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Fibrosis-4 Index for Prediction of the Severity of Acute Pulmary Embolism: Cross-sectional Research

Akut Pulmoner Embolinin Ciddiyetinin Tahmininde Fibrozis-4 İndeksi: Kesitsel Araştırma

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ABSTRACT Objective: In this study, we investigated whether the index of fibrosis-4 (fib-4), which is a parameter indicating liver fibrosis and stiffness, is related to the severity of acute pulmonary embolism (APE). **Material and Methods:** A total of 118 patients who were diagnosed with APE were divided into two groups according to hemodynamic status at the time of admission to the emergency department. Group 1 patients were high-risk patients with hemodynamic instability (42 patients, 24 male, mean age 66.2±13.6 years). Group 2 patients were non high-risk patients without hemodynamic instability (76 patients, 24 male, mean age 61.2±16.9 years). Biochemical parameters and cardiac markers were measured from venous blood at the time of admission. Right and left ventricular functions were examined using echocardiography. **Results:** Fib-4 scores were significantly higher in Group 1 than Group 2 (2.35±1.32 vs. 1.41±0.96, p=0.005). D-dimer, troponin and aspartate transaminase were significantly higher in Group 1 than in Group 2, and platelet count was significantly lower in Group 1 than in Group 2. The ejection fraction, tricuspid annular plane systolic excursion and fractional areal change were significantly lower in Group 1 than in Group 2. Correlation analysis showed that the fib-4 index correlated with hemodynamic and echocardiographic parameters that show the severity of pulmonary embolism, such as the pulmonary embolism severity index score. **Conclusion:** In patients presenting with APE, the fib-4 index, calculated at the time of presentation, is a parameter that can be used to calculate the severity of the disease and the risk stratification.

Keywords: Fibrosis-4 index; pulmonary embolism; liver fibrosis; transaminase

ÖZET Amaç: Bu çalışmada, karaciğer fibrozunu ve sertliğini gösteren parametrelerden birisi olan fibrozis-4 (fib-4) indeksinin akut pulmoner emboli (APE) şiddeti ile ilişkili olup olmadığını araştırdık. **Gereç ve Yöntemler:** APE tanısı alan toplam 118 hasta acil servise başvuru sırasındaki hemodinamik durumlarına göre 2 gruba ayrıldı. Grup 1 hastaları, hemodinamik dengesizliği olan yüksek riskli hastalardı (42 hasta, 24 erkek, ortalama yaş 66,2±13,6 yıl). Grup 2 hastalar, hemodinamik dengesizliği olmayan yüksek riskli olmayan hastalardı (76 hasta, 24 erkek, ortalama yaş 61,2±16,9 yıl). Biyokimyasal parametreler ve kardiyak belirteçler başvuru sırasında venöz kandan ölçüldü. Sol ve sağ ventrikül fonksiyonları transtorasik ekokardiyografi ile incelendi. **Bulgular:** Grup 1'de fib-4 skorları Grup 2'ye göre anlamlı olarak yüksekti (2,35±1,32'ye karşı 1,41±0,96, p=0,005). Grup 1'de D-dimer, troponin ve aspartat transaminaz Grup 2'ye göre anlamlı olarak daha yüksekti ve trombosit sayısı Grup 1'de Grup 2'ye göre anlamlı olarak daha düşüktü. Grup 1'de ejeksiyon fraksiyonu, triküspid anüler düzlem sistolik ayrılma ve fraksiyonel alan değişikliği Grup 2'ye göre anlamlı olarak daha düşüktü Korelasyon analizi, fib-4 indeksinin, pulmoner embolizm şiddet indeks skoru gibi pulmoner embolinin şiddetini gösteren, hemodinamik ve ekokardiyografik parametrelerle ilişkili olduğunu gösterdi. **Sonuç:** APE ile başvuran hastalarda, başvuru anında hesaplanan fib-4 indeksi, hastalığın şiddetini ve risk sınıflandırmasını hesaplamak için kullanılabilecek bir parametredir.

Anahtar Kelimeler: Fibrozis 4-indeksi; pulmoner emboli; karaciğer fibrozu; transaminaz

Acute pulmonary embolism (APE) is a serious and potentially fatal disease. Despite recent advances in the diagnosis and treatment of APE, delays in the diagnosis of pulmonary embolism (PE) may cause serious consequences such as high mortality and morbidity.[1] Short-term adverse results are attributed to the severity of hemodynamic instability of the disease. The Pulmonary Embolism Severity Index (PESI) is the one of the indices with the most relevant information. It has been obtained from patients

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with APE who admitted to the hospitals and evaluated extensively.[2] However, some researchers have reported that the PESI or the simplified PESI may not identify high-risk patients. Re-evaluation of low-risk patients 48 weeks after the admission will yield better results in some PE patient groups.[3,4] Besides, evaluation of right ventricular functions with echocardiography and myocardial injury markers play a role in risk stratification. The search for the role of laboratory parameters in determining cheaper, easier and more common laboratory parameters is still ongoing. The fibrosis-4 (fib-4) index is a relatively new parameter in liver fibrosis diagnosis, discovered in the year 2006. The fib-4 index is calculated by measuring aspartate transaminase (AST) and alanine transferase (ALT) as well as the combination of age and platelet counts, and it is thought that it can identify various liver diseases as well as liver stiffness indirectly.[5,6] Because the right ventricular interactions in APE are thought to be related to the liver, we aimed to investigate whether the index of fib-4 is related to the severity of APE.

MATERIAL AND METHODS

A total of 118 patients (48 male, 70 female, mean age 63.0±16.1 years) who were diagnosed with APE were included in the study. Detailed medical history of the patients and comorbidities were reported to the emergency department. The drugs they used were recorded in detail. After a detailed physical examination, pulmonary embolism severity indices (PESI scores) were calculated. Oxygen saturation upon hospital admission was evaluated, D-dimer, troponin, electrocardiography, echocardiography, lower extremity venous Doppler, contrast-enhanced computed tomography and pulmonary angiography were performed and PE was diagnosed. Those who previously had chronic liver disease, previously used drugs that could be toxic to the liver or who could have elevated liver enzymes were excluded. Patients with previously diagnosed right, left and biventricular heart failure were also excluded. The patients were divided into two groups according to the hemodynamic status at the time of admission to the emergency department. Hemodynamic instability was defined as cardiac arrest, persistent hypotension (systolic BP < 90 mmHg or a systolic BP drop>40 mmHg for more than 15 minutes, not caused by new-onset arrhythmia, hypovolaemia or sepsis), obstructive shock (systolic BP < 90 mmHg or vasopressors required to achieve a BP > 90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion).

Group 1 patients were high-risk patients with hemodynamic instability (42 patients, 24 male, mean age 66.2±13.6 years). Group 2 were non high-risk patients without hemodynamic instability (76 patients, 24 male, mean age 61.2±16.9 years).

ETHICAL CONSIDERATION

All patients approved and signed the informed consent form. Local ethics committee (İstanbul Training and Research Hospital, ID number: 1839, 2019) approved the study. The study was was compatible with the 2008 Declaration of Helsinki.

Laboratory

A 10 to 15 ml venous blood sample was obtaioned from superficial veins of the forearm from each patient on admission. Cell blood count, urea, creatinine, AST, ALT, blood glucose and lipid panel were measured. Troponin I and D-dimer were also measured. Estimated GFR was calculated with the MDRD equation (abbreviated Modification of Diet in Renal Disease). The fib-4 index was calculated according to following formula:[7,8]

$$\frac{\text{Age (years)} \times \text{AST (IU/L)}/\text{platelet count } (10^9/\text{L})}{\sqrt{\text{ALT (IU/L)}}}$$

Electrocardiography

Standard 12-lead surface ECGs were recorded from patients in supine position (25 mm/S paper speed, 10 mV/mm (Marquette Case, Hellige Medical System, Cardiosmart Hellige Instrument Company, Freiburg, Germany).

Transthoracic Echocardiography

Standard electrocardiographic procedures were performed using a Philips EPIQ 7 device (Philips Healthcare, Andover, MA, USA). Measurements were obtained according to the American Society of Echocardiography guidelines. Measurements were

calculated from average of 3 cardiac cycles. Left ventricle dimensions and wall thickness were obtained from the parasternal long axis with an M-mode. The parameters of mitral inflow were recorded on apical 4- chamber views including diastolic early (E) velocity, late transmitral flow velocity (A), E to A ratio (E/A), and the mitral E wave deceleration time. LV ejection fraction was measured using Simpson's method. Tricuspid Annular Plane Systolic Excursion (TAPSE) is measured by aligning an M-mode cursor parallel with the RV free wall as it meets the tricuspid annulus from the RV apical four-chamber view. Fractional area change was calculated by subtracting the systolic area from the diastolic area and dividing the result by the original diastolic area. Diastolic and systolic eccentricity indices were calculated as the ratio of diameters in the parasternal short axis at the level of the papillary muscle. Isovolumic acceleration (IVA) was calculated by dividing the maximal isovolumic myocardial velocity to the time to peak velocity.

Venous Doppler

Venous Doppler examinations were performed using the Toshiba Xario (SSA-660A Cardiac - Vascular Ultrasound machine, Japan).

Computerized Tomography

Computerized tomography was performed with a 128-slice CT scanner (Philips Ingenuity, Philips Medical System, Netherlands). It was used to acquire images of the thorax during breath hold after inspiration. Intravenous injection of contrast was at rates of 1ml/kg and 4 ml/sec. (RadiAnt DICOM viewer, 4.6.518450 864-bit, Poland).

STATISTICAL ANALYSIS

SPSS 18.0 software package was used for analyzing study data (SPSS, Chicago, IL, USA). The numerical variables were expressed as the mean±standard deviation, and non-normally distributed variables were expressed with the median. Categoric variables were expressed as frequency (n) and percentage (%).The Shapiro-Wilk test was used to evaluate the normal distribution of numerical variables. Normally distributed variables were compared with independent samples t-tests and the Mann-Whitney U test was used for the comparing the variables without normal distributions. A Spearman correlation analysis was performed to assess the relationship between variables. Multivariate regression analysis was performed to evaluate the independent effects of age, PESI score, TAPSE, IVA, FAC, ejection fraction (EF), fib-4 variables on hemodynamic instability. The confidence interval was set at 95%. A p value of less than 0.05 was considered statistically significant.

RESULTS

Demographic data of the patients, blood pressure, heart rate and PESI scores are compared in Table 1. The fib-4 scores were significantly higher in Group 1 than in Group 2 (2.35±1.32 vs. 1.41±0.96, p=0.005) (Table 1). D-dimer, troponin and AST values were significantly higher in Group 1 than in Group 2 (Table 1). The platelet level was significantly lower in Group 1 than Group 2 (Table 1).

In terms of echocardiographic parameters, the EF, TAPSE, aortic velocity and FAC were significantly lower in Group 1 than in Group 2, and pulmonary artery systolic pressure was significantly higher in Group 1 than in Group 2 (Table 2).

Correlation analysis showed that the fib-4 index correlated with hemodynamic and echocardiographic parameters that showed the severity of PE (Table 3). There was a significant correlation between the classical PESI score and the fib-4 index (r=0.50, p<0.001). In the regression analysis including the whole study group, the model was created by including age, EF, TAPSE, IVA, troponin level, PESI score, FAC and fib-4 index as predictors of hemodynamic instability (Table 4). In the regression analysis, fib-4 level was the main parameter with the presence of hemodynamic instability (Table 4).

DISCUSSION

The main result of our study was that the fib-4 index, which is a parameter of liver stiffness, can be used as a parameter to indicate the severity of APE. The fib-4 index may be correlated with various indices and laboratory and echo findings in patients with PE. PE is a disease with a serious mortality rate. The guide-

TABLE 1: Demographic features, clinical characteristics and laboratory parameters of the groups.

	Grup 1 (n=39)	Grup 2 (n=70)	p value
Age (years)	66.2±13.6	61.2±16.9	0.08
Gender (M)	24	24	0.07
BMI (kg/m^2)	28.5±5.4	28.7±5.9	0.82
Systolic blood pressure (mm Hg)	89.8±13.7	130.7±19.7	<0.001
Diastolic blood pressure (mm Hg)	58.5±10.7	76.8±10.4	<0.001
Heart rate (beat/min)	103.0±13.5	98.1±15.5	0.07
D-dimer (mg/mL)*	4.92 (0.95-20.9)	2.76 (2.04-7.02)	0.07
Troponin I (pg/mL)*	0.176 (0.04-5.67)	0.081 (0.03-2.94)	0.35
PESI score	133.7±26.2	83.8±26.4	<0.001
Fib-4 index	2.35±1.32	1.41±0.96	<0.001
Urea (mg/dL)	42.7±20.7	44.3±25.0	0.64
Creatinine (mg/dL)	0.99±0.36	1.12±1.35	0.53
AST (mg/dL)	23 (10-150)	22 (15-174)	0.02
ALT (mg/dL)*	21.5 (3-288)	15 (7-113)	0.52
WBC (x10^3/L)*	10.7±5.4	10.3±3.8	0.60
Platelet count (x10^3/L)	208.3±71.5	274.0±91.5	<0.001
MPV (fL)	0.22±0.07	0.26±0.08	0.27
Hypertension (n)	28	40	0.14
Diabetes mellitus (n)	15	20	0.28
Smoking (n)	19	23	0.10
Deep vein thrombosis (n)	15	23	0.54
Pregnancy (n)	0	1	0.45
History of operation (n)	12	22	0.96
History of cancer (n)	13	16	0.23
History of stroke (n)	6	4	0.09

*Median values were expressed because of the abnormal distribution.

BMI: Body mass index; PESI: Pulmonary embolism severity index; AST: Aspartate transaminase; ALT: Alanine transaminase; WBC: White blood cell; MPV: Mean platelet volume.

lines of the risk stratification of acute PE patients are based on three criteria: hemodynamic status and initial clinical features of the patient, right ventricular dysfunction displayed on echo or pulmonary angiogram and an increase in cardiac biomarkers such as troponin and natriuretic peptides.[9] It is essential to make the diagnosis as quickly as possible and to determine the risk stratification of the disease. In addition to these parameters, the PESI score was also found to be a highly effective and reliable method in determining the severity of the disease.[10] In fact, Moors et al. reported that multiple calculations of PESI score in the patient's follow-up may provide a higher reliability in the follow-up of parameters that may vary in this process.[10]

The fib-4 index is an easily calculated index that includes simple biochemical parameters such as platelet count, ALT and AST as well as the age of the

TABLE 2: Echocardiographic parameters of the groups.

	Grup 1 (n=39)	Grup 2 (n=70)	p value
LVEDD (cm)	4.27±0.72	4.20±0.70	0.66
LVESD (cm)	2.89±0.72	2.75±0.56	0.36
IVS (cm)	1.11±0.15	1.15±0.17	0.45
PW (cm)	1.05±0.14	1.05±0.20	0.83
Pulmonary velocity (m/s)	0.66±0.18	0.78±0.15	0.03
Aortic velocity m/s)	1.08±0.20	1.29±0.24	0.008
TAPSE (mm)	1.72±0.37	2.14±0.42	<0.001
IVA (m/s^2)	0.25±0.05	0.25±0.45	0.37
EF	54.1±5.1	57.1±5.6	0.02
PABs (mm Hg)	48.6±16.1	40.0±12.3	0.01
FAC (%)	30.2±8.5	44.7±11.5	<0.001
Systolic eccentricity index	1.86±0.20	1.62±0.55	0.34
Diastolic eccentricity index	1.33±0.24	1.20±0.23	0.04

LVEDD: Left ventricle end-diastolic diameter; LVESD: Left ventricle end-systolic diameter; IVS: Interventricular septum; PW: Posterior wall; TAPSE: Tricuspid annular plane systolic excursion; IVA: Isovolumic acceleration; EF: Ejection fraction; PABs: Pulmonary artery systolic pressure; FAC: Fractional area change.

TABLE 3: Correlation of fib-4 index with hemodynamic, echocardiographic and laboratory parameters.

	r value	p value
Troponin I	0.30	0.002
D-dimer	0.15	0.24
PABs	0.33	0.001
EF	-0.34	<0.001
TAPSE	-0.39	0.001
Systolic blood pressure	-0.25	0.008
Diastolic blood pressure	-0.31	0.001
Heart rate	0.06	0.51
PESI score	0.50	<0.001

PABs: Pulmonary artery systolic pressure; EF: Ejection fraction; TAPSE: Tricuspid annular plane systolic excursion; PESI: Pulmonary embolism severity index.

TABLE 4: Standartized beta coefficients, t-statistics and p values for lineer regression analyses predicting hemodynamic instability for patients with acute pulmonary embolism.

	βeta	t value	p value
PESI score	0.078	0.222	0.838
Age	-0.172	-0.220	0.840
Troponin	0.349	1.146	0.335
FAC	-0.514	-1.151	0.333
TAPSE	0.475	2.145	0.121
EF	0.090	0.271	0.804
IVA	-0.231	-0.794	0.485
Fibrosis-4	0.836	3.046	0.038

PESI: Pulmonary embolism severity index; FAC: Fractional area change; TAPSE: Tricuspid annular plane systolic excursion; EF: Ejection fraction; IVA: Isovolumic acceleration.

patient. It is a well-proven and internationally accepted parameter showing the degree of liver fibrosis.[7,8] The fib-4 index has been shown to be associated with increased mortality in the general population.[10] The index has been used not only in hepatitis C virus patients but also in HIV and in fatty and non-alcoholic fatty liver disease patients.[11,12] The main condition that determines the severity of the patient in the acute phase of PE is how much the right ventricular functions are affected. In this case, the pressure of the acute right cavities increases, and the septum shifts the flow in the left ventricular outflow tract. On the other hand, sudden deterioration of right ventricular function causes systemic venous congestion, thus affecting liver blood flow. Systemic venous congestion causes neurohormonal activation, such as reticular activating system, leading to a reduction in plasma natriuretic peptides, progression of insufficiency and further deterioration of organ failure.[13-15] These factors may lead to the worsening of right ventricular functions in the acute period. Eventually, increased central venous pressure leads to liver stiffness.[16-18] Increased liver stiffness may cause increased liver enzymes in the blood.

Biomarkers, especially cardiac troponins (cTn), are considered to be highly sensitive for myocardial damage, and it is known that both for risk stratification and the burden of PE on the right ventricle in patients presenting with acute PE.[19,20] Tong et al. investigated the efficacy of 16 separate biomarkers in predicting the short and long-term prognosis in patients with PE. As a result of the study, they showed that natriuretic peptides, heart type fatty acid binding protein, as well as troponin levels were among the best parameters in predicting the short and long-term prognosis and showing the severity of PE.[21] In our study, we found that in patients with APE with hemodynamic instability, echocardiographic parameters such as FAC, TAPSE and eccentricity indices that show the effect of APE on the right ventricle were impaired. However, although high sensitive troponin values were high in the group with hemodynamic instability, it was not statistically significant. This may be due to the low number of patient group.

In our study, we found significantly higher fib-4 indices in acute PE patients with impaired hemodynamics. We believe that the fib-4 index in acute PE patients can be used as a simple, easily accessible parameter in the differentiation of patients according to hemodynamics. We found that the fib-4 index was significantly associated particularly with PESI score and troponin I and also EF, TAPSE and diastolic blood pressure. This relationship suggests that the fib-4 index may be effective in determining the severity of PE and risk stratification in patients with acute PE.

STUDY LIMITATIONS

The main limitation of our study was the small population of study groups. Our study was a cross-sectional study. We included patients who were meeting the inclusion criteria at a certain period of time. Some correlations tested in this study were weak. We believe that these correlations would have been stronger if the number of high-risk patients were higher. Our inability to measure BNP levels was another limitation of our study.

CONCLUSION

In conclusion, in patients presenting with APE, the index of fibrosis-4, calculated at the time of admission, can be used in predicting the severity of the disease. The widespread use of the parameters it contains, the ease of measurement and the fact that it is an inexpensive method are advantages of this method. Larger scale prospective studies are needed for more widespread use of the index.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** Turgut Karabağ, Fulden Mutlu; **Design:** Turgut Karabağ, Fulden Mutlu;**Control/Supervision:** Turgut Karabağ; **Data Collection and/or Processing:** Süleyman Çağan Efe, Fulden Mutlu; **Analysis and/or Interpretation:** Turgut Karabağ; **Literature Review:** Turgut Karabağ, Süleymen Çağan Efe; **Writing the Article:** Turgut Karabağ, Süleymen Çağan Efe; **Critical Review:** Turgut Karabağ, Fulden Mutlu; **References and Fundings:** Turgut Karabağ; **Materials:**Turgut Karabağ.*

REFERENCES

1. Barra SN, Paiva L, Providência R, Fernandes A, Marques AL. A review on state-of-the-art data regarding safe early discharge following admission for pulmonary embolism: what do we know? Clin Cardiol. 2013;36(9):507-15. [Crossref] [Pubmed] [PMC]
2. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med. 2005;172(8):1041-6. [Crossref] [Pubmed] [PMC]
3. Van der Schouw YT, Verbeek AL, Ruijs JH. ROC curves for the initial assessment of new diagnostic tests. Fam Pract. 1992;9(4):506-11. [Crossref] [Pubmed]
4. Tamizifar B, Fereyduni F, Esfahani MA, Kheyri S. Comparing three clinical prediction rules for primarily predicting the 30-day mortality of patients with pulmonary embolism: The "Simplified Revised Geneva Score," the "Original PESI," and the "Simplified PESI". Adv Biomed Res. 2016;5:137. [Crossref] [Pubmed] [PMC]
5. Sato Y, Yoshihisa A, Kanno Y, Watanabe S, Yokokawa T, Abe S, et al. Liver stiffness assessed by Fibrosis-4 index predicts mortality in patients with heart failure. Open Heart. 2017;4(1):e000598. [Crossref] [Pubmed] [PMC]
6. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al; APRICOT Clinical Investigators. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317-25. [Crossref] [Pubmed]
7. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ; Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009;7(10):1104-12. [Crossref] [Pubmed] [PMC]
8. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology. 2007;46(1):32-6. [Crossref] [Pubmed]
9. Barco S, Mahmoudpour SH, Planquette B, Sanchez O, Konstantinides SV, Meyer G. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis. Eur Heart J. 2019;40(11):902-10. [Crossref] [Pubmed] [PMC]
10. Moores L, Zamarro C, Gómez V, Aujesky D, García L, Nieto R, et al; Instituto Ramón y Cajal de Investigación Sanitaria Pulmonary Embolism Study Group. Changes in PESI scores predict mortality in intermediate-risk patients with acute pulmonary embolism. Eur Respir J. 2013;41(2):354-9. [Crossref] [Pubmed]
11. Unalp-Arida A, Ruhl CE. Liver fibrosis scores predict liver disease mortality in the United States population. Hepatology. 2017;66(1):84-95. [Crossref] [Pubmed] [PMC]
12. Kariyama K, Nouso K, Toyoda H, Tada T, Hiraoka A, Tsuji K, Itobayashi E, et al. Utility of FIB4-T as a Prognostic Factor for Hepatocellular Carcinoma. Cancers (Basel). 2019;11(2):203. [Crossref] [Pubmed] [PMC]
13. Jain MK, Seremba E, Bhore R, Dao D, Joshi R, Attar N, et al. Change in fibrosis score as a predictor of mortality among HIV-infected patients with viral hepatitis. AIDS Patient Care STDS. 2012;26(2):73-80. [Crossref] [Pubmed] [PMC]
14. Kalra PR, Anagnostopoulos C, Bolger AP, Coats AJ, Anker SD. The regulation and measurement of plasma volume in heart failure. J Am Coll Cardiol. 2002;39(12):1901-8. [Crossref] [Pubmed]

15. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53(7):589-96. [Crossref] [Pubmed] [PMC]
16. Mohamed BA, Schnelle M, Khadjeh S, Lbik D, Herwig M, Linke WA, et al. Molecular and structural transition mechanisms in long-term volume overload. Eur J Heart Fail. 2016;18(4):362-71. [Crossref] [Pubmed] [PMC]
17. Jalal Z, Iriart X, De Lédinghen V, Barnetche T, Hiriart JB, Vergniol J, et al. Liver stiffness measurements for evaluation of central venous pressure in congenital heart diseases. Heart. 2015;101(18):1499-504. [Crossref] [Pubmed]
18. Millonig G, Friedrich S, Adolf S, Fonouni H, Golriz M, Mehrabi A, et al. Liver stiffness is directly influenced by central venous pressure. J Hepatol. 2010;52(2):206-10. [Crossref] [Pubmed]
19. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation. 2007;116(4):427-33. [Crossref] [Pubmed]
20. Demir N, Ekim N, Oguzulgen IK, Bukan N. The value of cardiac troponins in diagnosis and differential diagnosis of pulmonary embolism. J Pulmon Resp Med. 2012;2(8):1-6. [Link]
21. Tong C, Zhang Z. Evaluation factors of pulmonary embolism severity and prognosis. Clin Appl Thromb Hemost. 2015;21(3):273-84. [Crossref] [Pubmed]