 and albumin levels ($p<0.001$).

Based on the ROC curve, area under the curve (AUC) was 0.664 indicating that serum sCD25 was a fair differentiating marker between subjects with chronic and acute hepatic disorders and healthy individuals, at cutoff value of 12.35 ng/mL, with a specificity of 43.3% and sensitivity of 87.8%. However, in a study done by **Wagrees et al.**[9] sCD25 performed well in predicting HCC presence among patients with cirrhosis; specificity and sensitivity were both 65% at a cut-off value of 10.22 ng/ml for prediction of HCC in patients with cirrhosis. Furthermore, **Seidler et al.**[12] found that sIL-2R could distinguish between non-cirrhotic and cirrhotic patients using ROC curve analysis (AUC = 0.755).

CONCLUSION

It could be assumed from the current findings that CD25 is a poor immunological marker to predict the occurrence of liver fibrosis in pediatric hepatic disorders and likely couldn't differentiate between acute & chronic hepatic disorders. These observations need further clarifications and more research in different age groups, etiologies and stages of the disease.

This manuscript has not been previously published and is not under consideration in the same or substantially similar form in any other reviewed media. I have contributed sufficiently to the project to be included as author. To the best of my knowledge, no conflict of interest, financial or others exist. All authors have participated in the concept and design, analysis, and interpretation of data, drafting and revising of the manuscript, and that they have approved the manuscript as submitted.

Conflicts of interest:

All authors – none to declare.

Funding:

None to declare.

Acknowledgements:

The authors would like to thank professor/ Nermin Hassan Ibrahim professor of medical microbiology and immunology- faculty of medicine- Beni-Suef University who helped us in drafting the manuscript, dr/ Gehad Sabry assistant lecturer of public health- faculty of medicine- Beni-Suef University who helped us in the statistical analysis of data and thanks to all participants and other healthcare workers who helped all through the process of the research.

REFERENCES

1. Deep A, Saxena R and Jose B.: Acute kidney injury in children with chronic liver disease. Pediatric Nephrology; 2019; 34(1), 45-59.
2. Abou-Taleb A, Ahmed A and El-Hennawy A: Pediatric Chronic Liver Diseases: A clinicopathological study from a tertiary care center. *International* Journal of Pediatrics; 2019; 7(4), 9305-9315.
3. Adachi Y, Nojima M, Mori M, Yamashita K, Yamano H, Endo T and Tamakoshi A.: Tumor Marker Publication. Tumor Biology; 2017; 1, 21.
4. Zhou X, Xing J, Tang X, Sheng X, Chi H and Zhan W.: Interleukin-2 (IL-2) interacts with IL-2 receptor beta (IL-2Rβ): its potential to enhance the proliferation of CD4+ T lymphocytes in flounder (Paralichthys olivaceus). Frontiers in Immunology; 2020; 11, 2212.
5. Heming M, Lohmann L, Schulte-Mecklenbeck A, Brix T, Gross C, Wiendl H and zu Hörste G.: Leukocyte profiles in blood and CSF distinguish neurosarcoidosis from multiple sclerosis. Journal of Neuroimmunology; 2020; 341, 577171.
6. El-Shanawani F, Abdel-Hadi A, Abu Zikri N, Ismail A, El-Ansary M and El-Raai A.: Clinical significance of aflatoxin, mutant P53 gene and sIL-2 receptor in liver cirrhosis and hepatocellular carcinoma. J Egypt SocParasitol; 2006; 36(1):221–239.
7. Garcia Ruiz P, Canora Lebrato J, Diez Ruiz A, Fuchs D and Wachter H.: Soluble interleukin-2 and tumor necrosis factor receptor in liver cirrhosis. Relationship with clinical severity and prognosis. Med Clin (Barc); 2004; 122 (12):441–443
8. Kobayashi H, Enomoto A, Woods S, Burt A, Takahashi M and Worthley D.: Cancer-associated fibroblasts in gastrointestinal cancer. Nature reviews Gastroenterology & Hepatology; 2019; 16(5), 282-295.
9. Wagrees S, Abdelaziz H, Badr EL-Dein B and Omar S.: Assessment of the Level of Soluble CD25 as a Marker for the Detection of Hepatocellular Carcinoma in Chronic Hepatitis C virus (HCV) Infected Patients. Suez Canal University Medical Journal; 2018; 21(2), 99-106.
10. Barak V, Selmi C, Schlesinger M, Blank M, Agmon-Levin N, Kalickman I, Gershwin M, Shoenfeld Y. Serum inflammatory cytokines, complement components, and soluble interleukin 2 receptor in primary biliary cirrhosis. J Autoimmun.; 2009; 33(3–4):178–182.

11. Zhong-Hua Lu, Wei -Chen, Chao-Xia Ju. et al. CD25 is a novel marker of hepatic bile canaliculus. Int J Surg Pathol.; 2012; 20(5):455-61.
12. Seidler S, Zimmermann H, Weiskirchen R, Trautwein C, and Tacke F. Elevated circulating soluble interleukin-2 receptor in patients with chronic liver diseases is associated with non-classical monocytes, BMC Gastroenterol; 2012; 12-38.
13. Stoop J, van der Molen R, Baan C, van der Laan L, Kuipers E, Kusters J, Janssen HL. Regulatory T cells contribute to the impaired immune response in patients with chronic hepatitis B virus infection. Hepatology; 2005; 41:771–8.
14. Gusev, E and Zotova, N. Cellular stress and general pathological processes. Current pharmaceutical design; 2019; 25(3), 251-297.
15. Damoiseaux J. The IL-2 – IL-2 receptor pathway in health and disease: The role of the soluble IL-2 receptor; Clinical Immunology; 2020; 218; 108515.
16. Lindqvist C, Christiansson L, Simonsson B, Enblad G, Olsson-Stromberg U, Loskog A. T regulatory cells control T-cell proliferation partly by the release of soluble CD25 in patients with B-cell malignancies, Immunology; 2010; 131 (2010) 371–376.
17. Pedersen A, Lauritsen J. CD25 shedding by human natural occurring CD4+CD25+ regulatory T cells does not inhibit the action of IL-2, Scand. J. Immunol.; 2009; 70: 40–43.