ORIGINAL ARTICLE
UDC: 616.12-082:616.36
https://doi.org/10.2298/VSP180702171J

Risk factors profile for liver damage in cardiac inpatients

Profil faktora rizika od oštećenja jetre kod hospitalizovanih kardioloških bolesnika

Jovan Jovanović*, Dragan R. Milovanović†, Predrag Sazdanović†, Maja Sazdanović†, Milan Radovanović†, Ljiljana Novković†, Vladimir Zdravković*, Nemanja Zdravković‡, Ivan Simić*, Dejana Ružić Zečević†, Slobodan M. Janković†

Clinical Center "Kragujevac", *Clinic for Cardiology, Kragujevac, Serbia; University of Kragujevac, †Faculty of Medical Sciences, Kragujevac, Serbia

Abstract

Background/Aim. Liver damage, with potentially serious consequences, is not uncommon in hospitalized cardiac patients. The aim of our study was to determine the risk factor profile for liver damage in patients hospitalized from a deterioration of their acute or chronic cardiac illness. **Methods.** The study had observational case-control design with retrospective data collections from medical files of adult patients hospitalized in a tertiary health care center. The cases (n = 140) were subjects with novel liver injury (which emerged during hospital stay) and three control subjects were matched (age, date) for each case subject (n = 420). The primary outcome was hepatotoxicity (present or absent) and independent variables were proposed risk factors. Statistical analysis included descriptive methods, hypothesis testing and univariate and multivariate binary logistic regression, with $p \leq 0.05$. **Results.** In the whole study population, there were 432 (77.1%) females and the mean age of patients was 64.1 years [standard deviation (SD) = 10.7, range 24–85 years]. The most common illnesses were coronary heart disease (n = 385), hypertension (n = 334) and arrhythmia (n = 115). Mean value of Charlson Comorbidity Index (CCI) score was 3.8 (SD=1.7; range 1-10) corresponding to estimated CCI 10-years survival rate of 54.4% (SD = 33.5%). In the group of cases, 114 (81.4%) of the patients had hepatocellular, 9 (6.4%) cholestatic and 17 (12.2%) mixed type of hepatic injury. Factors independently associated with hepatotoxic event were previous occasional alcohol intake odds ratio (OR) 96.47; 95% confidence interval (CI) 28.95–321.43; $p < 0.001$), amiodarone (OR 3.70; 95% CI 1.82–7.53; $p < 0.001$), enoxaparin (OR 3.29; 95% CI 1.79–6.05; $p < 0.001$), obesity (OR 2.78; 95% CI 1.15–6.71; $p < 0.023$), atorvastatin (OR 2.67; 95% CI 1.33–5.38; $p < 0.006$) and CCI total score (OR 1.89; 95% CI 1.53–2.34; $p < 0.001$). **Conclusion.** Major factors associated with acute liver damage in patients hospitalized in cardiology ward of a tertiary health care institution were patient's constitutional and habitual characteristics (occasional alcohol intake, obesity, CCI total score) and drugs with known hepatotoxic properties (amiodarone, enoxaparin, atorvastatin).

Key words:
alcohol drinking; amiodarone; cardiovascular diseases; chemical and drug induced liver injury; drug toxicity; inpatients; obesity; risk factors.

Apstrakt

Uvod/Cilj. Oštećenje jetre, sa potencijalno ozbiljnim posledicama, nije retka pojava kod hospitalizovanih kardioloških bolesnika. Cilj studije bio je ispitivanje profila faktora rizika od oštećenja jetre kod bolesnika hospitalizovanih zbog pogoršanja akutne ili hronične kardiološke bolesti. **Metode.** Studija je bila opservacionog dizajna, tipa slučaj-kontrola, uz retrospektivno prikupljanje podataka uvidom u istorije bolesti odraslih bolesnika lečenih u tercijarnoj zdravstvenoj ustanovi. Slučajevi (n = 140) su bili bolesnici sa novonastalim oštećenjem jetre (koja se razvila tokom hospitalizacije), a po tri kontrolna bolesnika (n = 420), komparabilna po godinama i datumu hospitalizacije, pridruženi su svakom slučaju. Primarni ishod je bila hepatotoksičnost (simptomatska ili asimptomatska), a nezavisne varijable su bile predložene kao faktori rizika. Statistička analiza je uključivala deskriptivne metode, ispitivanje hipoteze i univarijantnu i multivarijantnu binarnu logističku regresiju, sa $p \leq 0.05$. **Rezultati.** Od ukupne studijske populacije, 432 (77,1%) osobe su bile ženskog pola, a srednja vrednost godina bolesnika iznosila je 64,1 godina [standardna devijacija (SD) = 10,7; opseg 24–85]. Najčešće bolesti su bile koronarna bolest (n = 385), hipertenzija (n = 334) i aritmija (n = 115). Srednja vrednost Charlson Comorbidity Index-a (CCI) bila je 3.8 (SD = 1,7; opseg 1–10), što je bilo u skladu sa procenjenim CCI 10-ogodišnjim preživljavanjem od 54,4% (SD = 33,5%). U grupi slučajeva,

Correspondence to: Jovan Jovanović, Clinical Center "Kragujevac", Clinic for Cardiology, Zmaj Jovina 30, 34 000 Kragujevac, Serbia.
E-mail: jovanovmejl1@gmail.com

114 (81.4%) bolesnika imalo je hepatocelularni tip, 9 (6,4%) holestatski tip, a 17 (12,2%) mešoviti tip oštećenja jetre. Nezavisni prediktori hepatotoksičnog događaja su bili: prethodna povremena konzumacija alkohola [odds ratio (OR) 96,47; 95% interval poverenja (IP) 28,95–321,43; $p < 0,001$], upotreba amiodarona (OR 3,70; 95% IP 1,82–7,53; $p < 0,001$), enoksaparina (OR 3,29; 95% IP 1,79–6,05; $p < 0,001$) i atorvastatina (OR 2,67; 95% IP 1,33–5,38; 0,006), gojaznost (OR 2,78; 95% IP 1,15–6,71; 0,023) i ukupni CCI skor (OR 1,89; 95% IP 1,53–2,34; $p < 0,001$). **Zaključak.** Glavni faktori povezani sa akutnim oštećenjem jetre kod bolesnika hospitalizovanih na kardiološkom odeljenju u institucijama tercijarne zdravstvene nege su konstitucionalne karakteristike i navike bolesnika (povremeni unos alkohola, gojaznost, CCI skor) i lekovi za koje se zna da imaju hepatotoksični potencijal (amjodaron, enoksaparin, atorvastatin).

Ključne reči:
alkohol, pijenje; amjodaron; kardiovaskularne bolesti; jetra, oštećenje, hemijsko i lekovima izazvano; lekovi, toksičnost; hospitalizacija; gojaznost; faktori rizika.

Introduction

Cardiac patients represent a population that is very prone to developing manifestations of the liver damage because they have many characteristics which are, in essence, risk factors for hepatic injury. The liver receives up to a quarter of cardiac output and any cardiovascular disease which causes significant reduction of arterial perfusion and increased cardiac preload could lead to concomitant hypoxia of the hepatic tissue and features of congestive hepatopathy. Such risk factors could be, for example, any cause of right ventricular heart failure, including constrictive pericarditis, tricuspid regurgitation, mitral stenosis, cardiomyopathy, and cor pulmonale [1]. In addition, physicians usually prescribe numerous drugs to patients suffering from cardiovascular disease, particularly within hospital settings and some of such pharmaceuticals have more or less the ability to induce liver injury. Recognizing particular risk factors for drug-induced hepatotoxicity in cardiac inpatients is an important clinical task. Such host factors can be divided into two groups: genetic (eg. polymorphism or variant involving drug-metabolizing enzymes and transport proteins) and non-genetic (eg. age, gender, concomitant somatic disease, pregnancy, alcohol, smoking, obesity) [2].

In general, drug-induced liver damage is nowadays recognized as one of the greatest problems in pharmacovigilance. Its incidence in developed countries on annual basis is significant, it is the major reason for drug withdrawal from the market as well as for stopping drug therapy due to safety issues and it causes important economic losses [3]. Cardiological drugs such as amiodarone, hydralazine, methyldopa, statins (atorvastatin, simvastatin), quinidine and ticlopidin as well as some other medicines frequently prescribed in hospitalized cardiac inpatients with associated comorbidity such as antibiotics (amoxicillin plus clavulanate, nitrofurantoin, sulfamethoxazole plus trimethoprim, sulfonamides), antigout agents (allopurinol) and nonsteroidal antiinflammatory drugs (diclofenac, ibuprofen, nimesulide) have been classified in the group of the pharmaceuticals with the most frequent reports of liver damage [4]. Other drugs, commonly prescribed to these patients are sometimes associated with hepatic damage. For example, among all reports of adverse events associated with the use of enoxaparin in a pharmacovigilance database, about 4% cases involve hepatic events [5].

Although liver toxicity of amiodarone (which is among the main cardiological drugs with known hepatotoxic potential) has been well described so far, additional research is needed for some features. Firstly, the mutual relationships of predisposing factors, which play synergistic role in the development of the amiodarone-induced hepatotoxicity, are still not completely understood. Drug-related (cumulative dose, pharmaceutical formulation, administration route), patient-dependent (age, gender, nutritional status, comorbidity, genetic polymorphism of metabolizing enzymes and target receptors) and treatment-associated issues (other hepatotoxic medications, adverse drug interactions) are examples of such factors [2, 6, 7].

Secondly, rare studies included exclusively cardiac inpatients and data in that subpopulation were rather limited [8]. Previous researchers examined hepatotoxicity caused by amiodarone in variety of ambulatory and/or inpatient groups including subjects with comorbid gastrointestinal, liver and other internal diseases [9, 10]. The patients primarily hospitalized from cardiovascular diseases have rather unique risk factor patterns for liver injury. Coronary heart disease, heart failure, coagulation disorders (eg. unstable prothrombin time), inflammatory illnesses (eg. bacterial endocarditis, myopericarditis), endocrine disturbances (eg. thyrotoxic cardiac disease) and circulatory instability due to extreme bradycardia or tachyarrhythmias are some of circumstances highly predisposing the inpatients to organ-specific or systemic ischemia. Frequent use of diagnostic and therapeutic vascular procedures (cardiac surgery, percutaneous coronary interventions) and medical devices (eg. intraaortic balloon pump, pacemakers, cardiac ablation and electrostimulation equipment) as well as high prescription rate of drugs with possible hepatic adverse reactions (eg. antilipemic drugs, anticoagulants, analgesics) add further risks for clinically-important liver damage.

Taking the above-mentioned facts into account, the aim of this study was to determine the risk factor profile for liver injury in patients hospitalized due to a deterioration of their acute or chronic cardiac illness.

Methods

This research was based upon a retrospective data collection and observational case-control design, similar to other studies in the field [10, 11]. The study was conducted in the

Clinic of Cardiology, the Clinical Center "Kragujevac" in Kragujevac, Serbia. It complied with the ethical principles of the scientific research and it was approved by the Institutional Ethics Committee. The medical records of all patients treated at the institution throughout the period of four years (2011–2014) was screened. The study cases were the subjects with novel liver injury, which emerged during the hospital stay ("the index day") and three control subjects were randomly chosen for each case subject among all patients from the ward that were matched with this case. The control subjects had no recorded signs of liver injury at admission nor until the index day. They were matched with case patients for gender and age (5-year intervals), and taking into account the inclusion and exclusion criteria. The selection of patients was performed successively in the described manner, until the estimated number of study subjects was fulfilled.

The case patient was included if he or she was male or female, 18 to 75 years old and had a hepatotoxic event during hospitalization which was identified as any of the following: a liver enzyme level increases more than three times above the upper limit of the reference values, a total bilirubin level two times higher than the upper limit of the reference values and clinically manifested symptoms of the acute liver damage (pain under the right rib, nausea, feeling sick, vomiting, jaundice, hemorrhagic syndrome, abdominal pain, hepatomegaly). The exclusion criteria for both the case and the control subjects were the following: age younger than 18 or older than 75 years, confirmed diagnosis of either acute or chronic liver disease such as liver cirrhosis, Wilson's disease, porphyry, alpha-1 antitrypsin deficiency, hepatitis virus infection, primary biliary cirrhosis, primary sclerosing cholangitis, substance abuse, biliary calculosis, cholecystitis, pancreatitis, abdominal trauma, the increased values of aspartate aminotransferase (AST) at baseline with an AST/alanine aminotransferase (ALT) ratio > 2 upon admission, increased values of ALT, gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), total bilirubin, direct bilirubin above the upper normal limits at admission and decreased platelet counts below the lower normal limits at admission. AST/ALT ratio > 2 was the exclusion criterion because it was considered highly suggestive for alcohol abuse and consequent patient's liver injury [12].

The probability of supposed drug-induced/associated liver damage was assessed using the Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) scale, a purposefully designed questionnaire aimed at evaluation of hepatotoxic effect of medications, herbal products and other xenobiotics. This questionnaire had already been used in numerous clinical studies as a valid method [13]. Drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system used by the World Health Organization (http://www.whocc.no/atc_ddd_index) and the medication exposure was expressed as the number of defining daily doses (DDD) per 100 patient's days (PD) of hospitalization. We used Charlson Comorbidity Index (CCI) in order to assess the influence of patients´ multiple comorbidities [14]. The composite score of CCI was calculated with assessing age and existence of diabetes mellitus, liver disease, malignancy, acquired immunodeficiency syndrome (AIDS), moderate to severe chronic kidney disease, chronic heart failure, myocardial infarction, chronic obstructive pulmonary disease, peripheral vascular disease, cerebrovascular accident or transitory ischemic attack, dementia, hemiplegia, connective tissue disease and peptic ulcer disease of study patients.

The primary dependent variable was the hepatotoxicity, expressed as a binary variable (present or absent). The primary independent variable was treatment with amiodarone, identified as the prescription of at least one of its oral or parenteral dose. There were numerous other secondary independent or confounding variables (eg. route of amiodarone administration, number of DDD of amiodarone per 100 PD, type of cardiovascular disease, important comorbid illness, prescription of drugs with known hepatotoxic properties, particularly hypolipidemics, nonsteroidal antiinflammatory drugs, antiepileptics and antibiotics, patients' sociodemographic characteristics, smoking, caffeine intake as well as use of dietary supplements, herbal remedies and other over-the-counter-preparations) [15, 16].

We performed study sample calculation using the appropriate computer program, setting up the alpha error at 0.05 and the study power at 0.8 for dichotomous variable (χ^2-test). The expected difference in the frequency of hepatotoxic-drug prescription rate (amiodarone) relating to the presence of primary variable (liver injury) was presumed based on a preliminary analysis of a small patient sample at the same institution [42.5% vs. 32.5%, odds ratio (OR) 1.49]. The calculation with above-mentioned input parameters gave the total sample size of 280 case patients and 840 control subjects. However, we prespecified the interim analysis after the inclusion of the half of study subjects with the study-ending rule if the analysis confirmed the statistically significant difference in the amiodarone-exposure rate (eg. significant OR) between the study groups. Therefore, the final study sample included 560 cardiology inpatients.

Statistical analysis of collected data included the descriptive methods (measures of central tendency and variability, frequencies), the methods for hypothesis testing (Student's *t*-test or Man-Whitney *U* test, χ^2-test, or Fisher's exact test) and the calculation of crude and adjusted ORs [with 95% confidence intervals (CI)] using univariable and multivariable binary logistic regression. The probability level of significance for observed differences between study groups for all statistical analyses was established at 5% (0.05) or less.

Results

The study included 2,500 hospital files of the patients treated during the study period of four years in the Clinic of Cardiology, Clinical Center "Kragujevac", Kragujevac, Serbia. After the first assessment for eligibility, we excluded a total of 1,500 patient records due to the presence of the exclusion criteria. The final sample included 140 patients' files in the case group and 420 patients' records in the control group, after exclusion of non-matched control patients and subsequent identification of noneligible criteria.

Most of the patients were females (432 of 560, 77.1%) and the mean age of patients in the whole study sample was 64.1 ± 10.7 years (from 24 to 85 years). Obesity was not significantly represented in the study population because only 46 (8.2%) of the study patients of whole study population were obese. Morphological hepatic lesion, ultrasonographic verified as fatty liver or hepatomegaly were observed in 116 (20.7%) of the patients from the whole study population, while clinically symptomatic hepatotoxicity had 28 (20.0%) of the case group patients.

Patients were hospitalized due to cardiovascular illnesses, among which the most common was coronary heart disease, followed by hypertension, arrhythmia and heart failure. Myocardial infarction with ST-segment elevation (STEMI) was the most frequent diagnosis of all coronary heart diseases, followed by myocardial infarction without ST-segment elevation (non-STEMI), non-stable angina, stable angina and ischemic cardiomyopathy. Among the patients who had arrhythmia, atrial fibrillation was the most frequent reason for commencement of drug treatment, followed by tachycardia and extrasystoles. Of all patients who had heart failure, about the three quarter of the patients had ejection fraction (EF) > 45%, while the others had heart failure with ejection fraction ≤ 45%. The most common non-cardiovascular comorbid disorder was diabetes mellitus. Only a minority of patients consumed alcohol periodically, and majority were non-smokers. The mean value of CCI score in the whole study population was 3.8 [standard deviation (SD) 1.7, from 1 to 10) with the estimated CCI 10-years survival rate of 54.4% (SD = 33.5%).

The patients' characteristics and laboratory values in all the study subjects and in the patients within study subgroups are presented in Tables 1 and 2. The median of days of hospitalization was 4 days (range 1–45 days) and the mean value 6.0 (SD = 5.6) days for all patients in the study group. In the case group, the median of hospitalization days was 7 (range 2–30 days) and the mean 7.7 (SD = 5.0) days while for the control group these values were 3 days (range 1–45 days) and 5.4 (SD = 5.7) days, respšectively. Overall mortality rate was 4 (0.7%) in the group of all study patients, considering that no fatal outcome was observed in the control group.

Table 1

Demographic and clinical characteristics of study patients

Variable	Case group (n = 140)	Control group (n = 420)	p^*
Gender (male)	32 (22.9)	96 (22.9)	1.000‖
Age (years)	64.2 ± 11.3	64.0 ± 10.5	0.914§
Obesity	25 (17.9)	21 (5.0)	< 0.001‖
Fatty liver	32 (22.9)	18 (4.3)	< 0.001‖
Hepatomegaly	36 (25.7)	20 (4.8)	< 0.001‖
Heart failure	32 (22.9)	62 (14.8)	0.026‖
EF < 45%	12 (8.6)	12 (2.9)	0.010‖
Hypertension	79 (56.4)	255 (60.7)	0.371‖
Coronary heart disease	108 (77.1)	277 (66.0)	0.013‖
STEMI	68 (48.6)	107 (25.5)	< 0.001‖
non-STEMI	21(15.0)	52 (12.4)	0.425‖
unstable angina	13 (9.3)	54 (12.9)	0.260‖
stable angina	4 (2.9)	36 (8.6)	0.023‖
Arrhythmia	47 (33.6)	68 (16.2)	< 0.001‖
atrial fibrillation	39 (27.9)	54 (12.9)	< 0.001‖
tachycardia	4 (2.9)	7 (1.7)	0.480¶
extrasystole	4 (2.9)	7 (1.7)	0.480¶
Diabetes mellitus			
type 1	11 (7.9)	68 (16.2)	0.014‖
type 2	25 (17.9)	46 (11.00)	0.033‖
Alcohol intake†	73 (52.1)	4 (1.0)	< 0.001‖
Smoking habit	35 (25.0)	47 (11.2)	0.001‖
CCI score (points)	4.9 ± 1.5 (5; 1–10)	3.4 ± 1.6 (3; 1–7)	< 0.001**
CCI estimated survival (percent)	32.0 ± 30.2 (21; 0–96)	61.0 ± 31.1 (77; 0–96)	< 0.001**
Time to the index day‡	4 ± 3 (3; 1–14)	4 ± 5 (2; 1–44)	< 0.001**
Hospital stay (days)	8 ± 5 (7; 2–30)	5 ± 6 (3; 1–45)	0.001**

Results are present as mean ± standard deviation (median; range) for continuous variables, and number (percent) of patients (frequencies), as appropriate; * – probability for difference between the values of the case and the control group; † – occasionally, not satisfying exclusion criteria (regular alcohol use was exclusion criterion, see methods); CCI – Charlson Comorbidity Index; ‡ – index day-day on which novel liver injury emerged during the hospital stay); EF – ejection fraction; STEMI – myocardial infarction with ST segment elevation; nonSTEMI – myocardial infarction without STsegment elevation; ‖ – χ^2 test, § – *t*-test; ¶ – Fisher's exact test; ** – Mann–Whitney U test.

Table 2
Laboratory parameters in patients of study groups (Case – hepatotoxicity, Control – without hepatotoxicity)

Variables	All patients (n = 560)	Case group (n = 140)	Control group (n = 420)	p^*
Alanine transaminase (U/L)	95 ± 226 (24; 6–2,760) (n = 560)	305 ± 382 (221; 150–2760) (n = 140)	25 ± 15 (20; 6–125) (n = 420)	n.a.†
Aspartate transaminase (U/L)	98 ± 463 (23; 9–8,811) (n = 560)	303 ± 895 (129; 16–811) (n = 140)	29 ± 34 (20; 9–372) (n = 420)	na†
Gamma-glutamyltransferase (U/L)	38 ± 64 (22; 5-858) (n = 312)	45 ± 41 (29; 7–224) (n = 131)	33 ± 76 (20; 5–858) (n = 181)	< 0.001‡
Total bilirubin (μmol/L)	15 ± 10 (12.3; 3–83) (n = 560)	24 ± 15 (20, 5.7–83) (n = 140)	12 ± 5 (11; 3–35.5) (n = 420)	n.a.†
Alkaline phosphatase (U/L)	71 ± 85 (56.5; 3.24–1,185) (n = 306)	91 ± 126 (62; 31–1,185) (n = 128)	57 ± 21 (55; 3–227) (n = 178)	< 0.001‡
Lactate dehydrogenase (U/L)	452 ± 233 (419; 13–1,723) (n = 294)	464 ± 280 (449; 55–1,723) (n = 123)	442 ± 192 (407; 13–1,228) (n = 171)	0.728‡
Creatine phosphokinase (U/L)	505 ± 1027 (118; 8.2–8,030) (n = 386)	885 ± 1384 (289.5; 25–8,030) (n = 136)	299 ± 686 (103; 8–5,680) (n = 250)	< 0.001‡
Creatine phosphokinase-MB (U/L)	84 ± 310 (16.3; 3.4–3,869) (n = 381)	161 ± 497 (31; 4–3869) (n = 135)	42 ± 94 (14.35; 3–908) (n = 246)	< 0.001‡
Amylase (U/L)	70 ± 56 (60; 4–603) (n = 218)	63 ± 44 (56; 4–404) (n = 104)	75 ± 65 (64; 16–603) (n = 114)	0.036‡
Troponin (ng/mL)	16.1 ± 60.9 (0.95; 0.002–797) (n = 234)	24.2 ± 84.7 (2.49; 0–797) (n = 102)	9.8 ± 31.1 (0.3; 0–242) (n = 132)	< 0.001‡
Proteins (g/L)	66 ± 8 (n = 361)	67 ± 7 (129)	65 ± 8 (n = 232)	0.006‖
Albumins (g/L)	40 ± 6 (n = 376)	39 ± 6 (n = 132)	40 ± 6 (n = 244)	0.526‖
Fibrinogen (g/L)	4.2 ± 7.3 (3.76; 0.54–127) (n = 294)	3.8 ± 1.4 (3.66; 0.5–11) (n = 116)	4.6 ± 9.3 (3.85; 1.48–127) (n = 178)	0.352‡
International normalized ratio (INR)	1.3 ± 0.7 (1.083; 0.9–6) (n = 326)	1.4 ± 0.7 (1.1, 0.9–4.9) (117)	1.3 ± 0.7 (1.08; 0.9–6) (n = 209)	0.344‡
C-reactive protein (mg/L)	22 ± 36 (7; 0.2–256) (n = 367)	31 ± 40 (12.15; 1.3–196) (n = 130)	17 ± 32 (5.5; 0.2–256) (n = 237)	< 0.001‡
Glucose (mmol/L)	6.4 ± 2.5 (n = 465)	6.7 ± 2.6 (n = 138)	6.2 ± 2.4 (n = 327)	0.067‖
Cholesterol (mmol/L)	4.9 ± 1.2 (n = 425)	5.0 ± 1.3 (n = 133)	4.8 ± 1.1 (n = 292)	0.037‖
Triglycerides (mmol/L)	1.8 ± 1.0 (1.4; 0.5–7.4) (n = 419)	1.8 ± 1.0 (1.52; 0.66–6) (n = 131)	1.7 ± 1.0 (1.3; 0.5–7.4) (n = 288)	0.092‡
Urea (mmol/L)	7.7 ± 8.3 (6.1; 1.9–145) (n = 415)	7.5 ± 3.8 (7; 2.4–24.5) (139)	7.8 ± 9.6 (6; 1.9–145) (n = 276)	0.073‡
Creatinine (μmol/L)	100 ± 45 (n = 417)	100 ± 36 (n = 139)	99 ± 49 (n = 278)	0.880‖
Leukocytes ($x10^9$/L)	8.6 ± 2.5 (n = 409)	9.4 ± 2.4 (n = 136)	8.3 ± 2.5 (n = 273)	< 0.001‖
Platelets ($x10^9$/L)	219 ± 64 (n = 408)	213 ± 61 (n = 135)	222 ± 64 (n = 273)	0.122‖

Results are present as mean ± standard deviation and (median; range) with (number of patients); * – probability for difference between the values of the case and the control group; † n.a. – not applicable (testing was not done as the values above upper normal limits during the whole study period were an exclusion criterion for the control group); ‡ – Mann–Whitney U test; ‖ – *t*-test.

The most frequently prescribed drug in the study population was acetylsalicylic acid, followed by the inhibitors of angiotensin-converting enzyme (ACE), selective beta blocking agents, clopidogrel, atorvastatin, proton pump inhibitors, organic nitrates, enoxaparin sodium, trimetazidine, high-ceiling diuretics, amiodarone, benzodiazepines, dihydropyridines, H_2 receptor antagonists, metformin, xanthines, spironolactone and sulphonylureas. Other drugs were prescribed in less than 5% of the study patients and due to low frequency of the use, they were excluded from further analysis.

The primary analysis of factors associated with liver injury was performed with hypothesis testing of differences of study variables between the case and control groups of study patients (Tables 1–3). In the case group, 114 (81.4%) of the patients had hepatocellular type of the liver injury, 9 (6.4%) cholestatic and 17 (12.2%) mixed-type of the hepatic injury. Numerous demographic and clinical characteristics, laboratory parameters and drugs were differently distributed between two study groups with statistical significance. Previous occasional alcohol intake and current obesity, type of arrhythmia and diabetes mellitus type 2, cholesterol levels and leukocytosis as well as amiodarone and enoxaparin had higher magnitude of association with the liver injury within their risk-factor groups (Table 1).

In the model of multivariable binary logistic regression among nine putative risk factors for hepatotoxicity, which

we selected based on statistical significance, existing knowledge and clinical reasoning, six (alcohol intake, amiodarone, enoxaparin, obesity, atorvastatin, CCI score) had independent association with the liver injury (Table 4).

Table 3

The most used drugs in the Case group (patients with hepatotoxicity) and the Control group (patients without hepatotoxicity)

Drugs	Case group (n=140)	Control group (n=420)	*p* (χ^2-test)
H_2 receptor antagonists	32 (22.9)	40 (9.5)	< 0.001
Proton pump inhibitors	96 (68.6)	174 (41.4)	< 0.001
Metformin	8 (5.7)	62 (14.8)	0.005
Sulphonylureas	7 (5.0)	33 (7.9)	0.256
Enoxaparin sodium	89 (63.6)	104 (24.8)	< 0.001
Clopidogrel	105 (75.0)	225 (53.6)	< 0.001
Acetylsalicylic acid	124 (88.6)	326 (77.6)	0.005
Amiodarone	70 (50)	66 (15.7)	< 0.001
Organic nitrates	75 (53.6)	192 (45.7)	0.107
Trimetazidine	54 (38.6)	120 (28.6)	0.027
High-ceiling diuretics	62 (44.3)	108 (25.7)	< 0.001
Spironolactone	16 (11.4)	44 (10.5)	0.752
Beta blocking agents, selective	93 (66.4)	256 (61.0)	0.247
Dihydropyridine derivatives	16 (11.4)	75 (17.9)	0.074
ACE inhibitors	97 (69.3)	253 (60.2)	0.055
Atorvastatin	105 (75.0)	222 (52.9)	< 0.001
Benzodiazepine derivatives	31 (22.1)	87 (20.7)	0.720
Xanthines	25 (17.9)	42 (10.0)	0.013

Results are present as the number (percentage) of patients.
ACE – angiotensin converting enzyme.

Table 4

Factors significantly associated with liver injury according to the univariable and multivariable binary logistic regression analysis

Variable	Logistic regression	
	univariable	multivariable
Obesity	4.13 (2.23–7.65; < 0.001)	2.78 (1.15–6.71; 0.023)
Coronary heart disease	1.74 (1.12–2.71; 0.014)	n.a.
Arrhythmia	2.62 (1.69–4.05; < 0.001)	n.a.
Heart failure (EF< 45%)	1.71 (1.06–2.76; 0.028)	n.a.
Diabetes mellitus		
type 1	0.44 (0.23–0.86; 0.016)	n.a.
type 2	1.77 (1.04–3.00; 0.035)	n.a.
CCI total score	1.80 (1.58–2.07; < 0.001)	1.89 (1.53–2.34; < 0.001)
Occasional alcohol intake	113.31 (40.09–320.27; < 0.001)	96.47 (28.95–321.43; < 0.001)
Smoking	2.64 (1.62–4.31; < 0.001)	1.92 (0.84–4.38; 0.121)
H_2 receptor antagonists	2.82 (1.69–4.70; < 0.001)	n.a.
Proton pump inhibitors	3.08 (2.06–4.63; < 0.001)	n.a.
Metformin	0.35 (0.16–0.75; 0.007)	0.14 (0.04–0.51; 0.003)
Enoxaparin	5.30 (3.52–7.98; < 0.001)	3.29 (1.79–6.05; < 0.001)
Clopidogrel	2.60 (1.70–3.99; < 0.001)	n.a.
Acetylsalicylic acid	2.24 (1.26–3.95; 0.006)	n.a.
Amiodarone	5.36 (3.51–8.19; < 0.001)	3.70 (1.82–7.53; < 0.001)
Trimetazidine	1.57 (1.05–2.34; 0.027)	n.a.
High-ceiling diuretics	2.30 (1.54–3.42; < 0.001)	1.04 (0.53–2.03; 0.916)
Atorvastatin	2.68 (1.74–4.10; < 0.001)	2.67 (1.33–5.38; 0.006)
Xanthines	1.96 (1.14–3.35; 0.014)	n.a.
Number of hepatotoxic drugs	1.77 (1.41–2.21; < 0.001)	n.a.

Results are present as odd ratios (95% confidence interval; probabilty); n.a. – not applicable (the variable was not included in the multivariable model).
EF ejection fraction; CCI – Charlson Comorbidity Index.

The whole model (with all putative predictors) was statistically significant ($p < 0.001$) with Cox & Snell R Square $p = 0.457$ and Hosmer-Lemeshow test $p = 0.279$. There was no significant multicollinearity between the predictors. The model was also stable after the introduction of interaction of amiodarone and CCI score which was insignificant ($p = 0.251$). Alkaline phosphatase, creatine phosphokinase, creatine phosphokinase-MB, total serum proteins, C-reactive protein, cholesterol, white blood cell count were also statistically associated with the liver injury within univariate binary logistic regression analysis, but the magnitudes of their Ors were very tiny and their lower confidence intervals touched the one and they were excluded from the model.

The analysis placed the drugs with possible hepatotoxic effects on the top among other risks for the liver injury in hospitalized cardiac patents. Causal assessment of drug-associated liver injury in the case group using CIOMS/RUCAM scoring scale additionally confirmed these findings. The average value of the total score in patients of the case group was 7.8 (SD = 1.3, from 5.0 to 11.0). Out of 140 cases, in 39 (27.8%) of the patients, the medicine causality was assessed as highly probable (CIOMS/RUCAM score ≥ 9), in 100 (71.4%) patients as probable (score 6-8) and in 1 (0.7%) patient as possible (score 3–5). Amiodarone had the highest prescription rate and the median of defined daily dose of amiodarone was 112.5 (range 3.6–800) per 100 patients' hospital days. In the case group amiodarone utilization was 193.8 (range 8.3–412.5) DDD per 100 patients' hospital days and 75.0 (range 3.6–800.0) DDD per 100 patients' hospital days in the control group ($p < 0.001$). Amiodarone was administered parenterally, orally and via both routes in 44 (31.4%), 5 (3.6%) and 21 (15.0%) of the case study subjects and in 11 (2.6%), 45 (10.7%) and 10 (2.4%) of the control study subjects, respectively ($p < 0.001$).

Discussion

The result of our research showed that occasional alcohol intake, obesity, combined significant comorbidities and prescription of amiodarone, enoxaparin and atorvastatin were independently associated with the liver injury in hospitalized patients with cardiac diseases. In addition, we established the rank order for hepatotoxicity of commonly prescribed drugs in patients of cardiology wards with amiodarone representing the greatest risk. We also noted significant strength of the association of drug prescription and liver damage, which has been little studied so far for the investigated study population.

Prehospital alcohol intake was the most significant independent risk factor for hepatotoxicity in subjects of our study despite the fact that manifested alcoholism was an exclusion criterion. Therefore, the study patients were those who either consumed alcohol infrequently or in small quantities, but who, at the time of being included in the study, had neither symptomatic nor asymptomatic liver damage. Unique characteristics of hospitalized cardiac patients (eg. hypotension, hepatic ischemia, liver congestion, hepatotoxic cardiovascular drugs) probably potentiate well-known hepatotoxic action of alcohol even if it has been consumed in minute quantities before hospital admission [17–19].

In our study, many patients had both obesity and ultrasound findings of fatty liver, which suggested the presence of nonalcoholic fatty liver degeneration. We did not obtain pathological findings of patients' liver tissues and hospital patient's record usually does not include data necessary for evaluation of visceral (central) type of obesity (eg. waist circumference) which is primarily associated with liver disease [20]. However, numerous previous published studies provided the strong association of obesity-triggered nonalcoholic fatty liver degeneration and coronary heart disease, the later being very prevalent in our study subjects [21–24].

Patients with a large number of comorbidities in our study, as assessed with CCI score, had significantly higher probability of the liver injury, independently of other factors. Several cardiovascular conditions associated with the case study subjects in univariable analysis; however, we decided to include variables of two main cardiac disorders (coronary heart disease, heart failure) as well as other condition related to atherosclerosis and metabolic disbalance (peripheral vascular disease, cardiovascular accident, transient ischemic attack, hemiplegia, diabetes) within the composite, comorbidity assessment tool in order to decrease confounding by indication (indication bias) and increase the model performance for detecting drug-induced liver injury. For example, congestive heart failure is a common cause of acute liver injury in hospitalized patients [25]. Previous studies confirmed that higher CCI scores did put the patient in increased mortality risk, but the association with acute hepatotoxic damage was little investigated, at least in patients treated in cardiology wards [26]. Therefore, our findings could be considered a novelty in the field, which deserves further validation research.

Three drugs in patients of our study, amiodarone, enoxaparin and atorvastatin, were strongly associated with newly appeared, acute hepatic damage. Drug pharmacological profiles and accumulated, overall knowledge about the role of pharmaceuticals, in general, for various types of hepatic injuries support such results [27]. Many patient-specific factors in subjects with advanced cardiovascular disease and/or cardiac emergencies admitted to hospital mutually interplay, predisposing to drug induced hepatotoxicity. For example, unstable coronary heart disease causes worsening of existing arrhythmia or emergence of novel rhythm disorders which need escalation of drug treatment. Indeed, prescription of amiodarone led other, numerous drugs with hepatotoxic actions.

Our study was neither designed nor adequately powered to discriminate hepatotoxic action of two amiodarone formulations, but some issues in our results and literature data (eg. short duration of hospital stay until the appearance of liver injury, higher defined daily doses, significant differences in route of use between study group, known facts about possible hepatotoxicity of pharmaceutical excipients in parenteral formulation) indirectly suggest that parenteral administration was a primary risk factor [28, 29].

Enoxaparin and atorvastatin had also positive and significant association with hepatotoxicity in our study in compa-

rison with the use in the control subjects. Enoxaparin could increase liver transaminase levels and, in some cases, may cause toxic hepatitis due to temporary necrosis of hepatocytes, usually around one week after the treatment initiation and in a dose-dependent manner [5, 30–32]. Atorvastatin had well-known hepatotoxic potential, which could manifest with a wide range of clinical features, from asymptomatic increase of liver enzymes to drug-induced hepatitis in different periods from the time of treatment initiation [4]. Prescription of lower doses (not exceeding 40 mg daily), delayed action and contribution of numerous other strong risks could diminish the magnitude of association of atorvastatin use with liver injury in our study subjects in comparisons with other two drugs.

The limitations of our study are mainly inherited from its observational design, which well comprehends feature of case-control research. Many important data, necessary for better characterization of the type and time course of liver injury were missing in medical records (eg. liver tissue pathology and higher-performance biomarkers). Although our study includes information from several hundreds of patients it seems that the final sample size was sufficiently powered to detect only the major determinates of acute hepatic damage. Even within our analysis we noted numerous significant associations of putative risks, but the majority of them were not included in the final regression model due to presumed statistical constraints and/or clinical reasoning (eg. confounding, collinearity). For example, it seems that the associations of factors such as smoking and high-ceiling diuretics use (almost exclusively furosemide) had been confounded with obesity and decompensated heart failure requiring escalation of drug treatment, respectively, rather than caused by their direct hepatotoxic actions [33].

Our finding that metformin takes independent and protective associations suggests that it was justifiable to exclude the majority of factors with doubtful direct influence on hepatic tissue from the final regression model. There are exceptional case reports of metformin-induced hepatotoxicity in humans, but the estimated incidence is extremely low, particularly considering the widespread use of this drug [34, 35]. In fact, true mechanism of hepatic damage due to metformin is unknown and evidence from both the animal models and the clinical settings clearly demonstrated its hepatoprotective effects, too [36–40]. It seems that the inclusion of a drug with the effects of direction opposite to other factors provide the approach more realistic to clinical practice. Taking into account the abovementioned facts as well as the values of parameter estimation of the model, we consider our results accurate and clinically significant.

Conclusion

Major factors associated with acute liver injury in patients hospitalized in cardiology ward of a tertiary health care institution are patient's constitutional and habitual characteristics (occasional alcohol intake, obesity, CCI total score) and drugs (amiodarone, enoxaparin, atorvastatin) with known hepatotoxic potential. Type and severity of primary cardiovascular disease or comorbid condition can increase the risk for liver injury primarily in synergy with other risks, jointly acting with of each other and/or other major hazards. Future studies focusing on individual factors are justified in order to better characterize their effects in different subpopulations of patients with particular cardiac illnesses.

Conflict of interest

There is no conflict of interest for any author.

Acknowledgement

The authors would like to thank the Faculty of Medical Sciences of the University of Kragujevac, Kragujevac, Serbia, for supporting the research with the Junior Project JP 09-12, as well as The Ministry of Education, Science and Technological Development of the Republic of Serbia, for supporting the research with the grant N°175007.

REFERENCES

1. *Hahn KJ, Morales SJ, Lewis JH.* Enoxaparin-Induced Liver Injury: Case Report and Review of the Literature and FDA Adverse Event Reporting System (FAERS). Drug Saf Case Rep 2015; 2(1): 17.
2. *Møller S, Bernardi M.* Interactions of the heart and the liver. Eur Heart J 2013; 34(36): 2804–11.
3. *Yu YC, Mao YM, Chen CW, Chen JJ, Chen J, Cong WM*, et al. CSH guidelines for the diagnosis and treatment of drug-induced liver injury. Hepatol Int 2017; 11(3): 221-41.
4. *Kullak-Ublick GA, Andrade RJ, Merz M, End P, Benesic A, Gerbes AL,* et al. Drug-induced liver injury: recent advances in diagnosis and risk assessment. Gut 2017; 66(6): 1154–64.
5. *Björnsson ES.* Hepatotoxicity by drugs: the most common implicated agents. Int J Mol Sci 2016; 17(2): 224.
6. *Kim SH, Kim SH, Lee JH, Lee BH, Yoon HJ, Shin DH*, et al. Superoxide dismutase gene (SOD1, SOD2, and SOD3) polymorphisms and antituberculosis drug-induced hepatitis. Allergy Asthma Immunol Res 2015; 7(1): 88–91.
7. *Cataldi A, Gonella D, Robutti N, Siri M, Buonocore S, Odetti P.* Hepatotoxicity after intravenous amiodarone. Aging Clin Exp Res 2008; 20(6): 593–6.
8. *Diab OA, Kamel J, Abd-Elhamid AA.* Predictors of intravenous amiodarone induced liver injury. Egypt Heart J 2017; 69(1): 45–54.
9. *Haque T, Sasatomi E, Hayashi PH.* Drug-induced liver injury: pattern recognition and future directions. Gut Liver 2016; 10(1): 27–36.
10. *Gluck N, Fried M, Porat R.* Acute amiodarone liver toxicity likely due to ischemic hepatitis. Isr Med Assoc J 2011; 13(12): 748–52.
11. *Douros A, Bronder E, Andersohn F, Klimpel A, Thomae M, Sarganas G,* et al. Drug-induced liver injury: results from the hospital-based Berlin Case-Control Surveillance Study. Br J Clin Pharmacol 2014; 79(6): 988–99.
12. *Nyblom H, Berggren U, Balldin J, Olsson R.* High AST/ALT ratio may indicate advanced alcoholic liver disease rather than heavy drinking. Alcohol Alcohol 2004, 39(4): 336–9.

13. *Teschke R, Wolff A, Frenzel C, Schwarzenboeck A, Schulze J, Eickhoff A.* Drug and herb induced liver injury: Council for International Organizations of Medical Sciences scale for causality assessment. World J Hepatol 2014; 6(1): 17–32.
14. *Charlson ME, Pompei P, Ales KL, MacKenzie CR.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40(5): 373–83.
15. *de Abajo FJ1, Montero D, Madurga M, García Rodríguez LA.* Acute and clinically relevant drug-induced liver injury: a population based case-control study. Br J Clin Pharmacol 2004; 58(1): 71–80.
16. *Pollak PT, Shafer SL.* Use of population modeling to define rational monitoring of amiodarone hepatic effects. Clin Pharmacol Ther 2004; 75(4): 342–51.
17. *Massey VL, Beier JI, Ritzenthaler JD, Roman J, Arteel GE.* Potential Role of the Gut/Liver/Lung Axis in Alcohol-Induced Tissue Pathology. Biomolecules 2015; 5(4): 2477–503.
18. *European Association for the Study of Liver.* EASL clinical practical guidelines: management of alcoholic liver disease. J Hepatol. 2012; 57(2): 399–420.
19. *Bertholet N, Winter MR, Cheng DM, Samet JH, Saitz R.* How accurate are blood (or breath) tests for identifying self-reported heavy drinking among people with alcohol dependence? Alcohol Alcohol 2014; 49(4): 423–9.
20. *Marchesini G, Moscatiello S, Di Domizio S, Forlani G.* Obesity-associated liver disease. J Clin Endocrinol Metab 2008; 93(11 Suppl 1): S74–80.
21. *Massart J, Begriche K, Moreau C, Fromenty B.* Role of nonalcoholic fatty liver disease as risk factor for drug-induced hepatotoxicity. J Clin Transl Res 2017; 3(Suppl 1): 212–32.
22. *Targher G, Bertolini L, Poli F, Rodella S, Scala L, Tessari R, Zenari L, Falezza G.* Nonalcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients. Diabetes 2005; 54(12): 3541–6.
23. *Ioannou GN, Weiss NS, Boyko EJ, Mozaffarian D, Lee SP.* Elevated serum alanine aminotransferase activity and calculated risk of coronary heart disease in the United States. Hepatology 2006; 43(5): 1145–51.
24. *Targher G, Arcaro G.* Non-alcoholic fatty liver disease and increased risk of cardiovascular disease. Atherosclerosis 2007; 191(2): 235–40.
25. *Tapper EB, Sengupta N, Bonder A.* The Incidence and Outcomes of Ischemic Hepatitis: A Systematic Review with Meta-analysis. Am J Med 2015; 128(12): 1314–21.
26. *Yurkovich M, Avina-Zubieta JA, Thomas J, Gorenchtein M, Lacaille D.* A systematic review identifies valid comorbidity indices derived from administrative health data. J Clin Epidemiol 2015; 68(1): 3–14.
27. *Reuben A, Koch DG, Lee WM.* Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52(6): 2065–76.
28. *Jaiswal P, Attar BM, Yap JE, Devani K, Jaiswal R, Wang Y,* et al. Acute liver failure with amiodarone infusion: A case report and systematic review. J Clin Pharm Ther 2018; 43(1): 129–33.
29. *Lahbabi M, Aqodad N, Ibrahimi A, Lahlou M, Aqodad H.* Acute hepatitis secondary to parenteral amiodarone does not preclude subsequent oral therapy. World J Hepatol 2012; 4(6): 196–8.
30. *Hahn KJ, Morales SJ, Lewis JH.* Enoxaparin-Induced Liver Injury: Case Report and Review of the Literature and FDA Adverse Event Reporting System (FAERS). Drug Saf Case Rep 2015; 2(1): 17.
31. *Hui CK, Yuen MF, Ng IOL, Tsang KW, Fong GC, Lai CL.* Low molecular weight heparin-induced liver toxicity. J Clin Pharmacol 2001; 41(6): 691-4.
32. *Arora N, Goldhaber SZ.* Anticoagulants and transaminase elevation. Circulation 2006; 113(15): e698–e702.
33. *Harrill AH, Roach J, Fier I, Eaddy JS, Kurtz CL, Antoine DJ,* et al. The effects of heparins on the liver: application of mechanistic serum biomarkers in a randomized study in healthy volunteers. Clin Pharmacol Ther 2012; 92(2): 214–20.
34. *Wild SH, Byrne CD.* ABC of obesity: risk factors for diabetes and coronary heart disease. BMJ 2006; 333(7576): 1009–11.
35. *Zheng J, Woo SL, Hu X, Botchlett R, Chen L, Huo Y, Wu C.* Metformin and metabolic diseases: a focus on hepatic aspects. Front Med 2015; 9(2): 173–86.
36. *Firneisz G.* Non-alcoholic fatty liver disease and type 2 diabetes mellitus: the liver disease of our age? World J Gastroenterol 2014; 20(27): 9072–89.
37. *Saeedi Saravi SS, Hasanvand A, Shahkarami K, Dehpour AR.* The protective potential of metformin against acetaminophen-induced hepatotoxicity in BALB/C mice. Pharm Biol 2016; 54(12): 2830–7.
38. *Ling S, Shan Q, Liu P, Feng T, Zhang X, Xiang P,* et al. Metformin ameliorates arsenic trioxide hepatotoxicity via inhibiting mitochondrial complex I. Cell Death Dis 2017; 8(11): e3159.
39. *Tan S, Vollmar N, Benson S, Sowa JP, Bechmann LP, Gerken G,* et al. Liver injury indicating fatty liver but not serologic NASH marker improves under metformin treatment in polycystic ovary syndrome. Int J Endocrinol 2015; 2015: 254169.
40. *Crowley MJ, Diamantidis CJ, McDuffie JR, Cameron CB, Stanifer JW, Mock CK,* et al. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. Ann Intern Med 2017; 166(3): 191–200.

Received on July 2, 2018.
Revised on October 15, 2018.
Accepted on October 15, 2018.
Online First October, 2018.