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Relationships between clinico-biochemical markers and echo parameter including right ventricle strain with severity of pulmonary arterial hypertension (group I) in Ibn-albitar cardiac center

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Abstract
Background: A quickly developing condition, pulmonary arterial hypertension eventually results in right heart failure and death. Increasing research suggests that early intervention rather than postponing therapy produces better outcomes. Several factors, including functional classification, exercise ability, cardiac imaging results, and biomarker levels, have been proven to predict longevity both at the time of diagnosis and after therapy. Aim of study: To determined 6MWT, biological marker (CRP, S. URIC ACID, BNP) & RV strain as predictor of PAH of according to MRASP.
Method: This a cross sectional study was conducted between the first of May, 2019 and the first of May, 2020 among patients with approved diagnosis of pulmonary artery hypertension and admitted to the Ibn AL- Baitar heart Center. This study excluded every patient with Poor image quality, Atrial fibrillation or Flutter, Pregnancy, Patients with other causes of PAH, Unable to perform 6MWT and Renal failure. BNP, CRP and uric acid were measured to all patients and echocardiography was done, also Six-minute walk distance measured than The modified risk assessment score of PAH was determined and according to it patients categorized into low-risk, intermediate-risk, and high-risk.
Result: a total of 31 patients were enrolled in this study. The percentage of patients with impaired GLS was 26(86.6%) patients, BNP was raised in 73.3% (22) of patients and there were 14(45.2%) patients with low score and 17 (58.8%) patients with intermediate- high score. The mean CRP was significantly lower in low MRASP score than intermediate – high MRASP score (4.1 vs 7.4) with p value =0.001, The echocardiography parameters that shown significant difference between patients with low and intermediate - high MRASP were inferior vena cava diameter, RV pulse velocity and GLS.
Conclusion: The approach to risk assessment is useful tool in assessing patient with PAH.

Keywords: Clinico-biochemical, markers, echo parameter, right ventricle strain, pulmonary arterial hypertension, Ibn-albitar cardiac center

Introduction

Pre-capillary pulmonary hypertension, which is defined as mean pulmonary arterial pressure (MAP) > 25 mmHg with a pulmonary artery wedge pressure (PAWP) 15 mmHg and a pulmonary vascular resistance > 3 Wood units (WU), is a clinical condition known as pulmonary artery hypertension (PAH)9 group I. This condition is characterized by the absence of other causes of pre-capillary pulmonary hypertension, such as pulmonary hyper [1]. Many registries have reported the epidemiology of PAH [2-4]. The prevalence estimates for PAH and idiopathic PAH (IPAH) are 15 cases and 5.9 cases per million adult populations, respectively, according to the lowest estimates. According to the lowest estimate, there are 2.4 incidents per million adult populations per year. The prevalence and incidence of PAH in Europe are around 15-60 subjects per million people and 5–10 cases per million years, respectively [4]. The majority of PAH patients in registries had idiopathic, hereditary, or drug-induced PAH. The primary cause of the subgroup of associated PAH diseases (APAH), primarily systemic sclerosis (SSc), is CTD [2]. Depending on the concomitant clinical problems, PAH may arise in various circumstances [5]. It has been determined that there are a variety of risk factors for the emergence of PAH, which are defined as any element or circumstance thought to predispose or facilitate the onset of the illness.

Based on the degree of their link with PH and their likely causative significance, risk variables were categorized as being either definite, likely, or plausible [5]. Heterozygous BMPR2 mutations cause 75% of familial PAH and 25% of seemingly random PAH [6]. BMP receptor type 2 (BMPR2) controls vascular cell growth. Mutations in genes coding for activin receptor-like kinase 1, endoglin, BMPR1B, and SMAD 9 have been found in PAH patients with a personal or familial history of hereditary hemorrhagic telangiectasia, supporting a major role for TGF-β family members in PAH [6]. Whole exome sequencing has shown unusual heterozygous mutations in proteins including caveolin 1 (CAV1) and potassium channel subfamily K member 3 (KCNK3) [6, 7]. Biomarkers are objectively measurable characteristics that indicate biological processes, pathogenic processes, or pharmacological responses to therapeutic interventions. To be effective, therapy-induced biomarker alterations should represent clinically significant end goals. In PH patients, biochemical markers may detect and monitor RV dysfunction noninvasively. Despite extensive biomarker research, no PAH or pulmonary vascular remodeling marker has been found. As no variable gives significant diagnostic and prognostic information, a complete examination is needed. Since the first US National Institutes of Health idiopathic PAH (IPAH) registry was published about three decades ago, PAH prediction has been a significant aspect of therapy [8]. The French Pulmonary Hypertension Network (FPHN) registry risk equation [9], the PH connection equation [10], the Scottish composite score (11), the US Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) risk equation [12], and others have been used individually or in formulas or calculators to predict outcome [13]. Aim of study: to determined 6MWT, biological marker (CRP, S. URIC ACID, BNP) & RV strain as predictor of severity of the PAH according to MRASP.

Method

A hospital basis study that was cross-sectional. Data collection was done among patients with a confirmed diagnosis of pulmonary artery hypertension (group I), the majority of whom were seen at the PHT clinic at the Ibn AL- Baitar hospital, between the first of May 2019 and the first of May 2020. (Center of cardiology). Throughout the period of data collection, a contiguous sample of patients with a confirmed diagnosis of pulmonary artery hypertension was used. Inclusion requirements: Right side cath or echo approved diagnosis for PAH (group 1). Exclusion standards: crappy picture quality Flutter or atrial fibrillation unable to complete the 6MWT (rheumatologic/orthopedic disease). Renal dysfunction a self-contained form created by the researcher and the supervisor to gather data from the participants via personal interviews. The necessary data included specific elements including gender, age, and a history of dyspnea. Each patient's respiration rate, heart rate, and weight were also assessed. Only BNP was performed at a single private laboratory because this test was not available at the Ibn AL-Baitar cardiac Center reference laboratory. All laboratory measurements were made in the morning between 08:00 and 12:00 using standardised methods at the Ibn AL- Baitar heart Center reference laboratory. Each patient had a clean, aseptic venipuncture performed to obtain 6cc of venous blood. We tested BNP, CRP, and uric acid. All patients have an echocardiographic examination using a GE Vivid E9 ultrasound machine (5 MHz) under the direction of an echocardiography expert, Dr. Sammera. Doppler measurement of the tricuspid valve's peak TR velocity required numerous windows, including the parasternal short axis view. Subcostal and modified view between PSAX and A4C, RV inflow, Apical 4 chamber view (PSAX), and A4C). Next, PASP was calculated using the abbreviated Bernoulli equation, RAP was calculated using the inferior vena cava (IVC) diameter, and respiratory variation was calculated using an echo: In situations where the IVC diameter and collapse do not fit this paradigm, an intermediate value of 8 mmHg (range 5-10 mmHg) may be used. If the IVC diameter is less than 2.1 cm and collapses more than 50% with a sniff, this suggests a normal RA pressure of 3 mmHg (range 0-5 mmHg), and if it collapses less than 50% with a sniff or less than 20% on quiet inspiration, this suggests a high RA pressure of The following variables were then estimated: The RV endocardial boundary is manually traced from the lateral tricuspid annulus along the free wall to the apex and back along the interventricular septum to the medial tricuspid valve annulus at the end of diastole and the end of systole using the equation 100(RVEDA-RVESA)/RVEDA in (A4C view 2D). Tapse, or Tricuspid Annular Plane Systolic Excursion M-mode is used to quantify the excursion of the lateral tricuspid annulus between the end of diastole and the peak of systole (A4C view M-mode). Pulsed tissue by RV The lateral tricuspid annulus was employed as the site for the Doppler s' wave (RVs) velocity measurement in the A4C view. Via M-mode in PLAX view, LVEF% The time to peak strain and the global longitudinal strain were estimated. The endocardial borders were automatically tracked throughout the cardiac cycle while the GLSRV was assessed from an RV-focused, apical 4-chamber view. The GLSRV was then calculated using the average of six segmental values of the lateral wall and interventricular septum, following the same procedure used to calculate the GLS of the LV. However we just utilised the apical 4 chamber view in the RV. Every patient acts The six-minute walk distance was calculated for each patient who walked swiftly on a level, hard surface across a distance of 30 metres, stopping every three metres along the way. The amount of fatigue and dyspnea are assessed using the Borg scale both before and after the test, and the heart rate, blood pressure, and oxygen saturation (SpO2) are all evaluated at rest. The patient then begins to move continuously for six minutes over a designated plain course of 30 metres in length, until the patient requests to end the test or exhibits symptoms, such as severe dyspnea or fatigue. After six minutes, the patient's total distance travelled is measured in metres. At the conclusion of the test, premeasure the blood pressure, SpO2, and pulse rate. The 6-MWD less than 380m was considered an impaired test, with the mean and standard deviation being 571 and 90, respectively [14]. SPSS version 23 was used to process the data. Frequency tables were used to provide descriptive statistics, where categorical variables were represented by percentages and numbers and continuous variables by means and standard deviation. Analytical statistics like the Student -t test are used to determine whether there is a relationship between categorical and continuous variables, the Fisher Exact test is used to determine whether there is a relationship between two categorical variables because the chi-square test cannot be used because of the small sample size, and the correlation

test is used to determine whether there is a relationship between two continuous variables when the Pearson correlation coefficients are 00-0.19, 0.20-0.39, 0.40-0.59, and 0.6 A P-value of 0.05 was required for statistical significance.

Results

A total of 31 patients were enrolled in this study, the mean ± SD was 38.13±15.41years, ranging between 8-77 years. With female to male ratio was 5.2:1. The mean ± SD of BMI was 27.8±6 Kg/m^2 with 32.3% of patients had normal BMI and 67.7% of patients were overweight and obese. The clinical evaluation of patients shown that 51.6% (16) of patients had NYHA class III, and 80.6% (25) of patients had impaired 6 Minute walk test. The biochemical markers for studied patients shown that: uric acid level raised in 32.3% (10) of patients with mean ± SD was 5.4±2.3 mg/dl, CRP raised in only 9.7% (3) of patients with mean ± SD was 5.9±7.7 mg/L and BNP was raised in 71% (22) of patients with mean 233.1±236 pg/ml, table 1. The baseline echo parameters were shown in table 2.

Table 1: Description of the studied patients.

Variable		Number	Percentage
Gender	Male	5	16.13%
	Female	26	83.87%
BMI in Kg/m^2	Normal	10	32.3%
	Overweight or obese	21	67.7%
NYHA Class	II	13	41.9%
	III	16	51.6%
	IV	2	6.5%
6 Minute walk test	Impair	25	80.6%
	Normal	6	19.4%
Uric acid In mg/dl	Raised	10	32.3%
	Normal	21	67.7%
CRP In mg/L	Raised	3	9.7%
	Normal	28	90.3%
BNP in pg/ml	Raised	22	71%
	Normal	9	29%

Table 2: Echo parameters of studied group.

Echo parameters	Mean ± SD	MIN	MAX
EF %	60.7±4.1	42	67
Peak TR gradient	51.2±15	31	110
pulmonary artery diameter	2.4±0.6	1.3	4
RVOT PW AT	0.1±0.03	0.03	0.17
RV/LV diameter ratio	1.15±0.44	0.49	2.6
inferior vena cava diameter	1.9±0.38	0.9	2.7
RAA in cm^2	26.6±7.2	15	39
FAC	24.6±8.1	10	38
RV pulse velocity	1.2±2.5	0.06	7
TAPSE	1.7±0.57	0.7	3.2
RV GLS	-12.6±4.4	-5	–23

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The 6 Minute walk test shown no significant association with GLS (P=0.24). The mean CRP was lower in impaired GLS than normal GLS (5.5 vs 7.7), but the difference was not significant (p=0.56) also there were no significant difference in the mean uric acid between normal and impair GLS. The mean BNP was higher in impaired GLS than normal but difference was not significant, table 3.

Table 3: Relation of 6MWT with GLS. And Difference in the mean biochemical with GLS.

6 Minute walk test	RV GLS		P value
	Normal	Impaired	
Impair	3(12%)	22(88%)	0.241^{*NS}
Normal	2(33.3%)	4(66.7%)	
Biochemical markers	**RV GLS**		**P value**
	Normal	**Impaired**	
Mean ± SD CRP	7.7±5.9	5.5±7.9	0.56^{*NS}
Mean ± SD Uric acid	4.3±1.1	5.6±2.5	0.242^{*NS}
Mean ± SD of BNP	155.1 156.5	248.1 248.1	0.43^{*NS}

NS = non-significant >0.05.

The BNP had no correlation with CRP, but there was a weak positive correlation with uric acid (r= 0.38, p=0.031), The echocardiography parameters that shown significant difference between patients with normal and raised BNP were inferior vena cava diameter, FAC and TAPSE ($p \leq 0.05$), while other parameters shown no significant differences ($p > 0.05$),

Table 4: Relation of 6MWT with BNP. Correlation of biochemical markers with BNP.

Clinical evaluation		BNP		P value
		Normal	Raised	
6 Minute walk test	Impair	7(77.8%)	18(81.8%)	0.98^{*NS}
	Normal	2(22.2%)	4(18.2%)	
Biochemical markers		**BNP**		
		Pearson's correlation		**p-value**
CRP		0.049		0.79^{*NS}
Uric acid		0.38		0.031^{*S}

The patients stratified according to MRASP score, there were 14 (45.2%) patients with low score and 17 (58.8%) patients with intermediate- high score, the overall mean score was 3.6±1.2, figure 1.

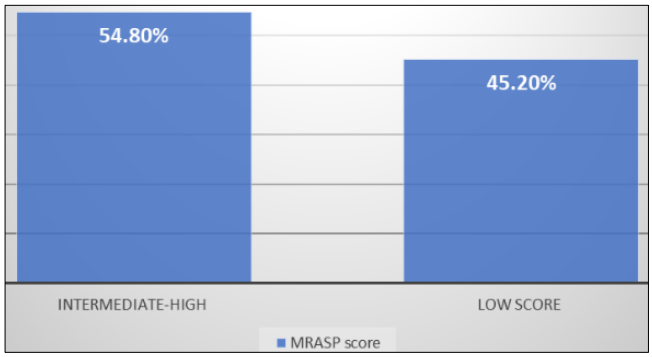

Fig 1: MRASP score for studied patients.

The mean CRP was significantly lower in low MRASP score than intermediate – high MRASP score (4.1 vs 7.4) with p value =0.001. regard uric acid, even the mean uric was lower in low MRASP score than intermediate - high MRASP score (4 vs 6.6) but that difference was non-significant with p value=0.243. The echocardiography parameters that shown significant difference between patients with low and intermediate MRASP were inferior vena cava diameter, RV pulse velocity and GLS ($p \leq 0.05$), while other parameters shown no significant differences ($p > 0.05$), table 5.

Table 5: Difference in the biochemical & echocardiography parameters between MRASP score.

Echo parameters Mean ± SD	MRASP Score		P value
	Low	Intermediate-high	
CRP	4.1±3.9	7.4±9.5	0.001*S
Uric acid	4±1	6.6±2.5	0.243*NS
EF %	59.8±5.6	61.5±2.2	0.26*NS
Peak TR velocity	48.4±10.8	53.6±17.7	0.34*NS
pulmonary artery diameter	2.6±0.7	2.2±0.5	0.188*NS
RVOT PW AT	0.11±0.03	0.1±0.03	0.408*NS
RV/LV diameter ratio	1.1±0.51	1.198±0.37	0.54*NS
inferior vena cava diameter	1.7±0.33	2±0.37	0.02*S
FAC	26.6±6.8	22.9±8.9	0.21*NS
RV pulse velocity	0.16±0.21	2.1±3.2	0.031*S
TAPSE	1.87±0.66	1.61±0.47	0.213*NS
RV GLS	-14.7±5	-11±3.2	0.019*S

*Student T test, S= significant ≤0.05, NS= non-significant >0.05.

Discussion

A significant portion of the patient assessment involves determining the severity of the illness as well as the patient's expected lifespan. It helps in the selection of treatment strategies, the timing of transplantation, and the counselling of patients [15], among other things. Patients who have pulmonary arterial hypertension have a mortality rate that is correlated with the severity of their symptoms as well as the degree to which they have right-sided heart failure. In addition, since there is no one factor that may reliably predict the results for PAH patients. As a result, risk assessment in PAH patients has to include a variety of clinical, biochemical, hemodynamic, and exercise measures, all of which have to be carried out in a sequential way so as to represent a patient's progression throughout the course of the illness. Clinicians are able to estimate the prognoses of their patients, set treatment objectives, assist patients in making informed choices, and track the development of illness when they do accurate risk assessments. As a result, this research was carried out with the purpose of determining the severity of PAH based on a variety of variables and determining its link to clinicobiochemical and echocardiographic indicators. The average age of participants in this research was 38 years old, which is somewhat comparable to the findings of Kopec G *et al.* [16], who found that the average age of patients with primary pulmonary hypertension (also known as IPAH) was 36.4 years old. Another study by Ling, Y, and others [17]. In the present study, it was shown that 83.9% of patients with PAH had a problem with their GLS. This finding is in agreement with previous research from researchers such as Fukuda RP *et al.* study [18], Meris A *et al.* study [19], and Li Y *et al.* study [20]. The present study found that the GLS acquired by echocardiographic was highly connected with other conventional indicators of RV systolic function on standard transthoracic echocardiographic examinations such as TAPSE. This was revealed by the researchers of the study. These findings are consistent with those found in a study by Li Y *et al.* [20], which also divided patients into two groups based on GLS and used a cut-off value of 19%. That study also discovered that the RV function parameters, such as s', TAPSE, and FAC, were significantly different between the two groups, with the higher GLS group having better RV function. Patients whose RV GLS was less than or equal to 19% had worse RV function. Patients who had a GLS of less than or equal to 19% had a lower TAPSE, according to another research by Haeck ML *et al.* [21]. On the other hand, the results of our research showed that there was no significant association between the GLS RV and clinical or biochemical indicators. These results are in line with those found in earlier research, such as those conducted by Li Y *et al.* [22]. Patients with low BNP were younger, had better NYHA/WHO FC and longer 6-min walk distance (6MWD), this difference may be related to the small sample size of our sample in comparison to REVEAL study, and this study included patients who were already on treatment for PAH. In the current study, BNP was found to be raised in 71% of PAH patients, and there were no associations with clinical and biochemical markers. In addition, this inconstant with Frantz *et al.* study [23] that shown this is in accordance with what the research by Forfia PR *et al.* found [24]. This study also evaluates other biochemical markers that have shown to had benefit in the assessment of the severity of PAH. In the current study, CRP was found to be elevated in only 9.7%, and the mean CRP was significantly higher in intermediate-high risk MRASP score than low risk score. This is in line with Quarck R *et al.* study [25] that demonstrating an increase in circulating CRP levels in PAH patients compared with those in control subjects. This study also looked at the serum uric acid concentration in patients with PAH. They discovered that the serum uric acid concentration was raised in 32.3% of patients, and that uric acid correlated with BNP. These findings are comparable to those found in a study by Bendayan D *et al.* [26] that discovered the prevalence of hyperuricemia was 27.6% among PAH patients.

Conclusion

In standard transthoracic echocardiography examinations, such as TAPSE, global longitudinal strain was strongly connected with other traditional measures of RV systolic function, and the GLS might reflect the spectrum of right ventricular function loss in PH patients. The suggested modified risk assessment score is a helpful tool for evaluating patients with PAH.

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