

## Prognostic Significance of Echocardiographic Parameters for Right Heart Assessment and Risk of Developing Advanced Gold Classes in Patients with Chronic Obstructive Pulmonary Disease (COPD)

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### Abstract

**Background:** Chronic obstructive pulmonary disease (COPD) according to World Health Organization is the third leading cause for early death and disability in 2022. COPD is characterized by persistent airflow limitation that is typically progressive and associated with an enhanced chronic inflammatory response in the airways and lung tissue. As the disease progresses more cardiovascular complication appear such as right ventricular hypertrophy with preserved systolic function, pulmonary artery pressure (which is slightly to moderately increased), and moderate tricuspid regurgitation.

### Material and methods:

The design of our study was a prospective-clinical cross-sectional study. We analyzed 94 patients with COPD. All patients were divided in groups according to degree of obstruction and classified by GOLD classification system into four groups from GOLD 1-GOLD4. In our study all patients during admission and hospital stay were thoroughly examined with anamnesis, physical examination and electrocardiogram (ECG), as well as with basic and advanced echocardiographic assessment. 13teen echo parameters were evaluated applying advanced echocardiographic analysis especially in terms of right heart features.

### Results:

All echocardiographic parameters were analyzed to understand their significance in disease progression in patients with COPD and increasing Gold classes. Twelve of 13teen echo-parameters evaluated in our study have quantitative values, while collapsibility of vena cava >50% is a qualitative parameter. Quantitative values of the same echo-parameters (DA, S TDV DV, TAPSE, FAC, AT a.pulmonalis, SPAP, v.max, MPI DV, Stain DV, DA area, PVR and collapsibility of vena cava > 50 %) were compared in terms of Gold classes by multivariate linear regression analysis. With multivariate linear regression analysis, there is a statistically significant correlation (with the following three echocardiographic parameters: S' TDV DV, DV basal and Global strain DV according to GOLD classes. In further analyses, binary categorization of GOLD classes into two binary categories was additionally used: lower GOLD

classes (1 and 2), and more advanced GOLD classes (3 and 4) by applying logistic regression model. The parameter basal dimension of the right ventricle (RV basal) has the highest values statistically, the parameters SPAP, AT a.pulm, GI strain of DV and TAPSE have somewhat lower values.

**Conclusion:**

Prevalence of pulmonary hypertension has a linear relationship with severity of COPD and severe pulmonary hypertension is almost every time associated with development of right heart failure. Echocardiography helps in early detection of cardiac complications in COPD cases giving time for early interventions. We suggest screening of all COPD patients for cardiac complications using echocardiography as a non-invasive and repeatable for their follow-up

**Keywords:** COPD, echocardiography, right heart failure, pulmonary hypertension

**Introduction:**

Chronic obstructive pulmonary disease (COPD) according to World Health Organization is the third leading cause for early death and disability in 2022. An estimated 200 million people have COPD, of which about 3.2 million die each year. Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease, with a worldwide prevalence of 10.1% in people aged 40 years or older.<sup>1)2)</sup>

COPD is characterized by persistent airflow limitation that is typically progressive and associated with an enhanced chronic inflammatory response in the airways and lung tissue. The disease is with typical presentation of progressive shortness of breath, chronic cough, recurrent wheezing and sputum production. The chronic airflow limitation in COPD is caused by the combination of parenchymal destruction (emphysema) and small airways disease (obstructive bronchiolitis). COPD was diagnosed based on an obstructive pre-bronchodilator spirometry (FEV1/FVC<0.70) and patients were divided by GOLD classification system into 4 stages. From GOLD 1 stage (FEV1 >80%), to GOLD 4 where patients have severely reduced lung capacity, (FEV1<30%).<sup>2)</sup>

As the disease progresses more cardiovascular complication appear. Right ventricular hypertrophy with preserved systolic function is most common finding in patients with COPD. COPD result in a relatively slow process of elevation of pulmonary artery pressure creating the opportunity for adequate adaptation of the right ventricle. COPD patients not so rarely have increased pulmonary vascular resistance (PVR). Pulmonary artery pressure in this group of patients is slightly to moderately increased, especially in patients with advanced form of the disease. Tricuspid regurgitation is not always visible and present in every patient, and the possibility of confirmation by echocardiography is in 24-66% of the patients.<sup>3)4)</sup>

The development of pulmonary hypertension leads to dilatation of the right ventricle (RV) and development of RV heart failure during the course of the disease. Echocardiography is an easy applicable and repeatable method that can provide information on the degree of right heart

dysfunction, the occurrence of tricuspid regurgitation and the development and degree of pulmonary hypertension.

Right ventricular systolic and diastolic function can be assessed both, qualitatively and quantitatively, by two and three-dimensional echocardiography (2D and 3D). Multiple echocardiographic windows are used to analyze a range of qualitative and quantitative parameters related to right heart chamber.5)6)

**Material and methods:**

The design of our study was a prospective-clinical cross-sectional study. We analyzed 94 patients with COPD. All patients were divided in groups according to degree of obstruction and classified by GOLD classification system into four groups from GOLD 1-GOLD4. Tiffneau index (FEV1/FVC <70%) defines GOLD groups into 4 stage of the disease according to the degree of obstruction.

GOLD 1 - patients with mild form of COPD (FEV/FVC >80%)

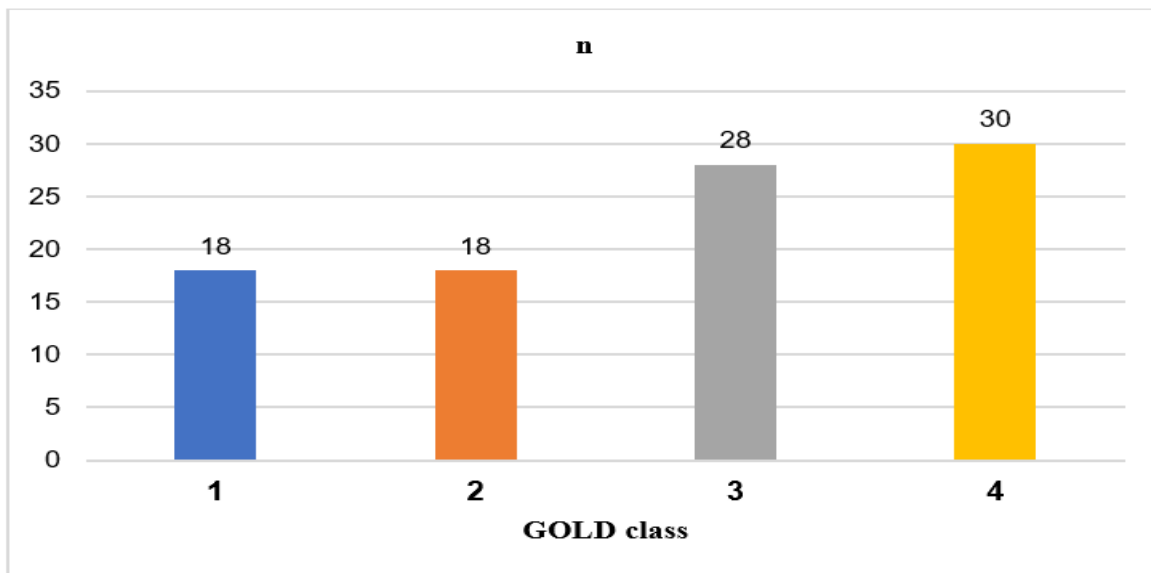
GOLD 2 - patients with moderate form of COPD (FEV1/FVC 50-80%)

GOLD 3 - patients with severe form of COPD (FEV1/FVC 30-50%)

GOLD 4-patients with very severe form of COPD (FEV1/FVC <30%)

In our study, Gold I and Gold II class had 18 patients each, Group III had 28 and Gold IV had 30 patients (Figure 1)

Figure 1. Distribution of patients in GOLD classification



In our study out of 94 patients with COPD, male gender was dominant with 64 patients in number. Their dominance was also expressed in the higher classes of Gold.

In our study all patients during admission and hospital stay were thoroughly examined with anamnesis, physical examination and electrocardiogram (ECG), as well as with basic and advanced echocardiographic assessment.

Echocardiographic parameters that were selected in our study, as indicators of right heart load were: right ventricle basal dimension (RV), right atrium (RA), right atrial area (RA area), S' wave of from Tissue Doppler echocardiography (TDI) estimated above the tricuspid annulus (S TDV DV), tricuspid annular systolic excursion (TAPSE), fractional area of change of the RV (FAC%), acceleration time of pulmonary artery of pulsed Doppler (AT a.pulm), systolic pulmonary artery pressure (SPAP) estimated by maximal tricuspid velocity on continuous Doppler and right atrial pressure, maximal velocity (V max) of tricuspid regurgitation on continuous Doppler, estimated myocardial performance index of the right ventricle (MPI DV), global strain of the right ventricle (Global strain of DV), estimated pulmonary vascular resistance (PVR), estimated dimension and collapsibility of vena cava inferior >50%.

The basal diameter of RV was measured in 4 chamber apical view, in end diastole at the level above the tricuspid annulus expressed in mm. DA dimension was measured in 4 chamber view, from the imaginary line of the tricuspid annulus, expressed in mm.7)8). S wave TDI is another measure for the longitudinal function of the right ventricle and it is used as a parameter for right ventricle systolic function. It is obtained by placing the marker on the free wall of the tricuspid annulus using tissue and pulse Doppler.8) TAPSE is obtained by placing the cursor on the free wall of the right ventricle at the level of the tricuspid annulus in 4 chamber view. The excursion of the tricuspid valve from the base to the apex is measured as the distance from the annulus to the apex.9). Fractional area of change of the RV (FAC%) gives us information for the global systolic function of the right ventricle expressed in percentage. The formula is: (EDA-ESA)/EDA X 100%, ie the difference in end-diastolic (EDA) and end-systolic area (ESA) divided by end-diastolic area and multiplied by 100.8). Acceleration time of pulmonary artery (AT a.pulm) is obtained by pulse Doppler, by placing the cursor just above the pulmonary valve while using short parasternal view. The pulse Doppler at the RVOT level usually has a symmetrical shape, with approximately the same duration of descent and ascent time of the curve. In patients with pulmonary hypertension there is a shorter descent time, or acceleration time. The occurrence of mid-systolic notch is another parameter that suggestible for pulmonary hypertension.8)

Systolic pulmonary artery pressure (SPAP) is obtained when tricuspid regurgitation rate and estimated right Atrial pressure (pDA) are put into Bernoulli equation, where value of pDA is the added pressure depending on the dimension and collapsibility of less of more than 50% of the inferior vena cava. 8)

Estimated myocardial performance index of the right ventricle (MPI DV) is an index used for early detection of right ventricular systolic and diastolic function. It is estimated by formula: isovolumetric contraction time (IVCT) + isovolumetric relaxation time (IVRT) divided by right ventricular ejection time (ET). These values are obtained when the cursor is placed on the free

wall of the right ventricle above the tricuspid annulus using tissue and pulse Doppler.8)9) In our study the parameters for MPI calculation were obtained from Tissue Doppler echocardiography (TDI). The Tissue Doppler RV MPI abnormal values was  $>0.55$ .

Global strain of the right ventricle (Global strain of DV) is estimated by speckle tracking modality. Obtained by analyzing the right ventricle in a focused apical window, with good visualization during the entire cardiac cycle independent of the angle. The endocardial borders of the right ventricle are marked as a region of interest. In our study interventricular septum was also marked. Normal value of RV global strain depends of the vendor, but if it is less than  $-19\%$ , it is in favor of reduced longitudinal function of RV. 8)

Estimation of collapsibility of vena cava is best done subcostal echo window. The measurement is made by placing the probe perpendicular to the inferior vena cava and 1-2 cm from the junction of the right atrium, while the patient is in supine position. The percentage of reduction in the diameter of inferior vena cava correlates with the pressure in the right atrium and determines the pulmonary vascular pressure.8)

Estimated pulmonary vascular resistance (PVR), it is estimated by formula in Wood units or dynes/sec/cm<sup>5</sup>.  $PVR = \frac{\text{maximal velocity of the tricuspid regurgitation (m/sec)}}{\text{flow velocity through the right ventricular outflow tract (cm)}} \times 10 + 0.16$ 10)

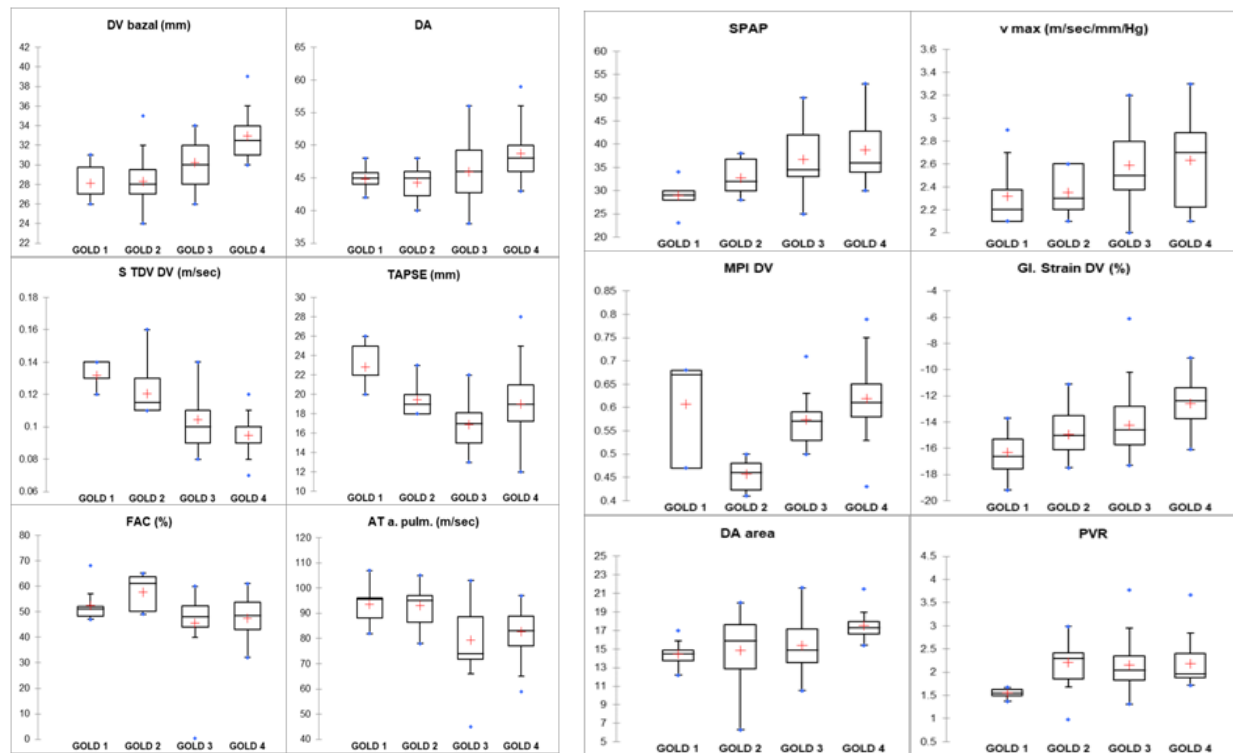
### **Results.**

All echocardiographic parameters were analyzed to understand their significance in disease progression in patients with COPD and increasing Gold classes.

Twelve of 13-teen echo-parameters evaluated in our study have quantitative values, while collapsibility of vena cava  $>50\%$  is a qualitative parameter. Quantitative values of the same echo-parameters (DA, S TDV DV, TAPSE, FAC, AT a.pulmonalis, SPAP, v.max, MPI DV, Stain DV, DA area, PVR and collapsibility of vena cava  $> 50\%$ ) were compared in terms of Gold classes by multivariate linear regression analysis.

With multivariate linear regression analysis, we got that there is a statistically significant correlation ( $p < 0,05$ ) with the following three echocardiographic parameters: S' TDV DV, DV basal and Global strain DV according to GOLD classes (Fig. 2)

Figure 2. Comparison of the values of echocardiographic parameters related to right heart load in relation to GOLD classes



In further analyses, binary categorization of GOLD classes into two binary categories was additionally used: lower GOLD classes (1 and 2), and more advanced GOLD classes (3 and 4). By applying logistic regression, a model was constructed that predicts these two categories of gold classes according to the value for each of the quantitative echo-parameters related to right heart load, but not for the quantitative parameter collapsibility of vena cava inferior >50%.

The parameter basal dimension of the right ventricle (RV basal) has the highest values and statistically increases the risk of progression in patients with milder form of the disease (GOLD 1 and 2), to more advanced ones by 1.814 times with high statistical significance ( $p < 0,01$ ). The parameters SPAP, AT a.pulm, GI strain of DV and TAPSE have somewhat lower values. The other echocardiographic parameters did not show a sufficiently high performance in predicting the gold classes according to the calculated logistic model (Tab.1).

To further determine the risk of COPD progression, this study also used a 2x2 tabular data analysis. Namely the echocardiographic parameters were classified according to reference values into two categories: normal and abnormal, and a binary categorization of gold classes into two categories was also used: lower GOLD classes (GOLD1 and 2) and more advanced (GOLD 3 and 4).

**Table 1.** Echocardiographic parameters and significance for progression of the diseases in patients with COPD

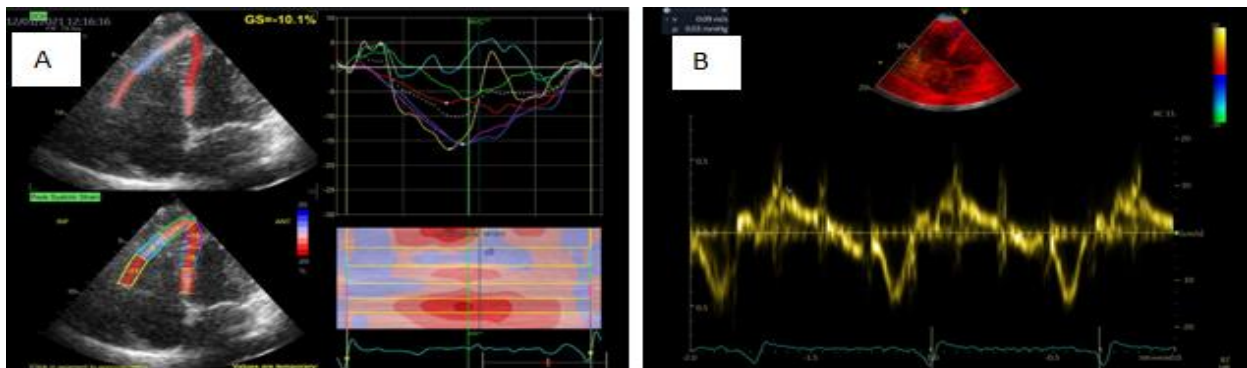
Parameters	values	GOLD 1+2		GOLD 3+4		P	RR (95% CI)
		n	%	n	%		
DV bazal(mm)	<33	35	97,22	38	65,52	0,0003	1,830 (1,439 - 2,326)
	>33	1	2,78	20	34,48		
	total	36	100,00	58	100,00		
DA (mm)	<50	36	100,00	42	72,41	0,0005	1,857 (1,512 - 2,281)
	>50	0	0,00	16	27,59		
	total	36	100,00	58	100,00		
S TDV DV (cm/sec)	>0,095	36	100,00	39	67,24	0,0001	1,923 (1,547 - 2,390)
	<0,095	0	0,00	19	32,76		
	total	36	100,00	58	100,00		
TAPSE (mm)	>17	36	100,00	39	67,24	0,0001	1,923 (1,547 - 2,390)
	<17	0	0,00	19	32,76		
	total	36	100,00	58	100,00		
FAC (%)	>35	36	100,00	55	94,83	0,1655	1,655 (1,401 - 1,954)
	<35	0	0,00	3	5,17		
	total	36	100,00	58	100,00		
AT a. pulm. (m/sec)	>105	4	11,11	0	0,00	0,0095	H. II.
	<105	32	88,89	58	100,00		
	total	36	100,00	58	100,00		
SPAP (mmHg)	<40	36	100,00	36	62,07	0,00002	2,000 (1,587 - 2,520)
	>40	0	0,00	22	37,93		
	total	36	100,00	58	100,00		
v max of TR (m/sec/mm/Hg)	<2,8	34	94,44	36	62,07	0,00047	1,782 (1,378 - 2,306)
	>2,8	2	5,56	22	37,93		
	total	36	100,00	58	100,00		
MPI DV TDI (msec)	<0,55	24	66,67	10	17,24	0,000001	2,720 (1,592 - 4,648)
	>0,55	12	33,33	48	82,76		
	total	36	100,00	58	100,00		
Gl. Strain DV (%)	<-14,5	26	72,22	20	34,48	0,00037	1,821 (1,270 - 2,610)
	>-14,5	10	27,78	38	65,52		
	total	36	100,00	58	100,00		

DA area (cm <sup>2</sup> )	<18	33	91,67	44	75,86	0,053	1,441 (1,075 - 1,932)
	>18	3	8,33	14	24,14		
	total	<b>36</b>	<b>100,00</b>	<b>58</b>	<b>100,00</b>		
PVR (wood units)	<1,5	5	13,89	2	3,45	0,061	2,253 (0,691 - 7,344)
	>1,5	31	86,11	56	96,55		
	total	<b>36</b>	<b>100,00</b>	<b>58</b>	<b>100,00</b>		
Collapsibility of vena cava >50%	>50%	31	86,11	13	22,41	$1,78 \times 10^{-9}$	3,046 (1,912 - 4,852)
	<50%	5	13,89	45	77,59		
	total	<b>36</b>	<b>100,00</b>	<b>58</b>	<b>100,00</b>		

As can be seen from the table 1, the analysis determined a statistically significant difference in 10 out of a total 13 echo-parameters related to right heart load, and a risk ratio with a confidence interval at 95% was calculated for 9 parameters. Similarly obtained with the logistic regression model, the parameter DV basal has a statistically highly significant association ( $p < 0,01$ ) with abnormal values (higher than 33mm). While patients who have higher values for this parameter have 1.8 times higher risk for disease progression in more advanced Gold 3 and Gold 4 classes than patients who have DV basal values below 33mm.

The parameter GL Strain DV and MPI of the right ventricle are markers for reduced longitudinal function of the right ventricle and have high sensitivity and specificity in disease progression. Their values are statistically relevant as the disease takes progression and it is seen in the table above. These parameters are related to the increase in the dimension of the right ventricle and the reduction of the longitudinal function that occurs before systolic dysfunction of the right ventricle. Parameters such as shortened acc time and pulmonary vascular resistance are statistically important in disease progression (as shown in table 1) with high sensitivity for but low specificity. sPAP and Vmax of TR are statistically relevant in disease progression and development of pulmonary hypertension especially in GOLD class 3 and 4.

The same principle of interpretation of the results is applicable for the rest of the parameters in the table.





**Figure 3.** (A) Reduction of global longitudinal strain of the right ventricle ( -10,1%); and (B) Reduction of the velocity of the S wave by TDI in patients with COPD in Gold class 4 (0,09m/s).

### Discussion

In our study we performed a series of correlation, analyzes and results, regarding echocardiographic parameters related to right heart function in patients with COPD with relevant world-wide studies. We once again confirmed the role of echocardiography as a non-invasive and repeatable method in this group of patients in their follow-up.

In a recent study of a larger series of COPD patients by a group of authors from Turkey, published 2015, it was found that right ventricular filling conditions can affect the right ventricular Tissue Doppler assessed wave S. Their results largely coincide ours, especially in the group of patients in the higher GOLD class (GOLD 3 and 4). All this is of particular importance because in patients with acute deterioration of the right ventricular parameters prognosis of disease progression is worse.<sup>11)</sup>

Regarding the index of myocardial performance in this group of patients, several studies have been published. In an observational and cross-sectional study in Nepal an analysis was done in patients with COPD where right ventricular dysfunction was evaluated through 2 echo-parameters, TAPSE and MPI of the right ventricle. TAPSE as an indicator for longitudinal right ventricular function, was reduced below reference value (17mm) in most of the patients in the study. This in other words means initial deterioration of right ventricular function. Myocardial performance index or MPI (as an index used for early detection of right systolic and diastolic impairment) was also analyzed using tissues Doppler, where most of the values were  $>0.55$ . In our study these two parameters were also evaluated and showed similar findings.<sup>12)13)14)</sup>

Another study done by a group of physicians in India in patients with COPD reported a positive correlation of TAPSE and MPI with pulmonary artery pressure and right ventricular dysfunction. Their study showed that TAPSE, MPI of the right ventricle, impaired right ventricular diastolic function are parameters that can be determined non-invasively by echocardiography and positively correlate with worsening of the disease. The higher the gold class is the worse echocardiographic parameters are obtained in terms of RV impaired function. In our study, we evaluated 13teen echo-parameters related to right heart load, where the parameter for the basal dimension of the right ventricle showed the strongest statistical difference. Also TAPSE, SPAP, GL strain of DV and shortened AT of a.pulm showed statistical significance moving from GOLD class 1 and 2 to GOLD class 3 and 4 in terms of right ventricular deterioration.<sup>12)13)14)</sup>

Additional statistic methods were used in our study to further determine the risk of COPD progression. We classified the echocardiographic parameters into two categories: normal and abnormal, and a binary categorization of gold classes into two categories: lower gold class (1 and 2) and more advanced gold class (3 and 4). As we mentioned in the result previously, basal dimension of RV had the highest statistical significance but also more subtle parameters such as GI strain of RV and MPI (as indicators for early deterioration of systolic and diastolic RV

function) showed positive correlation. SPAP and v max of tricuspid regurgitation showed positive correlation following more advanced gold classes as indicators for pulmonary hypertension development. TAPSE and S TDV DV as indicators for right ventricular longitudinal function, showed reduced values statistically significant in direction from lower Gold class (1 and 2) to more advanced.

In one study published couple years ago by the European society of pulmonology where patients with COPD were examined, confirmed that most of the patients have increased values of the basal dimensions of the right ventricle in 30%, and pulmonary artery hypertension in 19% of the respondents. Most of the patients had mild tricuspid regurgitation and only 2.8 % had moderate values of tricuspid regurgitation. They found that only a small percentage of patients had significant pulmonary hypertension. Additionally, another paper released recently in 2020, analyzed small group of patients with COPD. Increased values of the basal dimension of the right ventricle, increased area of the right atrium and increased values of pulmonary arterial pressure were obtained. Our study evaluated the same parameters such as basal dimensions of RV, SPAP and v max of tricuspid regurgitation, where we obtained similar i.e., identical results. 15)16)

From the data analyzed so far in our study, it is evident that S wave obtained with Tissue Doppler and Global longitudinal strain of the right ventricle obtained by speckle tracking echocardiography have the highest sensitivity and specificity for disease progression. The myocardial performance index is well correlated with tricuspid regurgitation which is basically manifestation of dilated right ventricle. The index reflects the degree of right ventricular weakness which is proportional to the rate of tricuspid regurgitation. This parameter was addressed in a small study in 2014 where its significance as a parameter in COPD patients was demonstrated. The study itself was significant because it indicated that FAC (%) of the right ventricle and MPI can be significant prognostic factors for right ventricular function independent of sPAP and TAPSE.17)

Global strain of the right ventricle determined noninvasively by echocardiography showed high sensitivity and specificity as a significant parameter in the assessment of right ventricular function. In a study done in China on a small group of patients with COPD where right heart echocardiographic parameters including global strain of the right ventricle were analyzed, found that the group of patients who had reduced values for Global strain of the right ventricle <-19%, had worse NYHA class and reduced values for TAPSE. This study analyzed the correlation of pulmonary hypertension and GLS of the right ventricle where it was found that patients with more pronounced pulmonary hypertension have worse values of degree of longitudinal deformation of the right ventricle. In our paper most of the patients in gold class 3 and 4 have lower values set for GLS of the right ventricle.

In one study published ten years ago, a correlation was made between two group of patients with COPD, with and without pulmonary hypertension. In the study it was confirmed that shortened AT on pulsed Doppler of the pulmonary valve, MPI and GLS are subtle and significant

especially in the early and subclinical form of the disease and thus the possibility to separate patients who have a mild degree of pulmonary hypertension.

This study showed that echocardiography has the power to show structural changes of the right heart in patients with COPD even when there is sub clinically reduced right ventricular function. Our study covered almost all the above-mentioned modalities and parameters and showed that the GLS and MPI index are positively correlated especially with higher gold classes.18)

Our study confirmed that the analysis of echo parameters related to right heart load showed statistically significant correlation ( $p < 0, 05$ ) in terms of GOLD classes in three echo values: increased basal dimension of the right ventricle (DV basal), decreased S wave velocity determined by TDI (S TDV DV), reduced longitudinal function of the right ventricle determined by Speckle tracking (GI strain of DV). These parameters were related to an increase of the dimensions of the right ventricle and reduction of the longitudinal function of the right ventricle that occurs before the systolic dysfunction of the right ventricle appears. The right ventricular basal parameter had the highest value in terms of predicting an increased risk of progression of patients with milder form of the disease (GOLD 1 and 2) to more advanced ones (GOLD 3 and 4) with high statistical significance.

**Conclusion:**

Prevalence of pulmonary hypertension has a linear relationship with severity of COPD and severe pulmonary hypertension is almost every time associated with development of right heart failure. Patient with more advanced stages of GOLD, especially in times of their exacerbation need more close monitoring because when permanent changes occur the success of the therapy is less. Echocardiography helps in early detection of cardiac complications in COPD cases giving time for early interventions. We suggest screening of all COPD patients for cardiac complications using echocardiography as a non-invasive and repeatable for their follow-up. Larger studies for COPD patients are warranted to define the exact time and echocardiographic parameters for their follow up.

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