**Evaluation of platelet indices in Egyptian cirrhotic patients**

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**Abstract**

**Background:**

Liver cirrhosis is an essential public health concern in Egypt. Platelet indices (PIs) are parameters routinely obtained as a part of a complete blood count. They are evolving as novel biomarkers of diagnostic and prognostic significance in hepatic disorders**. Aim:** A prospective study was planned to detect the diagnostic and prognostic potentials of Platelet indices (PIs) in cirrhotic individuals and hepatocellular carcinoma patients. **Materials and Methods:** 250 subjects participated in the study. Among them, 200 were diagnosed with liver cirrhosis and further classified into four groups: Groups I, II, and III: Each consists of 50 patients (Child-Pugh A, B, C) respectively, Group IV: 50 patients with hepatocellular carcinoma (HCC) and 50 healthy subjects as control Group V. Detection of PIs was done by Sysmex XT-1800i automated hematology analyzer.

**Results:** The mean platelet volume **(**MPV)value is positively correlated with INR and plasma bilirubin and negatively correlated with plasma albumin in all three groups of cirrhotic individuals without HCC.MPV showed a significant elevation in cases with more severe liver disease based on MELD and Child scores. MPV in HCC patients was positively related to tumor size, Child score, BCLC, and PV thrombosis but had no statistical significance. Plateletcrit (PCT) exhibited significant differences between different cirrhotic Child groups. Platelet distribution width (PDW) levels were significantly elevated in patients compared to healthy subjects, yet there was a non-significant difference in its value among patients.

**Conclusions:** Platelet indices might be utilized as progression and risk stratification markers in cirrhotic individuals.

***Keywords:*** *cirrhosis, mean platelet volume, platelet distribution width.*

**Introduction**

Liver cirrhosis is one of the significant causes of morbidity and death in Egypt, which has the most elevated prevalence of HCV infection worldwide.([1](#_ENREF_1), [2](#_ENREF_2))

Platelet indices refer to parameters routinely obtained as one of the automated blood count elements. They are potential markers describing platelet morphology, activation, and proliferation kinetics. Modern automated hematology analyzers can efficiently measure platelet indices (PIs). Platelet indices have been progressively evolving as novel biomarkers of diagnostic and prognostic significance in many acute and chronic disorders. ([3](#_ENREF_3), [4](#_ENREF_4))

Various studies addressed their clinical significance, involving patients with sepsis, thrombocytopenia, hepatic disorders, cardiovascular and surgical trauma, and malignancies. As noninvasive, cheap, and easily accessible laboratory tools, they have made them an attractive target for research on platelet kinetics over the past decade.([5](#_ENREF_5), [6](#_ENREF_6))

The most studied platelet (PLT) parameter is mean platelet volume (MPV). MPV describes the average size of PLTs in peripheral blood, which usually ranges from 7.2 to 11.7 fL.([7](#_ENREF_7))

Lots of factors, including race, age, physical activity, smoking, and alcohol intake, influence MPV. ([4](#_ENREF_4)). Higher MPV was associated with worse prognosis in pancreatic cancer and myocardial infarction,([8](#_ENREF_8), [9](#_ENREF_9)) Meanwhile, lower MPV values were correlated with adequate control of inflammation and disease activity in rheumatoid arthritis.([10](#_ENREF_10))

Platelet distribution width (PDW) refers to the size distribution of PLT synthesized by megakaryocytes, which rises upon activation of the PLT. It represents PLT anisocytosis.([11](#_ENREF_11)) Also, Plateletcrit (PCT) measures the total PLT mass as a proportion of the volume occupied in the bloodstream. In healthy individuals, PCT ranges from 0.22 to 0.24%. On the other hand, platelet large cell ratio (P-LCR) is the percentage of all PLTs that circulate in the blood. It usually ranges from 15-35%. A direct correlation between P-LCR, PDW, and MPV was reported. P-LCR was negatively correlated with PLT count in cases with thrombocytopenia.([12](#_ENREF_12)) P-LCR was found to be highly susceptible to changes in platelet size when compared to MPV.([13](#_ENREF_13))

A direct correlation between MPV and steatosis & hepatic fibrosis in HBV and HCV cases was reported.([14](#_ENREF_14))

Nevertheless, the potential role of these hematological indices needs to be further studied during hepatic fibrosis and cirrhosis. Thrombotic events, bone marrow activation, increased cellularity, and hypersplenism associated with the co-existing inflammation in the hepatic parenchymal tissue are essential players in the disturbance of platelet markers, which also need further investigation.

Therefore, we aimed to evaluate the diagnostic and prognostic potentials of PLT indices in cirrhotic individuals and compare them with some complications of hepatic cirrhosis, like HCC.

**Materials and Methods:**

The study was carried out on 250 subjects, of whom 200 cases were admitted to the Tropical Medicine Department, Faculty of Medicine, Alexandria University, with liver cirrhosis of various grades of severity and presentation. Patients were categorized into four groups: Group I: 50 patients with cirrhosis Child-Pugh A, Group II: 50 patients with cirrhosis Child-Pugh B, Group III: 50 cirrhotic patients Child-Pugh C, Group IV: 50 patients with hepatocellular carcinoma and 50 healthy subjects as controls.

Subjects with any of these criteria were ruled out: alcohol-related liver disease, receiving hepatotoxic medication, pregnant women, renal failure, vascular disease, treatment with any drug that may interact with platelets, presence of diseases that could affect Platelet counts like hematologic disorders, atherosclerotic diseases, and rheumatological diseases.

We had written informed consent from the participants, and the study procedures were by the 1975 Declaration of Helsinki. The study was approved by the authorization of the Medical Ethics Committee of Alexandria Faculty of Medicine (No:0306199).

Diagnosis of cirrhosis according to clinical and radiological findings of chronic liver disease (CLD). The cases were divided based on the Child-Pugh score as A, B, and C. All cases were assessed based on their age, gender, clinical findings, serum bilirubin, albumin, ALT, and AST, carried out using a chemistry analyzer (Beckmann CoulterAU480; Brea, California, USA), a model for end-stage liver disease (MELD), and Child scores.

Blood samples for PLT indices were placed into EDTAvacutainer tubes and analyzed within two hours of blood withdrawal. Platelet indices were assessed via an automated hematology analyzer (XT-1800i, Sysmex Corporation, Kobe, Japan).

**Statistical analysis of the data**

Data was fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. The chi-square test was applied to compare between two groups. Alternatively, the Fisher Exact correction test was used when more than 20% of the cells had an expected count of less than 5, and the Monte Carlo correction test was applied when more than 20% had an expected count of less than 5. For continuous data, they were tested for normality by the Kolmogorov- Smirnov test. Quantitative data were expressed as range (minimum and maximum), mean, standard deviation, and median. The ANOVA test was used to compare the different studied groups, followed by the Post Hoc test (Tukey) for pairwise comparison of normally distributed quantitative variables. In contrast, the Kruskal Wallis test was used to compare the different groups, followed by the Post Hoc test (Dunn's for multiple comparisons test) for pairwise comparison for non-normally Distributed Quantitative Variables. The significance of the obtained results was judged at the 5% level.

**Results:**

**Characteristics of the study population:**

A total of 250 individuals, including 200 cases with cirrhotic liver of various causes and severity and 50 healthy controls of matched age and sex, were recruited.

The studied population was divided into five groups, as represented **in Tab 1**

Regarding the cause of cirrhosis in the 200 patients, HCV antibodies were positive in 103 patients (51.5%), HBs Ag was positive in 19 (9.5%) cases, and ANA antibody was positive in 5 cases (2.5%) (Tab 2).

Tab 1. **Comparing the different studied groups based on the demographic data.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Demographic Data** | **Group 1**  **(n=50)** | **Group 2**  **(n=50)** | **Group 3**  **(n=50)** | **Group 4**  **(n=50)** | **Control**  **(n=50)** | **Test of sig.** | **p** |
| **Sex** |  |  |  |  |  |  |  |
| Male | 29 (58%) | 32 (64%) | 26 (52%) | 36 (72%) | 34 (68%) | =  5.411 | 0.248 |
| Female | 21 (42%) | 18 (36%) | 24 (48%) | 14 (28%) | 16 (32%) |
| **Age (years)** |  |  |  |  |  |  |  |
| Mean ± SD. | 58.76 ± 9.37 | 62.12 ± 8.7 | 61.8 ± 8.99 | 63.82 ± 7.73 | 61.36 ± 8.39 | F=  2.229 | 0.066 |
|  |  |  |  |  |  |

*SD:* ***Standard deviation,*** *χ2:* ***Chi-square test, F****:* ***F for One-way ANOVA test,*** *p: p-value for comparing* ***the different studied groups, Group 1****: Child A,* ***Group 2****: Child B,* ***Group 3****: Child C,* ***Group 4****: HCC.*

Tab 2.**Distribution of the various etiologies of liver cirrhosis in the patients’ groups**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Group 1** | | **Group 2** | | **Group 3** | | **Group 4** | | **Test of sig.** | | **p** | |
| **HCV Abs** | |  | |  | |  | |  | |  | |  | |
| Negative | | 26 (52%) | | 29 (58%) | | 24 (48%) | | 18 (36%) | |  | | 0.159 | |
| Positive | | 24 (48%) | | 21 (42%) | | 26 (52%) | | 32 (64%) | |
| **HBs Ag** | |  | |  | |  | |  | |  | |  | |
| Negative | | 45 (90%) | | 50 (100%) | | 44 (88%) | | 42 (84%) | |  | | MCp=0.020\* | |
| Positive | | 5 (10%) | | 0 (0%) | | 6 (12%) | | 8 (16%) | |
| **p1** | | **0.372** | | **FEp=0.006\*** | | **0.564** | |  | |  | |  | |
| **Sig. bet. grps** | | p2=0.056, p3=0.749, FEp4=0.027\* | | | | | |  | |  | |  | |
| **ANA** | |  | |  | |  | |  | |  | |  | |
| Negative | | 47 (94%) | | 50 (100%) | | 49 (98%) | | 49 (98%) | |  | | MCp=  0.404 | |
| Positive | | 3 (6%) | | 0 (0%) | | 1 (2%) | | 1 (2%) | |

*χ2:* ***Chi-square test,*** *MC:* ***Monte Carlo,*** *FE****: Fisher Exact. F****:* ***F for One-way ANOVA test and pairwise*** *comparison between each two groups were done using a* ***Post Hoc Test (Tukey).*** *H: A pairwise comparison was done using a Post Hoc Test (Dunn's for multiple comparisons test) for the Kruskal Wallis test****.*** *p: p-value for comparing* ***the four studied groups.*** *p1: p-value for comparing* ***Group 4*** *and* ***each other group.*** *p2: p-value for comparing Group 1 and Group 2. p3: p-value for comparing Group 1 and Group 3. p4: p-value for comparing* ***Group 2*** *and* ***Group 3.*** *\*: Statistically significant at p ≤ 0.05.* ***Group 1****: Child A,* ***Group 2****: Child B,* ***Group 3****: Child C,* ***Group 4****: HCC.*

**Clinical characteristics:**

Tab 3 illustrates the clinical criteria of the four studied patient groups regarding the prevalence of ascites, hepatic encephalopathy, and splenic size.

A statistically significant difference was found between the four studied groups of patients regarding ascites and hepatic encephalopathy, with the highest prevalence in group 3 for both. Similarly, statistically significant differences were observed regarding splenic span between groups one and the other groups, while no difference was between groups 2, 3, and 4.

MELD score was calculated for the four patient groups, and it was significantly higher with the progression of cirrhosis represented by the Child score. MELD exhibited significant differences between HCC cases in group 4 and cirrhotic patients in the 1st and 3rd groups, yet no significant differences were determined between the 4th and 2nd groups.

Tab 3. **Comparing the four studied groups based on the clinical findings.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **Group 1**  **(n=50)** | | **Group 2**  **(n=50)** | | **Group 3**  **(n=50)** | | **Group 4**  **(n=50)** | | **Test of sig.** | | **p** | |
| **Ascites** | |  | |  | |  | |  | |  | |  | |
| No ascites | | 42 (84%) | | 11 (22%) | | 0 (0%) | | 15 (30%) | |    | | <0.001\* | |
| Mild | | 7 (14%) | | 17 (34%) | | 16 (32%) | | 15 (30%) | |
| Moderate | | 1 (2%) | | 14 (28%) | | 25 (50%) | | 11 (22%) | |
| Severe | | 0 (0%) | | 8 (16%) | | 9 (18%) | | 9 (18%) | |
| **p1** | | **MCp1<0.001\*** | | **0.763** | | **<0.001\*** | |  | |  | |  | |
| **Sig. bet. grps** | | MCp2<0.001\*, MCp3<0.001\*, p4=0.003\* | | | | | |  | |  | |  | |
| **Hepatic encephalopathy** | |  | |  | |  | |  | |  | |  | |
| No | | 47 (94%) | | 38 (76%) | | 13 (26%) | | 29 (58%) | |    | | <0.001\* | |
| Grade 1–2 | | 3 (6%) | | 12 (24%) | | 19 (38%) | | 15 (30%) | |
| Grade 3–4 | | 0 (0%) | | 0 (0%) | | 18 (36%) | | 6 (12%) | |
| **p1** | | **MCp1<0.001\*** | | **MCp1=0.025\*** | | **0.002\*** | |  | |  | |  | |
| **Sig. bet. grps** | | p2=0.012\*, p3<0.001\*, p4<0.001\* | | | | | |  | |  | |  | |
|  | |  | |  | |  | |  | |  | |  | |
| **Splenectomy** | **3 (6%)** | | **6 (12%)** | | **8 (16%)** | | **7 (14%)** | |  | | 0.458 | |
| **Size (cm)** | **(n=47)** | | **(n=44)** | | **(n=42)** | | **(n=43)** | |  | |  | |
| Mean ± SD. | 14.94 ± 1.89 | | 16.59 ± 2.36 | | 16.8 ± 2.07 | | 16.93 ± 2.41 | | F   | | <0.001\* | |
|  |  | |  | |  | |  | |
| **p1** | **<0.001\*** | | **0.886** | | **0.993** | |  | |  | |  | |
| **Sig. bet. grps** | p2=0.002\*, p3<0.001\*, p4=0.970 | | | | | |  | |  | |  | |
|  | |  | |  | |  | |  | |  | |  | |
| **MELD score** | **(n=50)** | | **(n=50)** | | **(n=50)** | | **(n=50)** | |  | |  | |
| Mean ± SD. | 9.46 ± 2.96 | | 17.02 ± 5.3 | | 23.22 ± 4.9 | | 17.43 ± 8.26 | |    | | <0.001\* | |
| Median  (Min. – Max.) | 8  (6 – 19) | | 16  (9 – 31) | | 23  (14 – 39) | | 16  (6 – 39) | |
| **p1** | **<0.001\*** | | **0.725** | | **<0.001\*** | |  | |  | |  | |
| **Sig. bet. grps** | p2<0.001\*, p3<0.001\*, p4<0.001\* | | | | | |  | |  | |  | |
|  | |  | |  | |  | |  | |  | |  | |

*χ2:* ***Chi-square test,*** *MC:* ***Monte Carlo,*** *FE****: Fisher Exact, F****:* ***F for One-way ANOVA test and pairwise*** *comparison between each two groups were done using a* ***Post Hoc Test (Tukey),*** *H: H for* ***Kruskal Wallis test,*** *pairwise comparison between each two groups was done using a* ***Post Hoc Test (Dunn's for multiple comparisons test),*** *p: p-value to compare* ***the different groups.*** *p0: p-value to compare the control group and each other's* ***group.*** *p1: p-value to compare between the 4th Group* ***and each other group.*** *p2: p value to compare between* ***1st*** *& 2nd* ***Groups.*** *p3: p value to compare between* ***1st &3rd Groups.*** *p4: p value to compare between* ***2nd and 3rd Groups.*** *\*: Statistically significant at p ≤ 0.05.* ***Group I****: Child A,* ***Group II****: Child B,* ***Group III****: Child C,* ***Group IV****: HCC*

Tab 4. **Comparison between the different studied groups based on PLT count and indices.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Group 1**  **(n=50)** | **Group 2**  **(n=50)** | **Group 3**  **(n=50)** | **Group 4**  **(n=50)** | **Control**  **(n=50)** | **Test of sig.** | **p** |
| **PLT (×109/L)** |  |  |  |  |  |  |  |
| Mean ± SD. | 153.6 ±78.13 | 132.8 ± 80.2 | 99.22 ±45.32 | 133.12 ±63.6 | 295.7 ± 53.8 | H=111.728\* | <0.001\* |
| Median  (Min. – Max.) | 138(47 – 439) | 105.5(34 – 336) | 90(47 – 229) | 116 (48 – 292) | 297(177 – 399) |
| **p0** | **<0.001\*** | **<0.001\*** | **<0.001\*** | **<0.001\*** |  |  |  |
| **p1** | **0.296** | **0.608** | **0.014\*** |  |  |  |  |
| **Sig. bet. grps** | p2=0.119, p3<0.001\*, p4=0.052 | | |  |  |  |  |
| **PDWa (fL)** |  |  |  |  |  |  |  |
| Mean ± SD. | 14.52 ± 2.86 | 15.50 ± 3.24 | 15.40 ± 1.71 | 13.69±2.26 | 12.34 ± 0.82 | F=15.807\* | <0.001\* |
| Median (Min. – Max.) | 13.8(9.9 – 20.2) | 15(8.1 – 25) | 15.6(11.8 – 18.5) | 13.3  (10.2 – 19.7) | 12.5(10.7 – 13.9) |
| **p0** | **<0.001\*** | **<0.001\*** | **<0.001\*** | **0.033\*** |  |  |  |
| **p1** | **0.394** | **0.001\*** | **0.003\*** |  |  |  |  |
| **Sig. bet. grps** | p2=0.224, p3=0.331, p4=0.999 | | |  |  |  |  |
| **PCT (%)** |  |  |  |  |  |  |  |
| Mean ± SD. | 0.20 ± 0.16 | 0.19 ± 0.16 | 0.11 ± 0.07 | 0.14 ± 0.08 | 0.26 ± 0.05 | H=66.821\* | <0.001\* |
| Median (Min. – Max.) | 0.17 | 0.16 | 0.08 | 0.11 | 0.27 |
| **p0** | **<0.001\*** | **<0.001\*** | **<0.001\*** | **<0.001\*** |  |  |  |
| **p1** | **0.047\*** | **0.047\*** | **0.164** |  |  |  |  |
| **Sig. bet. grps** | p2=0.988, p3=0.001\*, p4=0.001\* | | |  |  |  |  |
| **P-LCR (%)** |  |  |  |  |  |  |  |
| Mean ± SD. | 28.85±10.82 | 33.18±12.25 | 36.36 ± 3.71 | 36.90 ±7.04 | 25.29 ± 3.48 | H=65.618\* | <0.001\* |
| Median (Min. – Max.) | 26.5(12.8 – 56) | 36 (16.7 – 55.2) | 36 (31 – 48.4) | 38(18.9 – 51) | 25.7 (17.5 – 31.2) |
| **p0** | **0.045\*** | **<0.001\*** | **<0.001\*** | **<0.001\*** |  |  |  |
| **p1** | **<0.001\*** | **0.015\*** | **0.540** |  |  |  |  |
| **Sig. bet. grps** | p2=0.018\*, p3<0.001\*, p4=0.068 | | |  |  |  |  |
| **MPV (fL)** |  |  |  |  |  |  |  |
| Mean ± SD. | 8.91 ± 1.04 | 10.27 ± 1.39 | 12.01 ± 0.98 | 10.29 ± 1.46 | 8.77 ± 0.74 | 64.790\* | <0.001\* |
| Median (Min. – Max.) | 9 (7.1–11.6) | 10.25 (7.3 – 13) | 12.03 (10.1 – 13.8) | 10.2(8.2 – 13.1) | 8.7(7.7 – 10.2) |
| **p0** | **0.978** | **<0.001\*** | **<0.001\*** | **<0.001\*** |  |  |  |
| **p1** | **<0.001\*** | **1.000** | **<0.001\*** |  |  |  |  |
| **Sig. bet. grps** | p2<0.001\*, p3<0.001\*, p4<0.001\* | | |  |  |  |  |

*SD:* ***Standard deviation. F****:* ***F for One-way ANOVA test, and pairwise comparison between each two groups was done using a Post Hoc Test (Tukey). H: H for Kruskal Wallis test, pairwise comparison bet. Every*** *two groups were done using a* ***Post Hoc Test (Dunn's for multiple comparisons test).*** *p: p-value for comparing* ***the different groups.*** *p0: p value* *to compare the control group and each other's* ***group.*** *p1: p-value to compare between the 4th* ***Group*** *and* ***each other group.*** *p2: p value to compare between 1st& 2nd* ***Groups.*** *p3: p value to compare between 1st &3rd* ***Groups.*** *p4: p value to compare between 2nd &3rd* ***Groups.*** *\*: Statistically significant at p ≤ 0.05*

***Group I****: Child A,* ***Group II****: Child B,* ***Group III****: Child C,* ***Group IV****: HCC*

Figure (1): Comparison between the different groups based on MPV.

Fig 1. **Comparison between the different groups based on MPV.**

The PLT count showed a significant reduction in Child C cases in Group 1 and Group 4, while there was a non-significant difference among other patients’ groups.

Comparison of mean platelet indices across the four studied patient groups with the controls exhibited statistically significant differences (p<0.001).

The MPV value showed significant elevation in cases suffering severe liver disease p 2, p3, p4 (p<0.001). A statistically significant difference was found between the HCC and 1st & 3rd groups. (figure 1)

A non-significant difference was concluded among different Child groups A, B, and C regarding PDWa (p2=0.224), (p3=0.331), and (p4=0.999), respectively, but a statistically significant difference was found between group 4 and the Child B and C groups.

Regarding PCT, statistically significant differences were observed between the Child A & C groups (p=0.001) and the Child B & C groups (p=0.001). P-LCR showed substantial differences in the Child A & B (p=0.018) and Child A & C (p0.001) groups. Also, both showed significant differences between the Child A & B groups and the HCCgroup.

Tab 5. **Comparison between the different groups according to liver profile.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **liver profile** | **Group 1**  **(n=50)** | **Group 2**  **(n=50)** | **Group 3**  **(n=50)** | **Group 4**  **(n=50)** | **Control**  **(n=50)** | **Test of sig.** | **p** | |
| **ALT (IU/L)** |  |  |  |  |  |  |  | |
| Mean ± SD. | 32.62 ± 25.03 | 38.86 ± 31.89 | 39.36 ± 25.91 | 40.84 ± 31.88 | 32.14 ± 4.97 | H=4.410 | 0.3536 | |
| Median (Min. – Max.) | 29.5(10 – 184) | 31(10 – 184) | 33(13 – 170) | 32(11 – 171) | 32.50(20 – 40) |
| **AST (IU/L)** |  |  |  |  |  |  |  | |
| Mean ± SD. | 38.56 ± 13.84 | 53.56 ± 34.61 | 60.07±36.09 | 76.06±52.88 | 37.20 ± 3.97 | H=61.512\* | <0.001\* | |
| Median (Min. – Max.) | 37(14 – 80) | 44(14 – 221) | 51(18 – 233) | 63.5(22.5 – 281) | 38(25 – 45) |
| **p0** | **0.579** | **0.001\*** | **<0.001\*** | **<0.001\*** |  |  |  | |
| **p1** | **<0.001\*** | **0.001\*** | **0.047\*** |  |  |  |  | |
| **Sig. bet. grps** | p2=0.006\*, p3<0.001\*, p4=0.186 | | |  |  |  |  | |
| **S.albumin (g/dL)** |  |  |  |  |  |  |  | |
| Mean ± SD. | 3.89 ± 0.37 | 2.94 ± 0.43 | 2.50 ± 0.32 | 3.06 ± 0.67 | 4.38 ± 0.46 | F=134.446 | <0.001\* | |
| Median (Min. – Max.) | 3.90(2.9 – 4.9) | 3 (2 – 4) | 2.50(1.7 – 3.4) | 3.05(1.1 – 4.2) | 4.3(3.5 – 5.2) |
| **p0** | **<0.001\*** | **<0.001\*** | **<0.001\*** | **<0.001\*** |  |  |  | |
| **p1** | **<0.001\*** | **0.719** | **<0.001\*** |  |  |  |  | |
| **Sig. bet. grps** | p2<0.001\*, p3<0.001\*, p4<0.001\* | | |  |  |  |  | |
| **Bilirubin (mg/dL)** |  |  |  |  |  |  |  | |
| Mean ± SD. | 1.05 ± 0.54 | 1.82 ± 1.36 | 3.75 ± 2.42 | 2.92 ± 2.98 | 0.69 ± 0.17 | H=123.876\* | <0.001\* | |
| Median (Min. – Max.) | 0.9(0.20 – 2.6) | 1.5(0.3 – 6.8) | 3.15(0.60–12.50) | 2.15(0.50 – 17.9) | 0.7(0.30 – 1) |
| **p0** | **0.011\*** | **<0.001\*** | **<0.001\*** | **<0.001\*** |  |  |  | |
| **p1** | **<0.001\*** | **0.048\*** | **0.012\*** |  |  |  |  | |
| **Sig. bet. grps** | p2=0.003\*, p3<0.001\*, p4<0.001\* | | |  |  |  |  | |
| **PT (second)** |  |  |  |  |  |  | |  | |
| Mean ± SD. | 13.65 ± 1.48 | 16.14 ± 2.52 | 18.7 ± 3.25 | 17.21 ± 4.57 | 12.29 ± 0.64 | 147.204\* | | <0.001\* | |
| Median (Min. – Max.) | 13.4(11.4 – 17.2) | 15.6(10.3 – 25.1) | 17.5(15 – 28.8) | 16.15(12 – 32) | 12.3(11.1 – 13.4) |
| **p0** | **0.002\*** | **<0.001\*** | **<0.001\*** | **<0.001\*** |  |  | |  | |
| **p1** | **<0.001\*** | **0.552** | **0.009\*** |  |  |  | |  | |
| **Sig. bet. grps** | p2<0.001\*, p3<0.001\*, p4=0.001\* | | |  |  |  | |  | |
| **INR** |  |  |  |  |  |  | |  | |
| Mean ± SD. | 1.17 ± 0.18 | 1.44 ± 0.22 | 1.92 ± 0.38 | 1.67 ± 0.56 | 1.1 ± 0.07 | 142.711\* | | <0.001\* | |
| Median (Min. – Max.) | 1.12(0.9 – 1.6) | 1.4(1 – 2.04) | 1.9(1.27 – 2.7) | 1.5(1 – 3) | 1.10(1 – 1.23) |
| **p0** | **0.155** | **<0.001\*** | **<0.001\*** | **<0.001\*** |  |  | |  | |
| **p1** | **<0.001\*** | **0.385** | **0.002\*** |  |  |  | |  | |
| **Sig. bet. grps** | p2<0.001\*, p3<0.001\*, p4<0.001\* | | |  |  |  | |  | |

*SD:* ***Standard deviation, F****:* ***F for One-way ANOVA test and pairwise*** *comparison between each two groups were done using a* ***Post Hoc Test (Tukey),*** *H: H for* ***Kruskal Wallis test,*** *pairwise comparison between each two groups was done using a* ***Post Hoc Test (Dunn's for multiple comparisons test),*** *p: p-value to compare* ***the different studied groups.*** *p0: p value to compare the control group and each other's* ***group.*** *p1: p-value to compare between the 4th Group* ***and each other group.*** *p2: p value to compare between* ***1st*** *& 2nd* ***Groups.*** *p3: p value to compare between* ***1st &3rd Groups.*** *p4: p value to compare between* ***2nd and 3rd Groups.***  *Statistically significant at p ≤ 0.05.*

***Group I****: Child A,* ***Group II****: Child B,* ***Group III****: Child C,* ***Group IV****: HCC*

Tab 6. **Correlation between MPV and different parameters in each group**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **MPV** | | | | | | | | | |
|  | **Group 1**  **(n=50)** | | **Group 2**  **(n=50)** | | **Group 3**  **(n=50)** | | **Group 4**  **(n=50)** | | **Control**  **(n=50)** | |
|  | **r** | **p** | **r** | **p** | **r** | **p** | **r** | **p** | **r** | **p** |
| **S.albumin** | -0.862\* | <0.001\* | -0.944\* | <0.001\* | -0.970\* | <0.001\* | -0.332\* | 0.019\* | -0.172 | 0.232 |
| **S.bilirubin** | 0.963\* | <0.001\* | 0.840\* | <0.001\* | 0.879\* | <0.001\* | -0.095 | 0.512 | 0.003 | 0.983 |
| **PT** | 0.378\* | 0.007\* | 0.036 | 0.803 | -0.242 | 0.091 | 0.036 | 0.802 | -0.146 | 0.311 |
| **INR** | 0.815\* | <0.001\* | 0.781\* | <0.001\* | 0.945\* | <0.001\* | 0.353\* | 0.012\* | -0.119 | 0.412 |
| **MELD score** | 0.930\* | <0.001\* | 0.965\* | <0.001\* | 0.751\* | <0.001\* | -0.026 | 0.858 | – | – |
| **Child score** | 0.351\* | 0.012\* | 0.831\* | <0.001\* | 0.877\* | <0.001\* | – | – | – | – |

***r: Pearson coefficient,*** *\*: Statistically significant at p ≤ 0.05*

Mean platelet volume value is positively correlated with INR and plasma bilirubin and negatively correlated with plasma albumin in all three groups of cirrhotic individuals without HCC, with statistical significance. Additionally, it reveals that MPV value showed a significant elevation in cases with more severe liver disease based on MELD and Child scores. In group 4, the only statistically significant correlation was between MPV values, serum albumin, and INR, with negative and positive correlations, respectively.

Tab 7.**Relationship between MPV and different parameters in group 4 (HCC) (n=50)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **N** | **MPV** | | **Test of sig.** | **p** |
| **Mean ± SD.** | **Median**  **(Min. – Max.)** |
| **Child score** |  |  |  |  |  |
| A | **15** | 9.95 ± 1.35 | 9.8 (8.2 – 13.1) | F=2.477 | 0.095 |
| B | **16** | 9.94 ± 1.11 | 10 (8.3 – 11.9) |
| C | **19** | 10.86 ± 1.67 | 11.2 (8.2 – 13.1) |
| **BCLC** |  |  |  |  |  |
| A | **9** | 9.49 ± 0.93 | 9.3 (8.2 – 11.2) | F=2.440 | 0.076 |
| B | **13** | 10.24 ± 1.39 | 10.6 (8.3 – 13.10) |
| C | **8** | 9.84 ± 1.16 | 9.55 (8.4 – 11.9) |
| D | **20** | 10.88 ± 1.62 | 11.15 (8.2 – 13.1) |
| **PV Thrombosis** |  |  |  |  |  |
| No PVT | **30** | 10.37 ± 1.52 | 10.25 (8.2 – 13.1) | t=0.428 | 0.670 |
| PVT | **20** | 10.19 ± 1.40 | 10.2 (8.4 – 12.2) |

F: F for One-way ANOVA test, t: Student t-test. p: p-value is used to compare the studied different categories.

Figure (2): Correlation between MPV and tumor size (cm) in group 4 (HCC)

Fig 2. **Correlation between MPV and tumor size (cm) in group 4 (HCC).**

Regarding tumor characteristics in HCC patients, MPV was positively related to the tumor size (p=0.062), Child score, BCLC, and the presence of PV thrombosis, but these relations were not statistically significant, as shown in (Tab 7) & fig 2.

**Discussion**

Platelet count is a well-known, easy, direct marker of CLD. It is included in many scoring systems, mainly APRI and FIB-4, and is used to predict the extent of hepatic fibrosis in a non-invasive manner. Recently, a decreased PLT count has been suggested to detect the development of HCC, which is accompanied by poor prognosis in patients with CLD.

A higher rate of platelet breakdown due to hypersplenism, in conjunction with increased release of the inflammatory cytokine IL-6, shortens the PLT life span. Consequently, the BM synthesis of PLTs increases with the production of more giant, reticulated platelets that appear in peripheral blood. Such events result in disturbances in platelet indices with increased MPV, PCT, P-LCR, and PDW.([15](#_ENREF_15))

Recently, several studies suggested that PLT indices are crucial markers in assessing liver cirrhosis and hepatic decompensation.([16](#_ENREF_16))

However, physicians still underestimate platelet indices, and data correlating MPV and P-LCR, the main platelet parameters associated with liver cirrhosis and portal hypertension in cirrhotic individuals and HCC, are still limited.

Our study concluded a significant reduction in PLT counts in cirrhotic cases compared to controls, which aligns with previous literature. There is a vital difference also between the early cirrhotic stage and the HCC group, with a higher level in Child A patients.

Our results confirmed previous observations in the literature, which demonstrated a more significant increase in PLT indices in cirrhotic patients than in the average population.([17](#_ENREF_17), [18](#_ENREF_18))

In the current study, among the three groups of cirrhotic patients without HCC, cases suffering advanced hepatic fibrosis showed a significantly reduced PLT count, a significant elevation in MPV, and a lower P-LCR value than cases suffering mild fibrosis.

MPV values significantly increased with cirrhosis progression, which was in concordance with previous studies that reported severe elevation in MPV accompanied by more advanced hepatic fibrosis. ([19](#_ENREF_19)) Recently, Shao et al. exhibited a significant correlation between platelet and PLT indices (including MPV, P-LCR, and PDW) and direct markers of HCV-induced hepatic cirrhosis and reported their ability to correlate with fibrosis progression and differentiation between mild and severe fibrosis. Investigators used Fibroscan to confirm these results. ([20](#_ENREF_20))

In the study by Kurt M et al., MPV level in cases suffering HCC was significantly high in comparison with cases suffering chronic hepatitis or control individuals, and it was suggested to be used as one of the HCC diagnosis markers in cases suffering CLD.([21](#_ENREF_21)) Our study found a statistically significant difference between the HCC group and Child A & C patients. In contrast, no significant difference was demonstrated between the HCC and Child B cases. This may explain the similar MELD scores in both groups and the MPV relation to hepatic fibrosis. MPV was positively related to tumor size, Child score, and BCLC, but these relations were not statistically significant. This previous finding suggests that MPV might be helpful as one of the prognostic markers more than a diagnostic marker in HCC patients, as previously indicated by Scheiner B et al.([22](#_ENREF_22))

PCT and PDW are simple PIs that are elevated during PLT activation. An elevated level of PDW and PCT is associated with advanced hepatic cirrhosis.([23](#_ENREF_23), [24](#_ENREF_24))Furthermore, PCT was reported to be one of the good prognostic markers in the early determination of NAFLD.([16](#_ENREF_16))

In our study, PCT showed a significant difference between Child A & B cases and Child C cases. A recent large multi-center cohort study by Xu W et al.([25](#_ENREF_25)) demonstrated PCT as an independent preoperative marker of fibrosis staging in cirrhotic patients with HCC. It did not reveal a significant correlation with the presence of HCC itself, which explains our results. There was a substantial difference between the HCC group and Child A and B patients. In contrast, a non-significant difference was demonstrated between the HCC group (where nearly 40% of cases are Child C) and the Child C cirrhotic patients’ group.

Nevertheless, although PDW levels in this study were significantly higher in patients than in control subjects, there were no significant differences in their value among patients compared to the previous survey of Shao L et al.([20](#_ENREF_20)) It was not significantly accompanied by the degree of hepatic decompensation. This agrees with other studies of PDW as a marker of fibrosis in NAFLD patients that suggested using PDW as a marker of fibrosis exacerbation only if it is performed on the patient regularly with each follow-up visit rather than performed once only. A gradual increase in its value on follow-up denotes the progression of fibrosis.([26](#_ENREF_26))

Our results supported previous observations by Michalak A. et al.([15](#_ENREF_15)) and Mohamed MS et al.([27](#_ENREF_27)), who suggested that MPV correlated positively with MELD score, in contrast to the older study by Giannini, E.G. et al.([28](#_ENREF_28)) As the MELD score is the commonest utilized score to detect organ allocation in liver transplants and predict survival in cases (aged 12+) with hepatic cirrhosis,([27](#_ENREF_27))This suggests the valuable utilization of MPV as a prognostic marker in cirrhotic individuals with various etiologies. Han L et al. previously suggested this finding in ACLF in HBV patients. ([29](#_ENREF_29))

Our study showed that MPV is significantly positively correlated with the extent of liver decompensation in cirrhotic cases without HCC, with a higher MPV value and an increased Child-Pugh score. This finding supports the potential function of MPV as a helpful indicator of the extent of fibrosis and systemic inflammation in those cases.

Upon assessing the correlation between various decompensation criteria and MPV value, we found that MPV value positively correlates with elevated plasma bilirubin, increased INR, and decreased plasma albumin. This is in concordance with other studies that concluded that increased MPV represents an independent predictor of the extent of hepatic cirrhosis in cases suffering chronic hepatitis.

In the HCC group, MPV showed a positive correlation with MELD score and other features of hepatic decompensation but only significantly correlated with high INR and low serum albumin, which may be due to a small and heterogeneous sample in this group.

Additionally, MPV was positively related to tumor size, Child score, BCLC, and PV thrombosis, but there were no statistically significant correlations, which was attributed to the small sample size. The correlation between MPV value and HCC patients’ characteristics has not been established yet. Shabana H et al. (30) showed that MPV was not significantly related to BCLC staging, CTP scoring, or MELD scoring in HCC patients. Changes in MPV value in the HCC group were attributed to platelet activation by the tumor itself. On the other hand, in another study by Scheiner B et al. ([22](#_ENREF_22))Higher MPV was associated with better OA survival. Therefore, the correlation between MPV and tumor characteristics and patient prognosis needs to be confirmed on larger samples to assess MPV's exact function as a prognostic marker of HCC.

However, it is worth mentioning that there are lots of factors, including physiological differences, co-morbidities, lifestyle, and drugs used, which may affect MPV levels. ([31](#_ENREF_31))A stricter prospective trial is suggested to confirm the results before clinically using this marker.

**Conclusion**

Our findings indicate that the PLT count, MPV, P-LCR, and PDW might serve as vital progression markers in cirrhotic individuals with a high risk of disease progression. MPV could be used as a prognostic marker in HCC.

MPV correlation with tumor characteristics and patient prognosis needs to be confirmed on a larger sample to assess the exact role of MPV as an HCC prognostic marker.

**Abbreviations**

|  |  |
| --- | --- |
| **PLT** | Platelet |
| **CLD** | Chronic Liver Disease |
| **HCC** | Hepatocellular carcinoma |
| **MPV** | Mean Platelet Volume |
| **MELD** | Model for end-stage liver disease |
| **PIs** | Platelet Indices |
| **BCLC** | Barcelona Clinic Liver Cancer |
| **PV** | Portal Vein |
| **PCT** | Plateletcrit |
| **PDW** | Platelet distribution width |
| **HCV** | Hepatitis C virus |
| **P-LCR** | Platelet large cell ratio |
| **HBV** | Hepatitis B virus |
| **AST** | Aspartate aminotransferase |
| **ALT** | Alanine aminotransferase |
| **PT** | Prothrombin Time |
| **APRI** | AST to Platelet Ratio Index |
| **IL-6** | Interleukin 6 |
| **BM** | Bone marrow |
| **NAFLD** | Non-Alcoholic Fatty Liver Disease |
| **CTP** | Child Turcotte Pugh |
| **OA** | Overall |

**Footnotes.**

Bassam Mansour Salama (Assistant professor of tropical medicine), Amany Mohammed (Assistant professor of community medicine, biostatistician), and Mohamed Hassan Ali Emara (professor of gastroenterology, hepatology, and infectious diseases) were the peer reviewers.

**E- Editor:** Salem Youssef Mohamed, Osama Ahmed Khalil, Amany Mohammed.

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**Authors’ contributions**

Asmaa M. Gouda and Mohamed A. Abdelaziz were responsible for conception and revision. Mayada Aly Mousa, Hussein M. Saad, and Nesrine A. Helaly were responsible for interpreting and analyzing data. Asmaa M. Gouda and Mohamed A. Abdelaziz wrote the manuscript, which was revised and approved by all co-authors.

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