Functional and morphological cardiac changes in myeloproliferative neoplasms

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Background
Myeloprolifer ative neoplasms (MPNs) are hematopoietic stem cell neoplasms caused by a clonal expansion in one or more myeloid lineages. The greatest obstacles for these neoplasms are cardiovascular consequences such as vascular thrombosis, myocardial infarction, and pulmonary hypertension (PH), which can lead to mortality.

Aim
This work aimed to understand the relationship between MPN and cardiovascular complications profoundly by transthoracic echocardiography.

Patients and methods
A prospective clinical study included 30 MPN patients recruited from the Clinical Haematology Unit in Assiut University Hospital from September 2017 to August 2018 to detect morphological and functional cardiac changes by the use the transthoracic echocardiography and two control groups, one group included 30 patients with other hematological disorders and the other group included 30 healthy persons.

Results
The left atrial diameter, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, posterior-wall diameter, and pulmonary arterial systolic pressure were significantly higher in MPN patients. The frequency of MR (40.7%) and tricuspid-regurgitation (50%) was significantly higher among the study group and 40% had PH.

Conclusions
Left atrial dilatation, left ventricular hypertrophy, PH, TR, and MR were the most prominent cardiovascular changes in MPN patients.

Keywords:
cardiovascular complications, myeloproliferative neoplasms, pulmonary hypertension

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Introduction

Myeloproliferative neoplasms (MPNs) are a heterogeneous group of clonal hematopoietic stem cell neoplasms characterized by excessive proliferation of one or more of the erythroid, megakaryocytic, or myeloid lineages, resulting in an increase in red cells, platelets, and/or granulocytes in the peripheral blood [1]. Fatigue, weight loss, abdominal fullness, bleeding, splenomegaly, leukocytosis, anemia, and thrombocytosis are all common findings of MPN [2]. MPNs are characterized by a high risk of thrombosis or hemorrhage, as well as a high rate of acute myeloid leukemia transformation, which is usually fatal. The presence of BCR–ABL, which is a result of t(9,22) known as the Philadelphia chromosome, is commonly regarded as a unique subtype of chronic myeloid leukemia (CML) [3]. The new edition of the 2016 revised MPN classification includes seven subcategories: primary myelofibrosis (PMF), essential thrombocythemia, chronic neutrophilic leukemia, CML, polycythemia vera, primary chronic eosinophilic leukemia – not otherwise specified, and MPN unclassifiable [4]. A few numbers of research have looked at cardiac lesions in MPNs. Previous research has found that individuals with MPNs have a high rate of cardiovascular complications, which can lead to death. However, research that correlates cardiac abnormalities to MPNs is still inadequate [5].

Aim

The aim of this study was to use transthoracic echocardiography to understand the relationship between MPN and cardiovascular problems profoundly.

Patients and methods

The current prospective, cross-sectional clinical study was conducted from September 1, 2017 to

August 31, 2018. The study included 30 MPN patients, 17 males and 13 females, who were admitted to the Clinical Haematology Unit of the Internal Medicine Department in Assiut University Hospital. In total, 13 cases with CML, eight with polycythemia vera, seven with essential thrombocythemia, and two with PMF. The study included two control groups, the first is the diseased control group and included 30 patients with other hematological disorders of the same age and sex of the main study group, the second is healthy control group that included 30 healthy persons of the same age and sex of the main study group.

Methods

All patients of the main study group, patients of the diseased control group, and the persons of the healthy control group were subjected to the following:

Thorough history taking focusing on the history of chronic illnesses like diabetes mellitus, hypertension, ischemic heart diseases, and history of drug intake. Thorough clinical examination, including general examination, chest examination, complete cardiac examination, and complete abdominal examination. Investigations included complete blood count, JAK2 mutation and bone marrow studies, and renal-function and liver-function tests. Chest radiograph and abdominal ultrasounds were done.

Transthoracic echocardiography was done for all groups using the PHILIPS HD11X device. The heart was assessed in different echocardiographic views: apical views, including apical two-chamber, four-chamber, three-chamber, and five-chamber views, as well as the parasternal long-axis and short-axis views. With M-mode echocardiography, ejection fraction was estimated as a percentage derived from the mid-left-ventricular diameters measured in end diastole and end systole, and was expressed as fractional shortening (% LV shortening) in parasternal short-axis view. Diastolic dysfunction was assessed using pulsed Doppler flow at the mitral flow (mitral E/A ratio) in four-chamber view. Pulmonary-artery systolic pressure was measured indirectly by the traditional echocardiographic approach using a derivation of right-ventricular pressure from the tricuspid-regurgitation velocity added to a qualitative assessment of right-atrial pressure.

The IRB Assiut Faculty of Medicine approved the study. IRB no: 17101389, consent statement: patients signed informed consent.

Statistical analysis

Data were collected and analyzed using SPSS (Statistical Package for the Social Science, version 20; IBM, Armonk, New York, USA). Continuous data were expressed in the form of mean ± SD or median (range), while nominal data were expressed in the form of frequency (percentage). χ^2 test was used to compare the nominal data of different groups in the study, while Student *t* test was used to compare the mean of different two groups. Analysis of variance test followed by post-hoc analysis was used to compare continuous data of the three enrolled groups. The level of confidence was kept at 95% and hence, the *P* value was significant if less than 0.05.

Ethical aspects

Before participant recruitment, the study protocol was reviewed and approved by the research ethics committee of the Faculty of Medicine Assiut University. Informed consent was obtained from all the participants in the study.

Results

Table 1: All recruited groups' baseline data revealed no significant differences between the three study groups (P> 0.05). Males made up the majority of all studied groups. Three patients from the study group and the diseased control group both had DM and HTN. Table 2: Most clinical data were found to be considerably higher in the study group and the diseased control group than in the control healthy group. In comparison to patients with myeloproliferative diseases, patients in the diseased control group have significantly greater rates of fever, purpura, and ecchymosis. In contrast, patients with myeloproliferative neoplasms had much greater rates of splenomegaly and hepatomegaly.

Table 3: With the exception of the leucocytic count, which was considerably higher among patients with myeloproliferative neoplasms in contrast to other groups, the baseline laboratory data for the other enrolled groups showed no statistically significant differences. While the diseased control group's hemoglobin level was the lowest, the healthy control group's hemoglobin and hematocrit values were much higher. Patients with myeloproliferative neoplasms had considerably greater platelet counts than patients in other groups.

Table 4: In comparison to other control groups, echocardiographic findings in all MPN patients that included in this study showed: Left atrial diameter and Left atrial dilatation were significantly higher (33.3%). LVEDD, LVESD were significantly higher. Posterior wall diameter was significantly higher; Frequency of MR (40.7%) and TR (50%) was significantly higher.

Table 1 Baseline data of enrolled groups

	Study group (*n*=30)	Diseased control group (*n*=30)	Healthy control group (*n*=30)	*P*1	*P*2	*P*3
Age (years)	48.36±15.89	50.11±11.23	49.02±6.98	0.11	0.20	0.09
Sex						
Male	17 (56.7)	17 (56.7)	15 (50)	–	0.98	0.98
Female	13 (43.3)	13 (43.3)	15 (50)			
Smoking	2 (6.7)	1 (3.3)	2 (6.7)	0.09	–	0.09
Diabetes mellitus	3 (10)	3 (10)	2 (6.7)	–	0.10	0.10
Hypertension	3 (10)	3 (10)	2 (6.7)	–	0.10	0.10

Data expressed as frequency (percentage) and mean (SD). *P* value was significant if less than 0.05. *P*1 compares between the study group and diseased control group. *P*2 compared between the study group and healthy control group. *P*3 compared between the diseased control group and healthy control group.

Table 2 Baseline clinical data of enrolled groups

	Study group (*n*=30)	Diseased control group (*n*=30)	Healthy control group (*n*=30)	*P*1	*P*2	*P*3
Fatigue	16 (53.3)	18 (60)	2 (6.7)	0.09	<0.001	<0.001
Dizziness	15 (50)	16 (53.3)	3 (10)	0.11	<0.001	<0.001
Headache	15 (50)	16 (53.3)	4 (13.3)	0.21	<0.001	<0.001
Dyspnea	7 (23.3)	6 (20)	0	0.21	0.01	0.01
Palpitation	12 (40)	18 (60)	2 (6.7)	0.06	<0.001	<0.001
Bleeding	1 (3.4)	2 (9.1)	0	0.22	0.16	0.47
Abdominal pain	11 (36.7)	10 (33.3)	3 (10)	0.12	0.02	0.02
Fever	0	19 (63.3)	0	<0.001	–	<0.001
Pallor	15 (50)	20 (66.7)	2 (6.7)	0.61	<0.001	<0.001
Lymphadenopathy	2 (6.7)	7 (23.3)	0	0.11	0.06	0.01
Ecchymosis	1 (3.3)	12 (40)	0	<0.001	0.07	<0.001
Purpura	0	10 (33.3)	0	<0.001	–	<0.001
Lower-limb edema	2 (7.4)	3 (10)	0	0.22	0.10	0.21
Hepatomegaly	13 (44.8)	7 (24.1)	0	0.01	<0.001	0.02
Splenomegaly	25 (83.3)	6 (20)	0	<0.001	<0.001	0.01
Pulse (beat/min)	90.13±10.49	92.07±21.93	84±4.78	0.60	0.10	0.30
DBP (mmHg)	79.99±8.98	80.01±4.59	80.45±2.15	0.11	0.09	0.08
SBP (mmHg)	124.11±5.09	123.11±3.09	125.05±4.40	0.12	0.19	0.07
Temperature (°C)	37.01±0.19	37.74±0.79	36.96±0.42	<0.001	0.71	<0.001
RR (cycle/min)	12.20±0.76	14.87±8.57	12±0.78	0.40	0.87	0.29

Data expressed as frequency (percentage) and mean (SD). DBP, diastolic blood pressure; RR, respiratory rate; SBP, systolic blood pressure. *P* value was significant if less than 0.05. *P*1 compares between the study group and diseased control group. *P*2 compared between the study group and healthy control group. *P*3 compared between the diseased control group and healthy control group.

Table 3 Baseline laboratory data of enrolled groups

	Study group (*n*=30)	Diseased control group (*n*=30)	Healthy control group (*n*=30)	*P*1	*P*2	*P*3
Leukocytes (10^9/l)	103.16±33.45	33.89±16.12	6.81±1.09	<0.001	<0.001	<0.001
Hemoglobin (g/dl)	11.02±4.80	8.39±3	12.58±0.79	<0.001	0.07	<0.001
Hematocrit value (%)	26.11±17.45	26.30±9.89	38.79±1.78	0.94	<0.001	<0.001
MCV (fl)	85.11±11.36	85.38±9.52	83.06±3.40	0.90	0.37	0.31
MCH (g/dl)	27.22±4.23	27.45±3.60	26.22±1.35	0.78	0.24	0.15
Platelets (10^9/l)	444.67±153.45	137.87±35.62	267.30±54.45	<0.001	<0.001	<0.001
PT (s)	14.24±4.22	13.10±1.31	12.81±0.54	0.09	0.06	0.66
aPTT (s)	33.99±7.77	33.12±5.94	32.75±3.07	0.57	0.41	0.80
Urea (mg/dl)	6.77±3.87	7.51±6.62	5.96±1.07	0.52	0.48	0.18
Creatinine (mg/dl)	72.69±30.73	79.16±11.38	71.93±11.48	0.26	0.98	0.25
Bilirubin (mmol/l)	14.79±4.49	10.30±1.01	15.56±2.22	0.38	0.09	0.06
AST (u/l)	22.27±12.45	25.79±9.49	17.80±3.02	0.17	0.75	0.09
ALT (u/l)	21.83±12.27	24.67±6.23	21.16±4.43	0.07	0.98	0.08
Protein (mg/dl)	60.20±19.51	61.82±24.18	80.46±5.06	0.73	0.09	0.34
Albumin (mg/dl)	33.81±11.44	32.39±12.61	34.63±3.50	0.11	0.53	0.21
Uric acid (mg/dl)	5.29 ± 1.46	4.51 ± 1.61	4.67 ± 1.08	0.06	0.09	0.66

ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; PT, prothrombin time. *P* value was significant if less than 0.05. *P*1 compares between the study group and diseased control group. *P*2 compared between the study group and healthy control group. *P*3 compared between the diseased control group and healthy control group.

Table 4 Echocardiography data of enrolled groups

	Study group (*n*=30)	Diseased control group (*n*=30)	Healthy control group (*n*=30)	*P*1	*P*2	*P*3
Aortic root (cm)	2.90±0.40	2.91±0.39	3.12±0.39	0.93	0.13	0.14
Left atrial diameter (cm)	3.78±0.61	3.75±0.68	2.90±0.57	0.85	<0.001	<0.001
IVSD (cm)	0.95±0.28	0.89±0.24	0.92±0.12	0.36	0.65	0.64
LVEDD (cm)	5.52±1.34	4.87±0.47	4.83±0.49	<0.001	<0.001	0.82
LVESD (cm)	3.90±1.12	3.20±0.33	3.19±0.37	<0.001	<0.001	0.98
PWD (cm)	1±0.21	0.91±0.21	0.92±0.10	0.03	0.07	0.72
Fractional shortening (%)	33.57±5.67	33.20±2.85	33.03±2.42	0.71	0.87	0.60
Ejection fraction (%)	62.07±9.08	64.83±4.43	61.33±3.06	0.08	0.64	0.11
Mitral valve PVD (m/s)	1.19±0.66	0.77±0.20	0.95±0.14	<0.001	0.02	0.8
E/A ratio						
<1	2 (6.7)					
=1	26 (86.7)	30 (100)	30 (100)	<0.001	<0.001	–
>1	2 (6.7)					
Mitral regurge	11 (40.7)	2 (6.7)	2 (6.7)	<0.001	<0.001	0.65
Mitral valve thickening	3 (10)	1 (3.3)	0	0.16	0.10	0.06
Aortic valve PVS (m/s)	1.38±0.36	1.17±0.22	1.17±0.17	<0.001	<0.001	0.92
Gmax (mmHg)	8.56±3.57	5.21±0.92	2.97±0.61	<0.001	<0.001	<0.001
Aortic regurge	4 (13.3)	0	0	0.01	0.01	–
Aortic valve thickening	2 (6.7)	0	0	0.12	0.10	–
Tricuspid-valve PVD (m/s)	0.68±0.17	0.70±0.13	0.86±0.22	0.72	<0.001	<0.001
Tricuspid regurge	15 (50)	4 (13.3)	3 (10)	<0.001	<0.001	0.21
PASP (mmHg)	36.46±11.05	32.28±10.39	31.16±2.15	0.07	0.02	0.63
Pulmonary hypertension	12 (40)	0	0	<0.001	<0.001	–
Abnormal wall motion	4 (13.3)	0	1 (3.3)	0.01	0.08	0.11
Right-atrial dilatation	3 (10)	2 (6.7)	2 (6.7)	0.34	0.34	0.62
Left-atrial dilatation	10 (33.3)	4 (13.3)	0	<0.001	<0.001	0.12
Right-ventricular hypertrophy	2 (6.7)	0	0	0.12	0.10	–
Left-ventricular hypertrophy	7 (23.3)	0	0	0.01	0.01	–
Intracardiac masses	2 (6.7)	0	0	0.12	0.10	–
Pericardial effusion	2 (6.7)	0	0	0.12	0.10	–
LVDD	2 (6.7)	0	0	0.12	0.10	–
LVSD	4 (13.3)	0	0	0.01	0.01	–

Data expressed as mean (SD). ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; E/A, early diastolic velocity/peak late diastolic velocity; IVSD, interventricular septal diameter; LVDD, left-ventricular diastolic dysfunction; LVEDD, left-ventricular end-diastolic diameter; LVESD, left-ventricular end-systolic diameter; LVSD, left-ventricular systolic dysfunction; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; PASP, pulmonary artery systolic pressure; PT, prothrombin time, PVD, pulmonary vein diastolic flow velocity; PVS, pulmonary vein systolic flow velocity; PWD, posterior-wall diameter. *P* value was significant if less than 0.05. *P*1 compares between study group and diseased control group. *P*2 compared between the study group and healthy control group. *P*3 compared between the diseased control group and healthy control group.

PASP was significantly higher among study group and 40% had pulmonary hypertension (PHTN) in the study group.

Table 5: Both newly diagnosed cases (13/30, 43.3%) and previously diagnosed cases (17/30, 56.7%) were included in the study group. Echocardiographic changes in newly and previously MPN patients showed that the previously diagnosed cases had significantly higher left atrial diameter, left atrial dilatation in 52.9% of cases and left ventricular hypertrophy in 41.2% of cases .

Discussion

According to pulmonary hypertension (PH), the current study's findings were consistent with those published by Kim *et al.* [6] PH was seen in 56% of patients, and it was more common in those who had had the disease for a longer time. MPN-associated PH may have a postcapillary component, as seen by LV remodeling and pulmonary-artery pressure, which can occur alone or in combination with precapillary pathology.

Also, the results were similar to those reported by Castiglione *et al.* [7], in which left ventricular end-diastolic diameter and left ventricular end-systolic diameter were increased, this can be enlightened as the JAK2V617F mutation promotes a proproliferative, pro-adhesive, and prothrombotic endothelium phenotype, all of which play essential roles in the progression of cardiovascular problems.

In a study by Roach *et al.* [8], 131 patients with PMF, CML, and aplastic anemia were enrolled in the Taussig Cancer Institute, Cleveland Clinic. In addition, the

Table 5 Echocardiography in patients with myeloproliferative neoplasms in the main study group (the newly and previously diagnosed)

	Newly diagnosed (*n*=13)	Previously diagnosed (*n*=17)	*P*
Aortic root (cm)	2.80±0.46	2.97±0.35	0.24
Left atrial diameter (cm)	3.37±0.52	4.04±0.67	**<0.001**
IVSD (cm)	0.87±0.18	1.01±0.33	0.22
LVEDD (cm)	5.30±1.54	5.69±1.18	0.44
LVESD (cm)	3.67±1.34	4.08±0.92	0.33
PWD (%)	0.95±0.13	1.04±0.24	0.22
Fractional shortening (%)	34.23±4.10	33.06±6.71	0.58
Ejection fraction (%)	63.46±5.45	61±11.15	0.47
Mitral valve PVD (m/s)	1.30±0.81	1.10±0.54	0.43
E/A ratio			
<1	1 (7.7)	1 (5.9)	0.43
=1	0	2 (11.8)	
>1	12 (92.3)	14 (82.4)	
Mitral regurge	6 (50)	5 (33.3)	0.31
Mitral valve thickening	2 (15.4)	1 (5.9)	0.39
Aortic valve PVS (m/s)	1.28±0.42	1.46±0.31	0.18
Gmax (mmHg)	8.20±4.55	8.84±2.71	0.63
Aortic regurge	1 (7.7)	3 (17.6)	0.40
Aortic valve thickening	0	2 (11.8)	0.31
Tricuspid-valve PVD (m/s)	0.70±0.12	0.67±0.21	0.66
Tricuspid regurge	6 (46.2)	9 (52.9)	0.50
PASP (mmHg)	34.07±10.02	38.29±11.75	0.30
Pulmonary hypertension	4 (30.8)	8 (47.1)	0.30
Abnormal wall motion	0	4 (23.5)	0.08
Right atrial dilatation	0	3 (17.6)	0.16
Left atrial dilatation	1 (7.7)	9 (52.9)	0.01
Right-ventricular hypertrophy	0	2 (11.8)	0.31
Left-ventricular hypertrophy	0	7 (41.2)	0.01
Intracardiac masses	0	2 (11.8)	0.31
Pericardial effusion	1 (7.7)	1 (5.9)	0.68
LVDD	0	2 (11.8)	0.31
LVSD	1 (7.7)	3 (17.6)	0.40

IVSD, interventricular septal diameter; LVDD, left-ventricular diastolic dysfunction; LVEDD, left-ventricular end-diastolic diameter; LVESD, left-ventricular end-systolic diameter; LVSD, left-ventricular systolic dysfunction; PASP, pulmonary artery systolic pressure; PWD, posterior-wall diameter. *P* value was significant if less than 0.05.

left-atrial systolic dimension was considerably larger in PMF patients, even though the left-sided function was not different among the groups and within normal, which was in agreement with the current study's results. PMF patients had highly significant PH [8].

Guilpain *et al.* [9] conducted a retrospective study in France to detect PHT in MPN, and the results were consistent with the current study, with 40% of patients having pulmonary arterial hypertension (PAH) associated with MPN without additional risk factors for PAH.

The incidence of PH in patients with chronic myeloproliferative diseases was assessed by TTE in an American study conducted at Coney Island Hospital, according to Gupta *et al.* [10]. The study comprised 27 patients, and the results were in agreement with current research, with 48% of patients having PH.

The highly significant hypertrophy in the current study was concordant with the multicenter study of Shi *et al.* [11], which reported that the JAK2V167F-positive murine model of MPN developed increased LV thickness due to extensive collagen deposition and fibrosis.

The results of this study agreed with those of Cortelezzi *et al.* [12] PAH was discovered in 36% of participants in a study. PAH is caused by several mechanisms, including pulmonary myeloid metaplasia, circulating megakaryocytes obstructing pulmonary arteries, smooth-muscle hyperplasia caused by platelet-derived growth factors, and thromboembolic events.

It has been found that the results of PH in the present study were discordant with published data by Yaylali *et al.* [13], only 5.5% of patients with PH, this variance could be explained as PMF was the most common subgroup, tyrosine-kinase inhibitors that were used in the treatment of MPNs in the current study were also found to be associated with the development of PH, and the duration of disease in Yaylali *et al.* [13] study was less than that of the current study.

In contrast to the current study's findings, Venton *et al.* [14] claimed that the number of cases with PH was lower. This disparity resulted from the exclusion of previously diagnosed patients, and the duration of the disease plays a significant influence in cardiovascular events, particularly in PH.

In a retrospective analysis of patients with PMF who underwent echocardiography in the United States, Lopez-Mattei *et al.* [15] found that 14% of patients had PHTN. The disparity in outcomes was related to the fact that the Mattei trial only included patients with PMF. In both studies, the number of patients and duration were varied.

The findings differed from those reported by Mattar *et al.* [16], an Egyptian study was conducted in Kasr Al Aini Hospital, with the results showing that 11.67% of patients had PHT, which is lower than the current study's findings. These differences could be attributable to the fact that Philadelphia-positive MPN patients were excluded from the study, while the current study included patients with CML who were being treated with various modalities that had cardiovascular side effects.

Recommendations

For greater accuracy, further prospectively designed and multicenter trials with long-term patient

follow-up using transesophageal echocardiography and right-heart catheterization are needed.

Conclusion

Cardiovascular issues are common in patients with MPNs and they are more common in previously diagnosed patients, implying that MPN's chronicity has a significant impact. The most common complications were left atrial dilation and left ventricular hypertrophy. Patients with MPN, both Philadelphia positive and Philadelphia negative, had a high rate of PH. Valvular lesions were found in nearly half of the patients.

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Conflicts of interest

None declared.

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