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CORRELATION OF INTERLEUKIN-33 WITH SOME BIOCHEMICAL VARIABLES IN CHRONIC HEPATITIS B PATIENTS IN AL-FALLUJAH CITY

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Abstract: Hepatitis B virus (HBV) disease is one of the main reasons of cirrhosis, chronic hepatitis, eventually hepatocellular carcinoma (HCC); as a result, it can be extremely harmful to the liver. Main goal of this paper to explore the correlation of interleukin (IL) 33with certain biochemical parameters in Iraqi patients with chronic hepatitis B (CHB). This research included 40 CHB patients from Al- Fallujah city and 40 healthy controls (HCs). The serum concentration of IL-33 was established using an enzyme linked immunosorbent assay (ELISA), while the ratio of waist to thoracic (W/T), waist to neck (W/N), waist to hip (W/H), systolic blood pressure (SBP), diastolic blood pressure (DBP), and rate of pulses (ROP) were carefully measured and documented. IL-33, was discovered to be increased in CHB patients in comparison to HCs ($P<0.000l$), BMI, W/T were higher in CHB patients compared to HCs with ($P<0.05$), also age, W/N, W/H, DBP and ROP were greater in patients with CHB in comparison to HCs, while SBP was greater in HCs than in CHB with ($P > 0.05$) for these parameters, there was a weak positive correlation between IL-33 with BMI ($r=0.254$, $P= 0.028$), other studied variables, did not show significant correlation with IL-33 which gave the following results DBP ($r=0.182$, $P=0.119$), W/N($r=0.0170$, $P=0.885$), ROP ($r = 0.103$, $P = 0.379$), Age ($r = 0.048$, $P = 0.675$), W/T ($r = 0.017$, $P = 0.885$) , SBP ($r = -0.045$, $P = 0.704$) and W/H ($r = -0.081$, $P = 0.492$), respectively. Serum IL-33 levels can be used in the detection of CHB and may be an effective biomarker in the diagnostic test of CHB.

Keywords: interleukin-33, CHB, Anthropometric Measurements, BMI.

1. Introduction

Hepatitis B virus infection is one of the most common and severe infectious diseases in the world; CHB has a high morbidity and is difficult to treat, HBV-related hepatitis causes a variety of adverse reactions that have a negative impact on patients' quality of life and have even resulted in patient deaths [1]. Infection with HBV results in infiltration of immune cells, which causes the mediates processes of infection, immune cells differentiation and necro inflammatory foci formation at the site of inflammatory, as well as the production of cytokines for proinflammatory, all practice in essential functions in the induction of liver injury [2]. The natural history and pathology of CHB infection entail a dynamic interplay between two virus infections and host immune cells, and thus could possibly be very variable; Cirrhosis, cirrhosis complications, and hepatocellular carcinoma affect a significant number of patients, while others have carcinoma with long-term quiet disease activity that does not require antiviral treatment term [3]. The phases of CHB infection are not necessarily sequential [4]. It can be categorised into five clinical phases [5]. The first phase, immune tolerance [3]. The second phase is positive of HBeAg- immune reactive; Third phase inactive carrier of HBV; forth phase is negative chronic hepatitis of HBeAg-; and fifth phase is negative phase of HBsAg [5]. Cytokines, the immune system's primary vehicles, act as inflammatory and anti-inflammatory molecules, resulting in acute or chronic inflammatory conditions [6]. T helper cell 17 (TH17) is a type of T helper cell that produces these cytokines [7]. IL-33 is one of IL-1 cytokines family with an increasing target cells number and different biological roles [8]. It is stimulated the manufacture of T helper-2 (Th2) and pro-inflammatory associated cytokines, and serum IL-33 was linked to liver damage in CHB patients [9]. Many local studies deal with inflammatory biomarkers in different diseases, but this study determines different variables in Iraqi patients with CHB comparing with previous studies [10, 11, 12]

Present study aims to evaluate serum levels of IL-33 in Iraqi CHB patients and HC subjects, also explore the association of IL-33 with a number of biochemical parameters and some anthropometric measurements.

2. Materials & Methods

In case-control study, 40 CHB patients were recruited from a number of private laboratories in Iraq, Fallujah from September 2020 to January 2021, duration of disease was 11.54±4.85 years, all CHB patients were non-diabetic, non-cardiovascular disease, any other endocrine disorders or metabolic kidney diseases and were free of acute or chronic infection at time of sampling.. Forty healthy individuals matched in gender and age (20-65 years) of patients were selecting as HCs group, the controls were selected among subjects who were apparently seems healthy in terms of not infected with hepatitis and non-diabetic, non-cardiovascular disease, non-hypertensive, any other endocrine disorders or metabolic kidney diseases and were free of acute or chronic infection at time of sampling., W/N, W/H and W/T were measured and calculated, while BMI was calculated by dividing weight (kilograms) by height squared (meter), also SBP, DBP and ROP were measured. A serum level of IL-33 was estimated by ELISA technique.

Statistical Analysis

All statistical analyses of findings were complete via GraphPad Prism program version 8. The outcomes are denoted by the terms mea, standard deviation (SD) and standard error of mean (SEM), two-tailed Pearson correlation analyses were used to test bivariate associations and the accuracy of the examination was determined by area under curve (AUC). The significance level of p-value less than 0.05 was determined to be significant difference.

3. Results and Discussion

This paper including 80 subjects, 40 of them with CHB infection and others were healthy people as HCs group, there was non-important statistical difference in mean age (years) between both CHB patients and HCs group (P = 0.7729), this findings revealed that the mean age of CHB patients (37.4 ± 10.79) was slightly higher than control (36.7 ± 10.83), as presented in fig (1), table (1), but mean of BMI (kg/m^2) was higher among CHB patients (31.28 ± 9.004) compared to controls (24.94 ± 1.835), BMI has shown significant differences (P< 0.0001), as shown in table (1), fig (2), the mean W/H showed non-significant difference in control and CHB patients (P=0.4298), as shown in table (1), fig (3), W/T shown significant differences (P= 0.0260), as illustrated in the table (1) , fig (4), and W/N presented non-significant difference (P=0.1365) between control and CHB patients, as shown in table (1), fig (5).

The results demonstrated that the mean W/N, W/H and W/T of CHB patients (2.39 ± 0.332), (0.9159 ± 0.1403) and (0.9276 ± 0.09307) were slightly higher than controls (0.8928 ± 0.1101), (0.8881 ± 0.05466) and (2.286 ± 0.2654) respectively, there were non-significant difference in mean blood pressure (mmHg) in both SBP (P= 0.7703), DBP (P = 0.0543). SBP level was increased in HCs (121.3 ± 4.965) compared with patients group (120.9 ± 4.931), but, the level of DBP was increased in CHB patients group (78.91±5.204) compared wssith healthy control group (76.63 ± 4.923) and, shown in table (1), fig (6 and 7), the ROP (1/min) showed non-significant difference (P= 0.4629), in CHB patients group as compared to controls (76.11 ± 8.581) *v* (74.5 ± 10.15), as shown in table (1), fig (8).

Serum concentrations of IL-33 were higher in patients CHB infection (404.3 ± 148 ng/mL) than in HCs group (59. 84 ± 13.57 ng/ mL) (P<0.0001) as displayed in fig (9), table (1).

Table 1. Medical and Anthropometric Characteristics of CHB Patients and Healthy controls

Variable	Healthy controls			Patients			p-value
	Mean	SD	SEM	Mean	SD	SEM	
Age Years	36.7	10.83	1.712	37.4	10.79	1.706	0.772
BMI kg/m2	24.94	1.835	0.290	31.28	9.004	1.424	<0.001
W/H	0.8928	0.1101	0.0174	0.916	0.1403	0.0241	0.430
W/T	0.8881	0.0547	0.009	0.927	0.09307	0.0157	0.026
W/N	2.286	0.2654	0.042	2.39	0.332	0.0561	0.137
SBP mmHg	121.3	4.965	0.785	120.9	4.931	0.8335	0.770
DBP mmHg	76.63	4.923	0.779	78.91	5.204	0.8796	0.054
ROP 1/Min	74.5	10.15	1.605	76.11	8.581	1.45	0.463
IL-33 (ng/mL)	59.84	13.57	2.173	404.3	148	23.4	<0.001

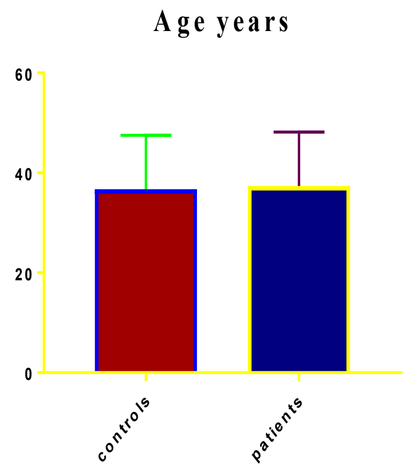


Fig. (1): Mean+ S.D for Age in Control and Patients

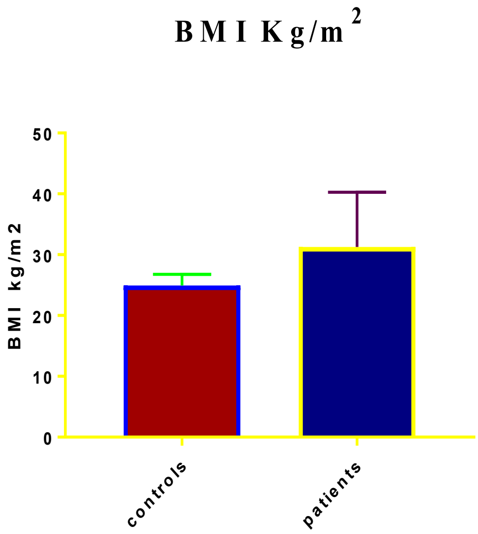


Fig. (2): Mean+ S.D for BMI in Control and Patients

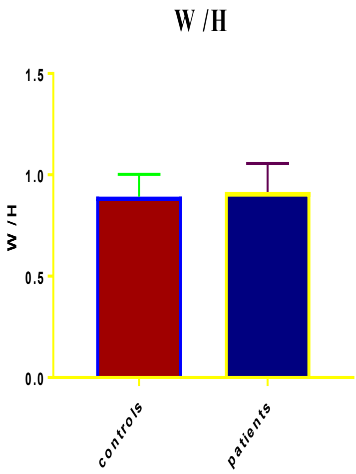


Fig. (3): Mean+ S.D for W/H in Control and Patients

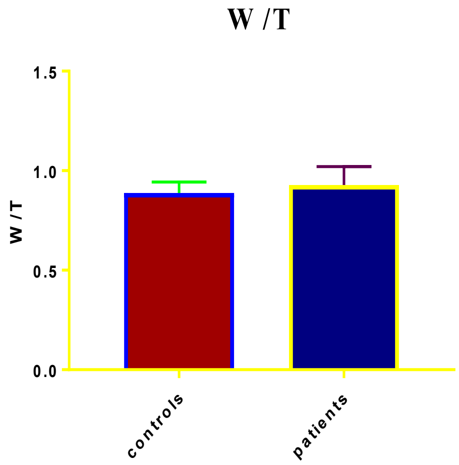


Fig. (4): Mean+ S.D for W/T in Control and Patients

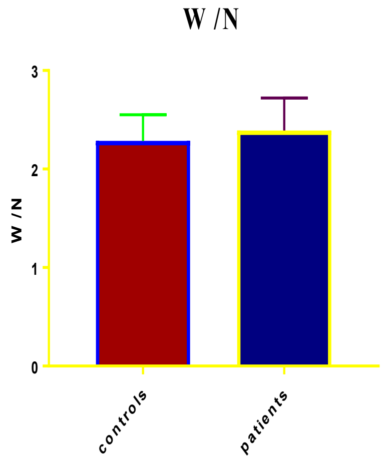


Fig. (5): Mean+ S.D for W/N in Control and Patients

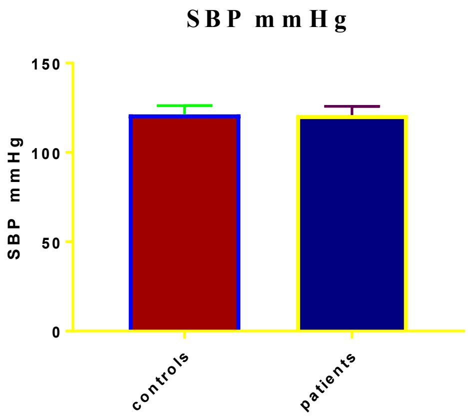


Fig. (6): Mean+ S.D for SBP in Control and Patients

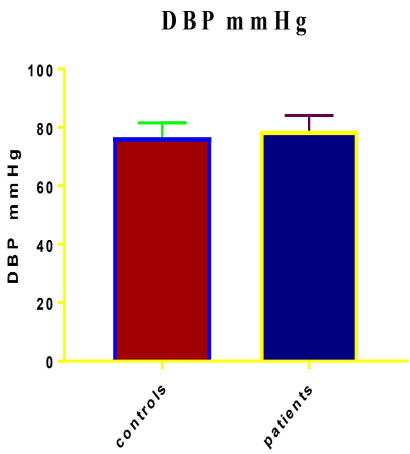


Fig. (7): Mean+ S.D for DBP in Control and Patients

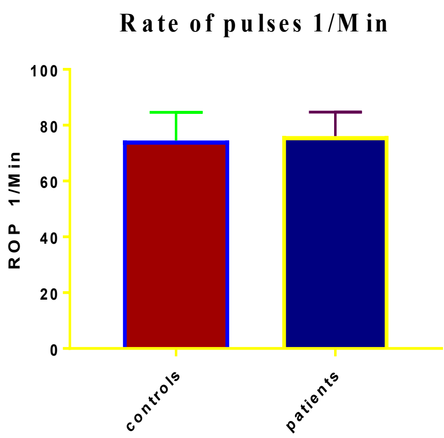


Fig. (8): Mean+ S.D for ROP in Control and Patients

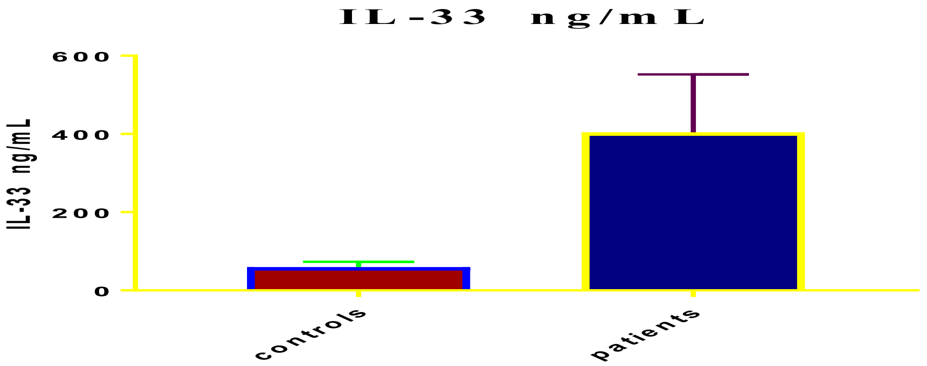


Fig. (9): Mean+ S.D for IL-33 in Control and Patients

This study was found a weak positive link of IL-33 serum levels with BMI (r = 0.254, P = 0.028) as shown in table (2) with figure (10), while other studied variables, did not show significant correlations with IL-33 which gave the following results DBP (r=0.182, P=0.119), W/N (r = 0.0170, P =0 .885), ROP (r = 0.103, P = 0.379), age (r = 0.048, P = 0.675), W/T (r = 0.017, P = 0.885) , SBP (r = -0.045, P = 0.704), W/H (r = -0.081, P = 0.492), respectively.

Table (2): Relationship of IL-33 with other Variables

IL-33 (ng/mL)	r	p-value
Age Years	0.048	0.675
BMI kg/m^2	0.254	0.028
W/H	-0.081	0.492
W/T	0.017	0.885
W/N	0.170	0.885
SBP mmHg	-0.045	0.704
DBP mmHg	0.182	0.119
ROP 1/Min	0.103	0.379

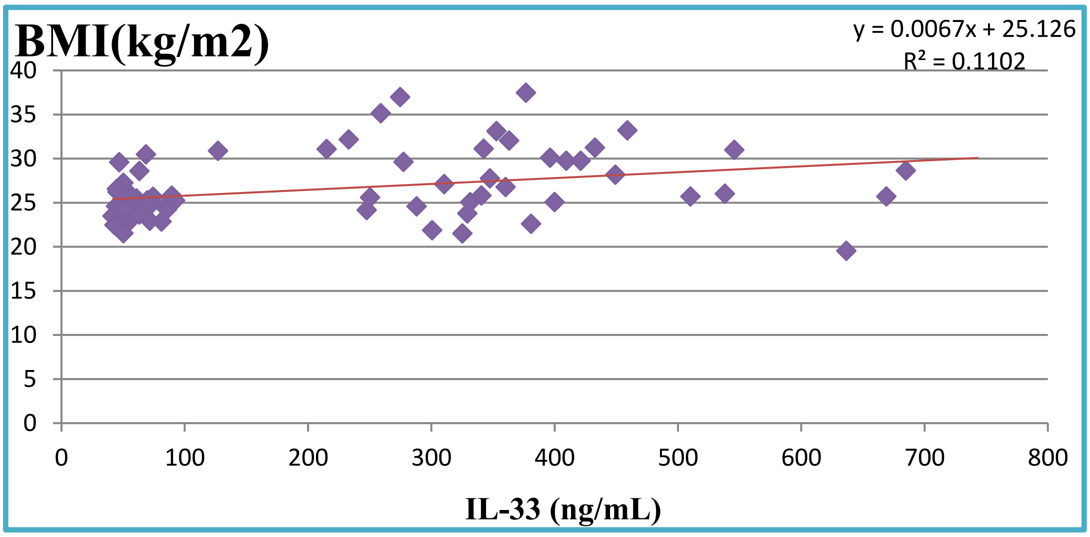


Figure (10): Correlation of IL-33 with BMI

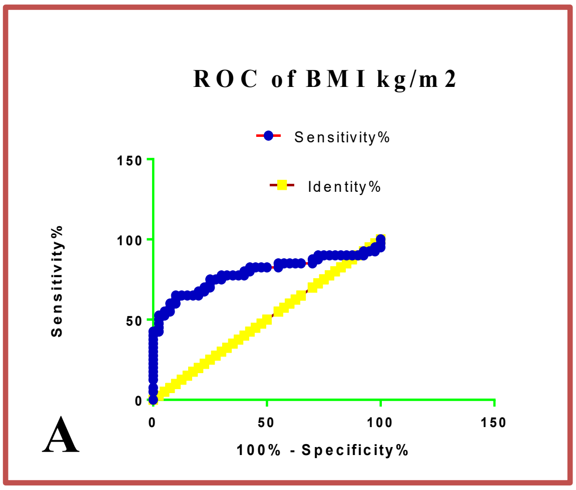
The ROC curve evaluation for the outcomes obtained from the experiments and assessments carried out within the scope of the current research was once carried out, and the details are provided in table (3) and fig.11. (A - H).

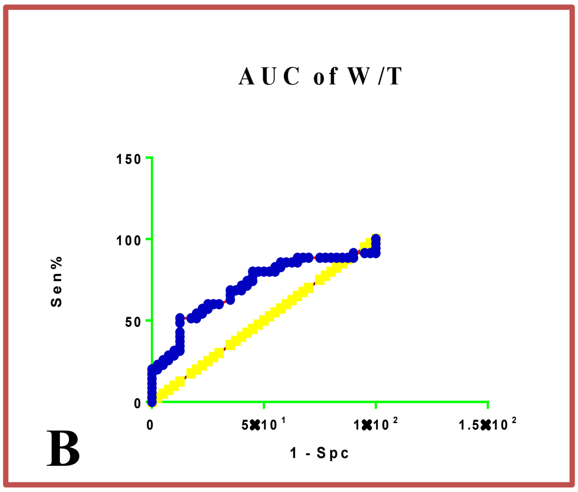
Table (3): Area under Curve for All Studied Biomarkers

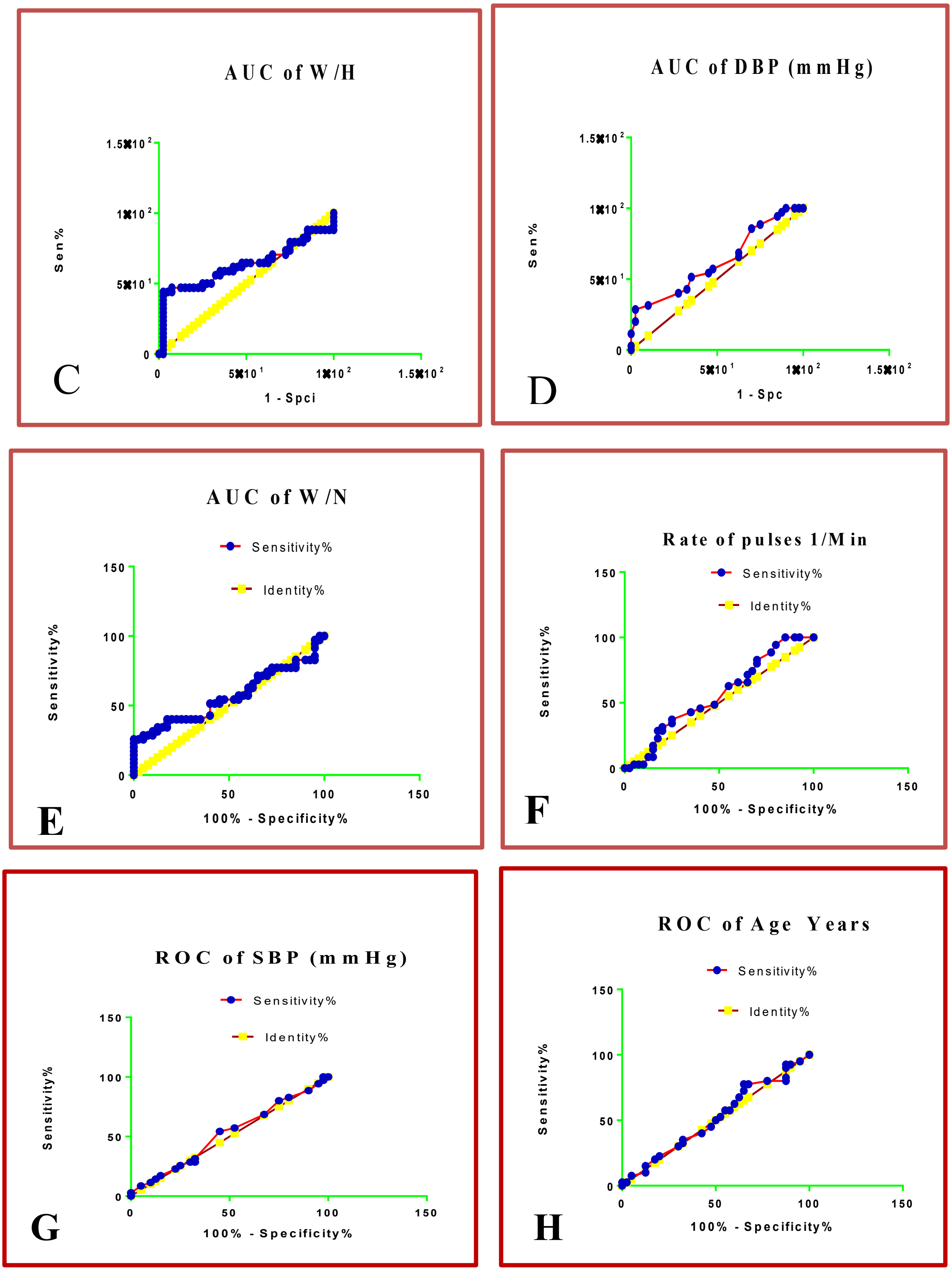
Biomarker	AUC	S. E	95% confidence interval	p-value
Age years	0. 5138	0. 0651	0. 3861 to 0. 6414	0. 8323
BMI kg/m2	0.7894	0.0541	0.6834 to 0.8954	0. 0001
W / H	0. 6294	0. 0700	0. 4922 to 0. 7666	0. 0563
W / T	0. 7079	0. 0620	0. 5863 to 0. 8295	0. 0020
W/N	0.5668	0.0692	0.4311 to 0.7024	0.3207
SBP (mmHg)	0.5232	0.0673	0.3913 to 0.6551	0.7300
DBP (mmHg)	0.6218	0.0652	0.494 to 0.7496	0.0702
POR (1/Min)	0.5614	0.0666	0.4309 to 0.6919	0.3611
IL-33 (ng/mL)	1	0	1 to 1	<0.0001

The results were showed following values of AUC [AUC value from (0.7-0.8) were evaluated and which represent the medium strength in diagnosing and detecting disease, this group includes BMI [AUC = 0.7894 ; P < 0.0001; 95 % CI: 0.6834 - 0.8954 with SE: 0.06511] (fig.11. A), W/T [AUC =0.7079; P 0.0020; 95% CI:0.5863 - 0.8295 with SE: 0.06204] (fig.11. B).

While group[AUC value from (0.5-0.7) showed low validity in predicting validity this group includes W/H, DBP, W/N, ROP, SBP, and age [AUC = 0.6294; P 0.0563; 95% CI:0.4922 - 0.7666 with SE: 0.07002] (fig.11. 3 C) [AUC = 0.6218; P= 0.0702; 95% CI: 0.494 - 0.7496 with SE: 0.06522] (fig.11. D), [AUC = 0.5668; P=3207 ; 95% CI: 0.4311 - 0.7024 with SE: 0.06921] (fig.11. E), [AUC =0.5614; P= 0.3611; 95% CI: 0.4309 - 0.6919 and SE: 0.06657] (fig.11. F), [AUC =0.5232; P= 0.7300; 95% CI: 0.3913 - 0.6551 with SE: 0.0673] (fig.11. G), [AUC =0.5138; P= 0.8323; 95% CI: 0.3861 - 0.6414 with SE: 0.06511] (fig.11. H), respectively. The best parameter which can use to discriminate CHB patients from HCs was IL-3 [AUC =1; <0.0001; 95% CI: 1 to 1with SE: 0] (fig.11. I).






AUC of W/H
Sen%
1 - Spci
C
AUC of DBP (mmHg)
Sen%
1 - Spc
D
AUC of W/N
Sensitivity%
Identity%
100% - Specificity%
E
Rate of pulses 1/Min
Sensitivity%
Identity%
100% - Specificity%
F
ROC of SBP (mmHg)
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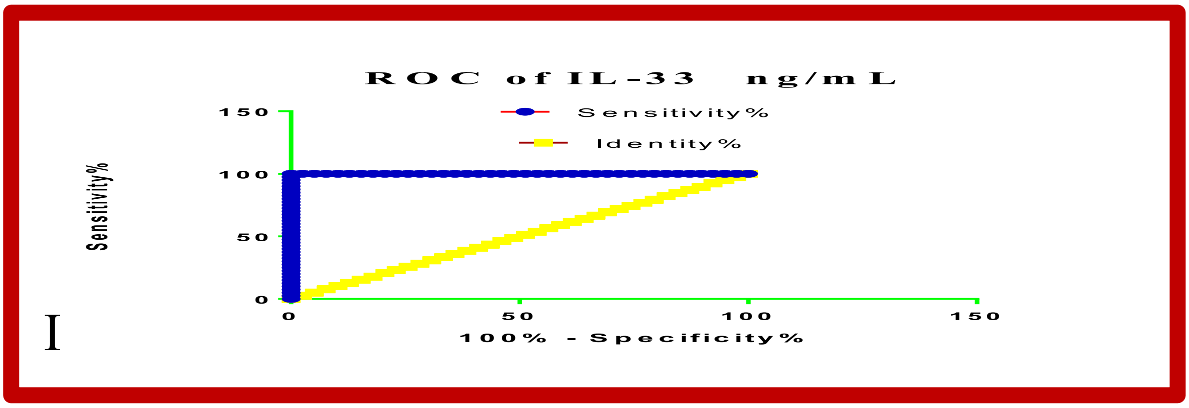

Figure 11 (A-I): The Receiver Operating Characteristic Curves Showing AUC between Sensitivity (Sen) and Specificity (Spc) for Studied Parameters.

The results of this study agreed with previous study by Huan S. L and others have studied the relevance of serum ST2 as well as IL33 levels in the natural progression for CHB disease, the results of this study showed varied over, in patients with CHB infection, these findings confirmed that IL-33 may exert an important functions [9]. Depending on disease, IL-33 has pro- and anti-inflammatory functions. IL-33 has been shown to be a pathogenic marker in chronic liver failure patients, CHB, HCV, liver cirrhosis. It has also been proposed that IL-33 be used as a pro-fibrotic factor in chronic liver disease because it is associated with liver fibrosis [13]. According to another study the IL-33 level in CHB patients was highly greater than in HCs, indicating that the role of the IL-33/ST2 axis has been studied during HBV and HCV infections in humans [14].

There is evidence that acute and massive liver damage occurs; the secretion of IL-33 by injured hepatocytes may serve as a defense mechanism, whereas IL-33 acts as a hepatic fibrosis-promoting factor in chronic injury [15]. Another study discovered that concentrations IL-33 were greater higher in patients with HBV than in healthy controls and highly decrease after treatment for 12 weeks, that means in CHB patients IL-33 may be a factor of pathogenic [16]. IL-33 stimulates both T helper cell 1 (Th1), T helper cell 2 (Th2) cytokines, but it suppresses TNF expression in the liver through direct effects and monocyte activation. Thus, in acute viral hepatitis, IL-33 functions as both an immune stimulator as well as a hepatoprotective cytokine, and It may also be a promising therapeutic candidate for the treatment of viral hepatitis [17]. Both men and women of all ages are susceptible to the Hepatitis B virus [18].

Body mass index (which measures overall obesity); and W/H measures abdominal obesity [19]. W/H was calculated as (waist circumference)/ (hip circumference) [20]. W/T maybe more related to musculature [21].

These findings are supported by a previous study published in 2019 by Fauziana, R. et al, which discovered increased BMI in CHB patients, and obesity (BMI 30 kg/m^2) has been linked to an increased risk of both HCC and mortality related to liver infection [22]. Obesity, due to increased body fat and leptin production, may impair an obese person's ability to mount an effective immune response to an HBV infection [23]. It is linked to dysregulation of adipokine, including increased production of leptin and lower levels of adiponectin, which play vital role to increased liver predispose to various pathological processes, including inflammation, and fibrosis, leptin and adiponectin secreted by white adipose tissue (WAT) [24]. Obese patients are more likely to develop serious CHB-related diseases, making them more vulnerable to HBV-related morbidity and mortality

[23]. The findings of this study corroborate previous findings that HBsAg positivity is not associated with high blood pressure [24].

The present data was the first which explore the link of IL-33 and increased the risk of CHB infection in Iraqi patients. IL-33 Serum concentration was not only screening biomarker of CHB but also may be vital predictors for diagnosis of Iraqi CHB patients.

In conclusion findings of this study support the hypothesis that high IL-33 levels may be contributing to rising incidence of CHB in Iraqi subjects, and may serve as a predictor of CHB diagnosis and progression in Iraqi patients.

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