ORIGINAL ARTICLE

Clinical Significance of Impaired Liver Function Tests in Decompensated Heart Failure

Significado clínico de las alteraciones en los tests de función hepática en la insuficiencia cardíaca descompensada

ENRIQUE B. FAIRMAN, VÍCTOR M. MAURO, ADRIÁN A. CHARASK, YANINA B. CASTILLO COSTA, SANTIAGO E. MARRODÁN, EMILIANO G. SPAMPINATO, ALESIS RAFFAELI, FRANCO BOTTINI, CARLOS M. BARRERO

ABSTRACT

Background: Therapeutic progress in chronic heart failure has not been reflected in decompensated patients, compelling the need for new therapeutic and prognostic tools. Although liver function tests are part of routine admission studies, their clinical significance is not clearly established.
Objective: The aim of this study was to evaluate the prognostic relevance of liver function tests in decompensated heart failure.
Methods: The study analyzed the prevalence and in-hospital mortality association of elevated (at least twice the normal value) total bilirubin (TB), alkaline phosphatase (APh) and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in 700 consecutive patients admitted into two coronary care units due to decompensated heart failure, with liver function tests at admission, and no previous liver disease.
Results: In 20.8% of cases, patients presented some abnormal liver function test: 6%, increased TB, 12.6% increased ALT or AST and 12.6% increased APh.
In the univariate analysis [(OR (95% CI)], any abnormal liver function test [2.34 (1.18-4.65)], TB [4.05 (1.66-9.83)], ALT/AST [3.56 (1.72-7.34)] but not APh was associated with higher in-hospital mortality. In the multivariate model, cardiogenic shock [9.48 (2.31-38.78)], TB [3.61 (1.29-10.04)], AST/ALT [2.83 (1.28-6.25)], renal failure at admission [3.55 (1.48-8.49)] and history of chronic obstructive pulmonary disease [2.66 (1.21-5.87)] were independently associated with mortality.
Conclusions: Accessible tests such as liver function assessment provide additional prognostic information at admission.
In an unselected patient population, abnormal liver function may probably express increased vulnerability rather than hemodynamic impairment.

Key words: Heart Failure - Liver Function Tests - Prognosis

RESUMEN

Introducción: Los progresos terapéuticos en la insuficiencia cardíaca crónica no se han reflejado en los pacientes descompensados, por lo que son necesarias nuevas herramientas terapéuticas, pero también pronósticas. Pese a formar parte de la rutina de ingreso, el significado pronóstico del hepatograma no es claro.
Objetivo: Evaluar la utilidad pronóstica del hepatograma en la insuficiencia cardíaca descompensada.
Material y métodos: En 700 pacientes con insuficiencia cardíaca, admitidos en forma consecutiva en dos unidades coronarias, con hepatograma de ingreso disponible y sin alteración conocida de la función hepática, se analizaron la prevalencia y la asociación con mortalidad hospitalaria de la elevación (al menos duplicación del valor normal) de la bilirrubina total (BT), la fosfatasa alcalina (FAL) y la alanina aminotransferasa (ALT) o la aspartato aminotransferasa (AST).
Resultados: El 20,8% de los pacientes tuvieron alguna alteración del hepatograma, el 6% presentaron aumento de BT, el 12,6% de ALT o AST y el 12,6% de FAL.
En el análisis univariado [OR (IC 95%)], alguna alteración del hepatograma [2,34 (1,18-4,65)], de BT [4,05 (1,66-9,83)], de ALT/AST [3,56 (1,72-7,34)] pero no de FAL se asoció con mayor mortalidad hospitalaria. En el modelo multivariado, el shock cardiogénico [9,48 (2,31-38,78)], la BT [3,61 (1,29-10,04)], la ALT o la AST [2,83 (1,28-6,25)], la insuficiencia renal al ingreso [3,55 (1,48-8,49)] y el antecedente de enfermedad pulmonar obstructiva crónica [2,66 (1,21-5,87)] se asociaron en forma independiente con mortalidad.
Conclusiones: Datos accesibles como el hepatograma aportan información pronóstica al ingreso.
En una población no seleccionada de pacientes, es probable que la alteración del hepatograma exprese mayor vulnerabilidad que compromiso hemodinámico.

Palabras clave: Insuficiencia cardíaca - Pruebas de función hepática - Pronóstico

Abbreviations

ALT	alanine aminotransferase	**IQR**	Interquartile range
AST	Aspartate aminotransferase	TB	Total bilirubin
APh	Alkaline phosphatase		

Rev Argent Cardiol 2017;85:210-215. http://dx.doi.org/10.7775/rac.v85.i3.10288

Received: 02/25/2017 - *Accepted:* 05/06 /2017

Address for reprints: Dr. Enrique B. Fairman - (4025) Juncal 3002 - Buenos Aires, Argentina - e-mail: enriquefairman@yahoo.com
Clínicas Bazterrica and Santa Isabel. Ciudad de Buenos Aires

INTRODUCTION

There is an unquestionable progress in the treatment of heart failure. However, the benefits are especially limited to outpatients with impaired systolic function (1).

Decompensated heart failure represents the main cause of hospitalization among patients over 65 years of age and yet there has been no relevant progress in its therapeutic strategy (2-4). In this context, the better understanding of its pathophysiology and prognostic indices emerges as very relevant for the decompensated patient.

It is known that the consequences of heart failure are systemic, generating in many patients deterioration in several organs. Probably, the cardiorenal syndrome is the most studied in the decompensated patient due to the clear relationship between heart failure and renal dysfunction. (5).

The link between liver function and heart failure, especially in advanced stages, has been raised in different conditions, leading to the explanation of its pathophysiology through a hepatorenal or even cardiohepatorenal syndrome (6).

However, there is limited information on the association between abnormal liver function tests and outcome in patients with decompensated heart failure.

The present study aims to establish the prognostic significance of abnormal liver function tests in patients admitted for decompensated heart failure and to attempt the interpretation of their pathophysiological rationale.

METHODS

All patients with a main diagnosis of decompensated heart failure admitted into two coronary care units of the City of Buenos Aires were recruited between 2010 and 2015. A retrospective, observational, consecutive study was performed of the 723 hospitalized patients with this diagnosis.

The inclusion criteria considered clinical diagnosis of heart failure as the main cause of admission to the coronary care unit according to compatible symptoms and signs. All patients included should have a liver function test that included total bilirubin (TB), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) and alkaline phosphatase (APh) within 24 hours of admission.

Patients in whom the diagnosis of heart failure was secondary to another acute event (acute coronary syndrome, acute atrial fibrillation or sepsis) or those with known previous liver disease were excluded from the study.

The variables analyzed in the liver function test were TB, ALT and/or AST (ALT/AST) and APh. For the purposes of the present study, admission liver function tests with twofold increase in the normal values of TB, APh or (ALT/AST) were considered abnormal. The normal upper limit values for the laboratory tests of both institutions were TB 1.10 mg/dl; APh 250 U/L in the period 2010-2013, and 104 U/L in the period 2014-2015; ALT 36 U/l and AST 28 U/L. We sought to evaluate the relationship between abnormal admission liver function tests with in-hospital mortality and also their significance as an independent variable.

Statistical analysis

Continuous variables are expressed as median and 25%-75% interquartile range (IQR), using Student's t test or the Wilcoxon test to compare between two groups, as appropriate. Discrete variables are expressed as percentage using the chi-square test to establish statistical significance. The risk ratio was expressed as odds ratio (OR) and its corresponding 95% confidence interval (95% CI). A two-tailed p value ≤ 0.05 was considered statistically significant.

A multivariate logistic regression model was used to analyze the risk of in-hospital mortality, including variables usually associated with prognosis or that would have been significantly associated with prognosis in the univariate analysis of the present study. This analysis was performed using EpiInfo 7 software.

Ethical considerations

The study was evaluated and approved by the Ethics Committee and the Scientific Committee of both institutions.

RESULTS

General data

Between January 2010 and December 2015, 723 patients were hospitalized with heart failure as main diagnosis. In 23 of these patients, an admission liver function test could not be obtained and as there were no patients with known previous liver disease, the analysis was finally performed on a total of 700 patients.

The population characteristics are shown in Table 1. Median age was 81 years (IQR: 73-87), 87.5% were over 65 years of age and 48.7% were women. In 42.9% of cases there was preserved systolic function with ejection fraction greater than 0.50. History of atrial fibrillation and previous myocardial infarction was 33.6% and 22.9%, respectively.

Congestion was the most frequent presentation (61%), with a low prevalence of patients in cardiogenic shock (1.7%). Median systolic blood pressure at admission was 140 mmHg (IQR 120-170) and the average heart rate was 90 beats per minute (IQR 75.5-100).

Regarding outcome; in-hospital mortality was 5.4% and hospital stay was 6 days (IQR 4.5-9).

Analysis based on liver function tests

An abnormal liver function test was observed in 20.8% of patients. The prevalence of altered TB was 6%, while that of APh and ALT/AST was 12.6% in both cases (see Table 1).

Table 1 shows that patients with some degree of altered liver function test presented greater proportion of systolic function deterioration (65.7% vs. 54.7%), and although with a very low prevalence, there was a greater proportion of severe forms such as anasarca or low cardiac output.

Prognostic significance of abnormal liver function tests

The univariate analysis of mortality predictors (Table 2 and Figure 1) showed that elevated TB [OR 4.05 (1.66-9.83); $p<0.01$], and ALT/AST [OR 3.56 (1.72-7.34); $p<0.01$] were associated with an increased risk of in-hospital mortality, wheras APh was not a predic-

Table 1. Baseline characteristics according to abnormal liver function test

	Total	Abnormal LFT	p (vs normal LFT)	Abnormal TB	p (vs normal TB)	Abnormal APh	p (vs normal APh)	Abnormal ALT/AST	p (vs normal ALT/AST)
n (%)	700(100)	146(20.8)		42(6)		88(12.6)		88(12.6)	
Age, median (IQR)	81 (73-87)	79 (69-85)	<0.01	79 (71-85.5)	0.0222	85 (69-85)	ns	80 (72.5-86.5)	0.0169
Women, %	48.7	54.1	ns	71.4	0.0035	43.7	ns	52.3	ns
Diabetes, %	25.1	28.7	ns	16.7	ns	25	ns	30.7	ns
Dyslipidemia, %	34.3	30.8	ns	26.2	ns	18.7	0.0080	33	ns
Renal failure, %	24.3	26	ns	19	ns	35.4	0.0373	23.8	ns
COPD, %	16.3	20.5	ns	16.6	ns	25	ns	22.7	0.0456
Atrial fibrillation, %	33.6	34.2	ns	42.8	ns	34	ns	30.7	ns
Hypertension, %	79.6	76.7	ns	69	0.0480	72.9	ns	81.8	ns
Ejection fraction <50%, %	57	65.7	0.0080	71.4	0.0255	54.2	ns	70.4	0.0029
Previous heart failure, %	73.8	78.7	ns	85.7	0.0325	79.2	ns	78.4	ns
Previous infarction, %	22.8	23.3	ns	26.2	NS	20.8	ns	22.7	ns
Median systolic BP (IQR)	140 (120.5-170)	140 (120.5-170)	ns	126 (100-150)	0.0020	135.5 (125-170)	ns	140 (120-171)	ns
Median heart rate (IQR)	90 (75.5-100)	85 (75-111.5)	ns	80	0.0449	85 (71.5-100)	ns	92.5 (75.5-111.5)	0.0414
Anasarca, %	2.14	3.4	ns	7.14	0.0323	6.2	0.0460	0	ns
Cardiogenic shock, %	1.7	2.74	ns	7.1	0.0170	2 (1)	ns	4.5	0.0315
Acute pulmonary edema, %	35.1	32.9	ns	21.4	0.0259	25 (12)	ns	40.9	ns
Congestion, %	61	60.9	ns	64.3	ns	66.7 (32)	ns	54.5	ns

LFT: Liver function test; TB: Total bilirubin; APh: Alkaline phosphatase; ALT/AST: Alanine aminotransferase /Aspartate aminotransferase; IQR: 25%-75% interquartile range. COPD: Chronic obstructive pulmonary disease. BP: Blood pressure. ns: Non-significant

tor of mortality. The other variables associated with mortality are detailed in Table 2.

The incorporation of liver function tests into a multivariate model including clinical-serological variables with prognostic value (Table 3) revealed that TB (OR: 3.61; 95% CI 1.29-10.04) and ALT/AST (OR: 2.83; 95% CI 1.28-6.25) were independent predictors of in-hospital mortality. Cardiogenic shock (OR: 9.48; 95% CI 2.31-38.78), history of chronic obstructive pulmonary disease (OR: 2.66, 95% CI 1.21-5. 87), and acute renal failure at admission (OR: 3.55; 95% CI 1.48-8.49) were also independent predictors of cardiogenic shock.

DISCUSSION

According to current records, decompensated heart failure mainly affects elderly populations, with median age generally over 70 years. In these populations, high blood pressure at admission is a recurrent characteristic and most patients present with signs of congestion and few with low cardiac output, except in referral centers of patients with advanced disease (7-11). In this sense, our registry which recruited more than 700 individuals, shares the general characteristics even with a more advanced age (median of 81 years), a predominantly congestive condition, median high systolic blood pressure at admission and few patients with signs of low cardiac output. With an in-hospital mortality rate of 5.4%, it is extremely useful to provide tools at admission to identify patients at higher risk.

In this context, liver function test abnormalities represent a potential complement to evaluate the prognosis of these patients.

What is the relationship between heart failure and the liver? It is known that the liver has a vascular system sensitive to systemic hemodynamic changes. It receives approximately 25% of the cardiac output, 70% of which is derived from the portal system and 30% from the hepatic artery (12, 13). This double circulation provides a certain protection to the liver in low-flow situations, so that, in general, a combination of low cardiac output with congestion is necessary to produce ischemic liver damage. On the other hand, it is interesting to note that the venous return from the

liver through the inferior vena cava has no valves, so increased right ventricular end diastolic pressure is transmitted directly to the liver. This means that in congestive conditions the liver is easily affected.

In a population with the characteristics of the present study, where most patients are elderly and have non-severe forms of presentation, hepatic dysfunction is probably an expression of the patient's vulnerability to instability rather than the expression of severe hemodynamic involvement

Table 2. Mortality predictors. Univariate analysis

Variable	OR (95% CI)	p
Abnormal liver function test	2.34 (1.18-4.65)	<0.05
TB	4.05 (1.66-9.83)	<0.01
ALT/AST	3.56 (1.72-7.34)	<0.01
APh	1.65 (0.56-4.87)	ns
>65 years	1.22 (0.42-3.52)	ns
Women	0.95 (0.49-1.82)	ns
Diabetes	0.78 (0.35-1.74)	ns
Dyslipidemia	0.77 (0.38-1.58)	ns
COPD	2.53 (1.24-5.18)	<0.05
Hypertension	0.96 (0.43-2.14)	ns
Chronic atrial fibrillation	2.06 (1.07-3.98)	<0.05
Previous infarction	0.75 (0.32-1.74)	ns
Acute renal failure	3.9 (1.7-8.9)	0.0002
Hospitalization due to heart failure	1.15 (0.53-2.48)	ns
Ejection fraction <50%	1.48 (0.74-2.95)	ns
Anasarca	0.78 (0.41-3.91)	ns
Acute pulmonary edema	0.84 (0.42-1.70)	ns
Cardiogenic shock	1.63 (1.01-2.63)	<0.05
Congestion	0.78 (0.40-1.50)	ns

TB: Total bilirubin; ALT/AST: Alanine aminotransferase/Aspartate aminotransferase. APh: Alkaline phosphatase. COPD: Chronic obstructive pulmonary disease. ns: Non-significant

Abnormal liver function tests in this population would have a prognostic role as markers and not as causes of poor outcome.

In this context, although the abnormality of all markers was scarcely prevalent, the increase in APh was not associated with worse outcome, perhaps because it is a congestive marker (of simple treatment) and not of vulnerability, as would be the case of the other markers analyzed.

Unlike other studies, the present series had no patient restriction criteria, either because they were not recruited from referral centers of patients with advanced disease nor had requisites such as Swan-Ganz catheter indication, or inclusion in an interventional study. Thus, it is probably more representative of the majority of patients admitted for decompensated heart failure.

In our country, Giordanino et al. (14) presented a high complexity center registry with very interesting conditions compared with the present registry. Although it includes a population with an average age over 10 years younger, both registries agree that mortality is higher in those with liver disorders. The hemodynamic differences between those with and without liver function test abnormalities are much more marked in the Giordanino et al. registry. It is then possible to identify two different pathophysiologies of hepatic abnormality. As already mentioned, one is the mobilization of markers as an expression of vulnerability and the other is hepatic failure as a consequence of heart failure severity, where the cardiorenohepatic axis (6) would have a more significant role than that of a mere marker.

A similar appreciation to the Giordanino et al. registry is presented in the Van Deursen et al. study (15) analyzing a population of patients with median age of 53 years, hospitalized with heart failure and

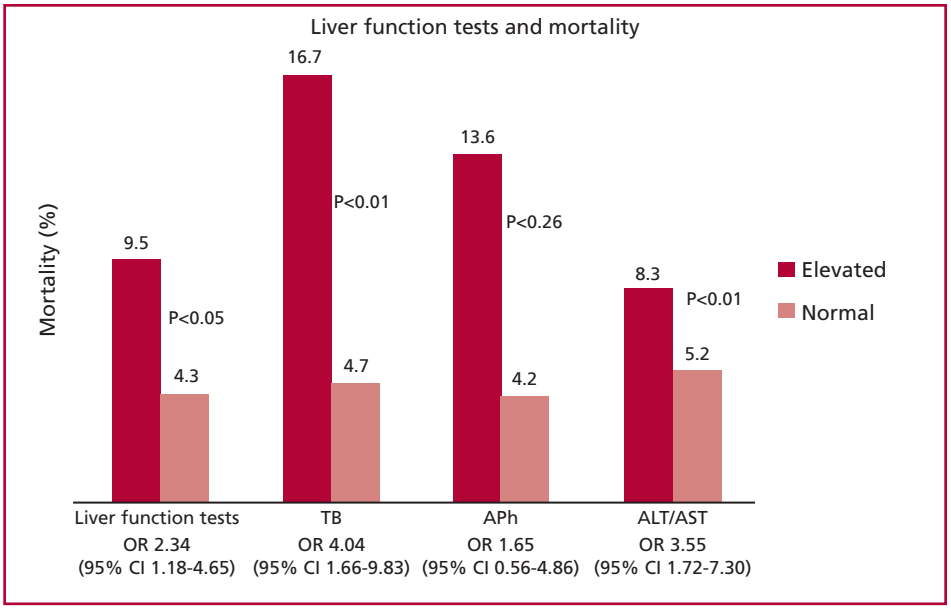

Fig. 1. Liver function tests and in-hospital mortality. TB: Total bilirubin; APh: Alkaline phosphatase; ALT/AST: Alanine aminotransferase/Aspartate aminotransferase

Table 3. Mortality predictors. Multivariate analysis.

	OR	95% CI	p
Age	1.02	0.98–1.06	0.1616
Gender	0.50	0.23–1.12	0.0943
COPD	2.66	1.21–5.87	0.0149
Acute renal failure	3.55	1.48–8.49	0.0044
Cardiogenic shock.	9.48	2.31–38.78	0.0017
ALT/AST	2.83	1.28–6.25	0.0099
TB	3.61	1.29–10.04	0.0138

COPD: Chronic obstructive pulmonary disease ALT/AST: Alanine aminotransferase/Aspartate aminotransferase. TB: Total billirubin

controlled by Swan-Ganz catheter. These authors observed that liver function test abnormalities were especially associated with congestion and liver enzymes were also related to low cardiac output. In this retrospective analysis, hemodynamic variables predicted mortality, but the prognostic value of liver function was secondary to the hemodynamic condition, i.e., it was not an independent predictor. Also in this study, abnormal liver function tests would be an expression of hemodynamic involvement.

Nikolau et al. (16) analyzed the significance of liver function tests at admission in 1,134 patients with a median age of 66 years and decompensated heart failure requiring inotropic agents, which were included in the SURVIVE study. Alkaline phosphatase was associated with systemic congestion and mortality at 6 months and liver enzymes were associated with signs of hypoperfusion and mortality at 1 and 6 months. Again, these are younger patients but with more severe forms of heart failure, where hepatic dysfunction is associated with hemodynamic severity and even the authors suggest that altered liver function could be used as a surrogate for the hemodynamic condition.

Two other interventional studies, the PROTECT (17) and ASCEND HF (18) trials also analyzed liver function test abnormalities, finding similar results.

Biegus et al. (19) incorporated the interesting concept of cardiohepatorenal damage as a consequence of the inadequate peripheral adaptability to decompensation due to heart failure. For this purpose, they employed the MELD-XI score (originally proposed for end-stage liver disease) in the long-term prognostic assessment of patients with decompensated heart failure. This score jointly analyzes hepatic dysfunction (through bilirubin) and renal injury (through creatinine). They found that an elevated MELD score was independently associated with mortality at one year follow-up. This analysis reinforces the concept of the multisystemic involvement of heart failure whose consequences do not depend solely on the severity of the presentation but also on the systemic response.

A liver function test is almost always present in routine laboratory tests at admission of patients with decompensated heart failure; however, it is not clear what clinical interpretation should be given to a discreet upward mobilization of its components. According to the present study, this abnormality does not reflect liver disease, and its prognostic significance is independent of the presentation form; i.e., in the case of a similar presentation, the patient with altered liver function test has a worse prognosis. Based on the proposed interpretation, it is likely that the patient will require a closer follow-up due to his/her greater vulnerability.

No therapeutic strategy emerges from the study, although it may be reasonable to expect different responses in patients with abnormal liver function tests, which might constitute a potential field of evaluation.

The greatest added value of the present study is probably the fact that it is not a selected population, but representative of the average patient admitted to non-specialized heart failure centers, where liver function test abnormalities probably respond to the proposed explanation.

Limitations

Despite being a series with a significant number of patients; the present study is a retrospective analysis performed only in two centers, so it would be interesting to validate it in other series.

CONCLUSIONS

Accessible data such as liver function tests provide prognostic information at admission.

In an unselected population of patients, and abnormal liver function test probably expresses more vulnerability than hemodynamic involvement.

Conflicts of interest

None declared. (See authors' conflicts of interest forms on the website/Supplementary material).

REFERENCES

1. Barisani JL, Fernández A, Fairman E, Diez M, Thierer J, Christen A. Consenso de Insuficiencia Cardíaca Aguda y Avanzada. Rev Argent Cardiol 2010;78:265-81.

2. Gheorghiade M, Pang PS. Acute heart failure syndromes. J Am Coll Cardiol 2009;53:557-73. http://doi.org/c9p744

3. Mozaffarian D, Benjamin E, Go S, Arnett D, Blaha M, Cushman M, et al. Heart Disease and Stroke Statistics- 2016 Update. Circulation 2016;133:e38-360.
4. Ponikowski P, Voors A, Anker S, Bueno H, Cleland J, Coats A, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891-975. http://doi.org/b8bd
5. Damman K, Valente M, Voors A, O'Connor Ch, van Veldhuisen D, Hillege H, et al. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J 2014;35:455-69. http://doi.org/rr3
6. Parissis J, Nikolaou M, Mebazaa A. The Model for End-stage Liver Disease score in acute heart failure: hepatorenal disfunction hides behind. Eur J Heart Fail 2016;18:1522-3. http://doi.org/b8bf
7. Fairman E, Thierer J, Rodríguez L, Blanco P, Guetta J, Fernández S y cols. Registro Nacional de Internación por Insuficiencia Cardíaca 2007. Rev Argent Cardiol 2009;77:33-9.
8. Corradi L, Pérez G, Costabel J, González N, Da Rosa W, Altamirano M et al. XVIII CONAREC Registry on Decompensated Heart Failure in Argentina. Rev Argent Cardiol 2014;82:519-28.
9. Bocchi E, Arias A, Verdejo H, Diez M, Gomez E, Castro P. The reality of heart failure in Latin America. J Am Coll Cardiol 2013;62:949-58. http://doi.org/f2fnwf
10. Crespo Leiro M, Anker S, Maggioni A, Coats A, Filippatos M, Ruschitzka F, et al. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. Eur J Heart Fail 2016;18:613-25. http://doi.org/f3rsc8
11. Milo-Cotter O, Adams K, O'Connor C, Uriel N, Kaluski E, Felker M, et al. Acute heart failure associated with high admission blood pressure. A distinct vascular disorder? Eur J Heart Fail 2007;9:178-83. http://doi.org/dtxvmn
12. Kavoliuniene A, Vaitiekiene A, Cesnaite G. Congestive hepatopathy and hepatitis in heart failure: A cardiologist's point of view. Int J Cardiol 2013;166:554-8. http://doi.org/f4x8ch
13. Naschitz J, Slobodin G, Lewis R, Zuckerman E, Yeshurun D. Heart diseases affecting the liver and liver diseases affecting the heart. Am Heart J 2000;140:111-20. http://doi.org/c7kgxh
14. Giordanino E, Zambrano C, Klin P. Síndrome cardiohepático en insuficiencia cardíaca aguda descompensada: clasificación y valor pronóstico. Revista CONAREC 2015;31:100-3.
15. Van Deursen V, Damman K, Hillege H, van Beek A, van Veldhuisen D, Voors A. Abnormal liver function in relation to hemodynamic profile in heart failure patients. J Card Fail 2010;16:84-90. http://doi.org/dkjddn
16. Nikolau M, Parissis J, Birham Yilmaz M, Seronde M, Kivivvo M, Laribi S, et al. Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure. Eur Heart J 2013;34:742-9. http://doi.org/f4phs5
17. Biegus J, Hillege H, Postmus D, Valente M, Bloomfield D, Cleland J, et al. Abnormal liver function tests in acute heart failure: relationship with clinical characteristics and outcome in the PROTECT study. Eur J Heart Fail 2016;18:830-9. http://doi.org/f8x8qp
18. Samsky M, Dunning A, DeVore A, Schulte P, Starling R, Tang W, et al. Liver function tests in patients with acute heart failure and associated outcomes: insights from ASCEND-HF. Eur J Heart Fail 2016;18:424-32. http://doi.org/b8bg
19. Biegus J, Zymlinski R, Sokolski M, Siwołowski P, Gajewski P, Nawrocka-Millward S, et al. Impaired hepato-renal function defined by the MELD-XI score as prognosticator in acute heart failure. Eur J Heart Fail 2016;18:1518-21. http://doi.org/f9dnkq