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Predictors of intravenous amiodarone induced liver injury

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KEYWORDS

Intravenous amiodarone;
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Abstract *Background:* Intravenous (IV) amiodarone may be associated with liver injury that may necessitate drug discontinuation. The prediction of amiodarone induced liver injury (AILI) and its severity may help careful patient monitoring or the choice of other measures alternative to amiodarone in high risk patients. Little is known regarding predictors of AILI.

Objectives: To address the predictors of AILI and its severity.

Methods: The study included 180 patients indicated for IV amiodarone therapy who were divided into 2 groups: cases (90 patients) who developed AILI, and controls (90 patients) who did not develop AILI. AILI was defined as aminotransferase (ALT and AST) elevation by ≥ 2 folds of baseline levels. Severe AILI was defined as enzyme elevation by > 5 folds of baseline values.

Results: Multivariate analysis showed that the presence of cardiomyopathy ($P = 0.032$), congestive hepatomegaly ($P = 0.001$), increasing baseline total bilirubin ($P < 0.0001$), direct current cardioversion ($P = 0.015$), and increasing dose of amiodarone ($P = 0.014$) to be independent predictors for AILI. Regarding severity of AILI, inotropic support ($P = 0.034$), congestive hepatomegaly ($P = 0.012$), increasing baseline total bilirubin ($P = 0.001$), and increasing dose of amiodarone ($P = 0.002$) were found to be independent predictors for severe AILI. Among cases, linear regression analysis showed that baseline ALT was the only significant independent predictor of post-amiodarone ALT ($P < 0.0001$), while baseline AST ($P < 0.0001$) and EF ($P = 0.012$) were the only significant independent predictors of post-amiodarone AST.

Conclusions: Compromised cardiac, hepatic, and hemodynamic conditions, with increasing dose of IV amiodarone were associated with AILI. Severity of liver injury had linear relationship with baseline aminotransferase levels and left ventricular systolic function.

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1. Introduction

Drug induced liver injury (DILI) due to oral amiodarone was extensively studied. However, the available data regarding acute hepatotoxicity form intravenous (IV) amiodarone are not far beyond case reports.^{1–16} The mechanisms of liver injury

with IV amiodarone are controversial. Ischemic injury due to compromised hemodynamic conditions may have a role.⁵ Solubilizers in the IV amiodarone preparation such as polysorbate 80 were reported to be responsible for hepatotoxicity, possibly due to immune-mediated alteration of hepatocellular membrane.^{6,16} Importantly, the mechanism of injury with IV amiodarone is different from that in chronic exposure to oral therapy; therefore, acute hepatic injury following IV amiodarone does not preclude subsequent oral therapy.^{6,17}

Acute elevation of liver enzymes following IV amiodarone use ranged from mild asymptomatic to severe life threatening, and frequently necessitates drug discontinuation. In most of the reported cases, the liver injury occurred within 24–48 h of therapy and reversed within 2–3 weeks of discontinuation.

Parenteral amiodarone is commonly used in critically ill and hemodynamically unstable intensive care unit patients. Therefore, multiple factors may predispose patients to IV amiodarone induced liver injury (AILI). Possible predisposing factors for AILI were variably reported in different case studies. Underlying liver injury from heart failure, high dose of IV amiodarone, hypotension from ventricular arrhythmias (VAs), and postoperative therapy following coronary artery bypass grafting (CABG) were observed in case reports.^{4,8,18,19} Up to our knowledge, there are no prospective clinical studies that addressed the predictors of AILI.

2. Methods

The study included 180 intensive and coronary care unit patients who received IV amiodarone therapy. Patients were divided into 2 groups:

- Cases: Included 90 patients who developed AILI defined as acute rise in serum aminotransferase levels by at least 2 folds of the baseline levels within 24–48 h of IV amiodarone therapy.
- Controls: Included 90 patients who did not develop AILI.

Patients with underlying decompensated liver cell failure, hepatic coma, active hepatitis, patients with > 5 fold elevation of aminotransferases relative to upper limit of normal (ULN), patients who had acute myocardial infarction (MI) within the past 3 days, and those who received multiple (> one) direct current (DC) shocks were not enrolled in the study.

2.1. Clinical assessment

Patients were subjected to history taking and physical examination emphasizing on risk factors (such as hypertension, diabetes mellitus, smoking), signs of underlying liver disease, heart failure, concomitant drug therapy.

2.2. Laboratory investigations

Before initiation of IV amiodarone therapy, liver function tests, viral markers, hemoglobin level, serum creatinine, serum sodium and potassium, INR, and random blood sugar were measured. Liver function tests and viral markers included the following:

- Aminotransferases: Baseline ALT (alanine aminotransferase) and AST (aspartate aminotransferase) were measured using standard reagents by reaction rate assay based on the conversion of NADH to NAD.²⁰ Upper limit of normal (ULN) values was 44 IU/L for ALT and 34 IU/L for AST. Post-amiodarone aminotransferase levels were taken on the same day, 24, and 48 h following IV amiodarone. Peak levels were taken as post-treatment values.
- Other liver function tests included serum total and direct bilirubin (reference levels up to 1.2 and 0.3 mg/dl respectively), serum albumin (reference range 3.5 to 5.5 g/dl), and INR (international normalized ratio) that was considered high if > 1.5.
- Viral markers: Included hepatitis B virus (HBV) surface antigen detected by ELISA (enzyme linked immunosorbent assay), and hepatitis C virus (HCV) antibody detected by EIA (enzyme immunoassay).

Severity AILI was graded according to rise in aminotransferase level. Due to inclusion of patients with elevated baseline aminotransferase levels, the severity grading was classified based on changes relative to their baseline value rather than ULN as follows²¹:

- Grade 1: 1.25–2.5 folds of baseline value.
- Grade 2: 2.6–3.5 folds of baseline value.
- Grade 3: 3.6–5 folds of baseline value.
- Grade 4: > 5 folds of baseline value.

2.3. Radiologic investigations

Transthoracic echocardiography was done to all patients. Left ventricular dimensions were measured by M-mode in short axis parasternal view. Left ventricular ejection fraction (EF) was calculated by M-mode in case of normal regional wall motions and by 2D (modified Simpson's equation) in the presence of segmental wall motion abnormalities. Valve assessment including morphology, motion, transvalvular flow, and valve regurgitation was done. Structural heart disease was defined as the presence of dilated chambers, akinetic segments, low EF (< 50%), or any significant (more than moderate) valve lesion. Cardiomyopathy (CM) was defined as dilated left ventricle (LV) with or without low EF.

Abdominal ultrasound was done to assess liver size and parenchyma, any abdominal fluid collection, or splenomegaly. Congestive hepatomegaly was defined as increased liver size (with or without splenomegaly), attributed to right sided heart failure or severe tricuspid regurge on echocardiography, with tender hepatomegaly and hepatojugular reflux on physical examination.

2.4. Amiodarone therapy and in-hospital course

Amiodarone was given by IV loading of 5 mg/kg as a 30 min IV infusion, followed by infusion of 10 mg/kg/day over 24–48 h. Indication of therapy was documented by 12-lead surface electrocardiogram (ECG). The duration, total dose received, and the need of amiodarone discontinuation were recorded. Causes of discontinuation included significant liver injury defined as > 10 fold rise in aminotransferases relative to ULN, hemodynamically significant bradyarrhythmias, ineffec-

tiveness (failure to cardiovert arrhythmias), or QTc (corrected QT interval calculated by Bazett formula) prolongation > 500 ms with or without polymorphic ventricular tachycardia. In-hospital course included cardiac arrest, DC cardioversion, cardiopulmonary resuscitation (CPR) before or after amiodarone, the need for inotropic/vasopressor support (including dobutamine, dopamine, adrenaline, or noradrenaline), hepatic coma, or death.

2.5. Statistical analysis

Statistical Package for Social Sciences (SPSS, Inc, version 21, Chicago, IL) was used. D'Agostino–Pearson test was used to ascertain normality of continuous data distribution. Categorical data were expressed as frequencies, while continuous data were expressed as mean \pm SD or median according to data distribution. Comparison between categorical variables was done using Chi square or Fisher's exact test as appropriate. Comparison between continuous variables was done using unpaired *t*-test or Mann–Whitney test as appropriate. Predictors of AILI and severe (grade 4) AILI were listed in logistic regression models. Clinically relevant or variables with <0.1 significance on univariate analysis were further tested in multivariate models with conditional backward method. ROC curve analysis was used to find a cutoff value for continuous variables found to be significant predictors on multivariate analysis. Linear regression analysis was used to find predictors of post-amiodarone aminotransferases. Correlations with post-amiodarone transaminases were done using Spearman's rho. P value was considered significant if <0.05.

3. Results

3.1. Baseline characteristics

Baseline characteristics and comparison between cases and controls are shown in Table 1. All patients had baseline aminotransferase levels <5 folds of ULN before initiating amiodarone therapy. None of the studied patients was alcohol user. Cases had more frequent male gender ($P = 0.017$), underlying structural heart disease (predominantly cardiomyopathy, $P = 0.024$), chronic liver disease (predominantly congestive hepatomegaly, $P < 0.0001$), and +ve viral markers (predominantly HCV, $P = 0.026$) than controls. Inotropic support was more frequent in cases than in controls with borderline significance. Baseline AST ($P = 0.022$), total bilirubin ($P < 0.0001$), direct bilirubin ($P < 0.0001$), and serum creatinine ($P = 0.016$) were higher, while serum albumin ($P = 0.002$) was lower in cases than in controls.

3.2. Amiodarone therapy and in-hospital course

Indications of IV amiodarone therapy varied between atrial fibrillation (AF), supraventricular tachycardia (SVT), and ventricular arrhythmias (VAs) with no difference between cases and controls (Table 2). Discontinuation rate was 26.6% for the whole study population, 52.2% among cases, and 1.1% among controls. The main cause of discontinuation was liver enzyme elevation. Among cases, IV amiodarone was initiated in 16 patients following CPR from cardiac arrest due to VAs, and all received DC cardioversion, while in controls,

CPR was done to 6 patients ($P = 0.023$), 3 of whom received DC cardioversion before amiodarone therapy ($P = 0.002$). There were no significant differences between cases and controls regarding a number of patients who developed hepatic coma (although more in cases than in controls) and in-hospital deaths within 48 h of amiodarone therapy.

3.3. Predictors of AILI

Univariate logistic regression analysis with AILI as dependent variable and each of the variables shown in Table 3 as independent variables, showed that male gender, underlying CM, congestive hepatomegaly, +ve viral markers, increasing baseline total and direct bilirubin, lower serum albumin, increasing random blood sugar, CPR, and DC cardioversion were found to be significant predictors of AILI.

On multivariate analysis, male gender, CM, inotropic support, congestive hepatomegaly, +ve viral markers, baseline transaminases, total and direct bilirubin, serum albumin, random blood sugar, CPR, DC cardioversion, and dose of amiodarone were listed as independent variables in a logistic regression model. Backward-conditional method retained the presence of CM ($P = 0.032$), congestive hepatomegaly ($P = 0.001$), increasing baseline total bilirubin ($P < 0.0001$), DC cardioversion ($P = 0.015$), and increasing dose of amiodarone ($P = 0.014$) as independent predictors for AILI.

Continuous variables found to be significant predictors for AILI on multivariate analysis (baseline total bilirubin and dose of amiodarone) were further tested in a ROC curve. ROC curve analysis (Fig. 1A) showed that a total bilirubin > 1.3 mg/dl could predict AILI with a sensitivity and specificity of 64.4% and 77.8% respectively (AUC: 0.72, 95% CI: 0.64–0.79, $P < 0.0001$). Regarding dose of amiodarone, ROC curve analysis did not show a significant cutoff value (AUC: 0.54, 95% CI: 0.46–0.63, $P = 0.25$).

3.4. Predictors of severe AILI

Among patients with AILI (90 patients), grades 1, 2, 3, and 4 liver injury occurred in 0 (0%), 1 (1.1%), 19 (21.1%), and 70 (77.8%) patients (mean grade: 3.76 ± 0.45). In grade 4 AILI, mean rise of ALT and AST was 8.53 ± 4.33 and 7.67 ± 5.12 folds from baseline respectively.

Among the whole study population, univariate logistic regression analysis with severe (grade 4) AILI as dependent variable and each of the variables shown in Table 4 as independent variables showed that inotropic support, congestive hepatomegaly, increasing baseline total and direct bilirubins, lower serum albumin, and increasing dose of amiodarone were found to be significant predictors for severe AILI.

On multivariate analysis, inotropic support, congestive hepatomegaly, +ve viral markers, total and direct bilirubins, serum albumin, random blood sugar, DC cardioversion, and dose of amiodarone were listed as independent variables in a logistic regression model. Backward-conditional method retained inotropic support ($P = 0.034$), congestive hepatomegaly ($P = 0.012$), increasing baseline total bilirubin ($P = 0.001$), and increasing dose of amiodarone ($P = 0.002$) as independent predictors for severe AILI.

Continuous variables found to be significant predictors for severe AILI on multivariate analysis (baseline total bilirubin and dose of amiodarone) were further tested in a ROC curve.

Table 1 Baseline characteristics and comparison between cases and controls.

	All N = 180	Cases N = 90	Controls N = 90	P value
Age (years)	62.78 ± 12.78	63.65 ± 12.3	61.92 ± 13.25	0.36
Sex (M, F)	92, 88	54, 36	38, 52	0.017
Risk factors				
DM	107	52	55	0.64
HTN	123	61	62	0.87
Dyslipidemia	55	29	26	0.62
Smoking	65	36	29	0.27
Structural heart disease				
IHD	90	52	38	0.037
RHD	93	43	50	0.29
CM	12	5	7	0.55
AF/flutter	79	47	32	0.024
Statin use	88	41	47	0.37
Warfarin use	56	26	30	0.52
Antimicrobials	23	9	14	0.26
Inotropic support	133	70	63	0.23
Chronic liver disease	15	11	4	0.05
Congestive hepatomegaly	93	56	37	0.005
Cirrhotic changes	47	36	11	<0.0001
	46	20	26	0.39
Viral markers				
+ve/-ve	45/135	30/60	15/75	0.01
HBV	2	1	1	
HCV	38	24	14	0.026
Both HBV and HCV	5	5	0	
EF (%)	45.93 ± 12.39	46.54 ± 13.64	45.33 ± 11	0.51
EF < 40%	54	32	22	0.11
LVEDD (mm)	56.33 ± 9.5	56.2 ± 9.16	56.46 ± 9.88	0.85
LVESD (mm)	41.03 ± 9.88	40.56 ± 9.89	41.5 ± 9.9	0.52
TR				
Normal TV	88	42	46	
Mild/moderate	69	35	34	0.74
Severe	23	13	10	
MVD				
Normal MV	43	20	23	
Mild/moderate	126	61	65	0.09
Severe	11	9	2	
AVD				
Normal AV	111	59	52	0.24
Mild/moderate	67	31	36	
Severe	2	0	2	
Baseline laboratory tests				
ALT (IU/L)	29.94 ± 20.04 (median 23)	32.44 ± 21.97 (median 26)	27.44 ± 17.68 (median 21)	0.14
AST (IU/L)	37.61 ± 22.54 (median 30)	40.96 ± 25.31 (median 35.5)	34.26 ± 18.95 (median 28.5)	0.022
Total bilirubin (mg/dl)	1.71 ± 2.16 (median 1.2)	2.27 ± 2.87 (median 1.7)	1.15 ± 0.72 (median 0.9)	<0.0001
Direct bilirubin (mg/dl)	0.82 ± 1.67 (median 0.5)	1.15 ± 2.25 (median 0.8)	0.48 ± 0.57 (median 0.3)	<0.0001
Albumin (g/dl)	3.15 ± 0.65	3.01 ± 0.7	3.3 ± 0.57	0.002
INR	1.72 ± 1.38 (median 1.35)	1.79 ± 1.02 (median 1.4)	1.64 ± 1.67 (median 1.3)	0.08
Creatinine (mg/dl)	2.33 ± 3.23 (median 1.4)	2.42 ± 2.36 (median 1.7)	2.24 ± 3.93 (median 1.15)	0.016
Na ⁺ (mEq/L)	135.96 ± 9.46 (median 136)	135.02 ± 11.47 (median 135)	136.91 ± 6.82 (median 137)	0.069
K ⁺ (mEq/L)	4.08 ± 0.96 (median 4)	4.03 ± 1.12 (median 3.9)	4.14 ± 0.77 (median 4.1)	0.19
Hb (gm%)	10.27 ± 2.18	10.17 ± 2.28	10.38 ± 2.09	0.52
Random sugar (mg/dl)	210.1 ± 101.73 (median 192.5)	226.93 ± 121.3 (median 207.5)	193.26 ± 74.35 (median 190)	0.15

M: Male, F:Female, DM: Diabetes Mellitus, HTN: Hypertension, IHD: Ischemic heart disease, RHD: Rheumatic heart disease, CM: Cardiomyopathy, AF: Atrial fibrillation, HSM: Hepatosplenomegaly, HBV: Hepatitis B virus, HCV: Hepatitis C virus, EF: Ejection fraction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, TR: Tricuspid regurge, MVD: Mitral valve disease, AVD: Aortic valve disease, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase and Hb: Hemoglobin.

Table 2 Comparison between cases and controls regarding amiodarone therapy and in-hospital course.

	Cases <i>N</i> = 90	Controls <i>N</i> = 90	<i>P</i> value
Indication			
AF	48	50	
SVT	21	19	0.93
VAs	21	21	
Dose received (mg)	1198.33 ± 368.45 (median 1200)	1116.66 ± 238.08 (median 1200)	0.13
Duration (h)	27.33 ± 15.88 (median 24)	24.28 ± 6.2 (median 24)	0.64
Discontinuation			
Elevated liver enzymes	46	0	
Bradycardia	1	0	< 0.0001
Ineffectiveness	0	1	
QTc interval prolongation	0	0	
Post-amiodarone ALT (IU/L)	199.05 ± 117.5 (median 169.5)	29.63 ± 16.55 (median 25)	< 0.0001
ALT rise (folds of baseline values)	7.51 ± 4.28	1.16 ± 0.38	< 0.0001
Post-amiodarone AST (IU/L)	229.82 ± 102.76 (median 200.5)	39.02 ± 20.5 (median 31.5)	< 0.0001
AST rise (folds of baseline values)	6.82 ± 4.8	1.2 ± 0.45	< 0.0001
Hepatic coma	3	1	0.62
CPR	16	6	0.023
DC shock	16	3	0.002
Death	9	10	0.8

AF: Atrial fibrillation, SVT: Supraventricular tachycardia, VAs: Ventricular Arrhythmias, QTc: Corrected QT interval, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CPR: Cardiopulmonary resuscitation and DC: Direct current.

Table 3 Predictors of amiodarone induced liver injury on univariate and multivariate logistic regression analyses.

	Univariate			Multivariate		
	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value
Male gender	2.05	1.13–3.71	0.018	–		
CM	1.98	1.09–3.6	0.025	2.19	1.06–4.49	0.032
Inotropic support	2.99	0.91–9.78	0.07	–		
Congestive hepatomegaly	4.78	2.24–10.22	< 0.0001	4.24	1.81–9.93	0.001
+ve viral markers	2.5	1.23–5.06	0.011	–		
Increasing baseline ALT ^a	1.01	0.99–1.02	0.09	–		
Increasing baseline AST ^d	1.01	1–1.02	0.053	–		
Increasing baseline T. bilirubin ^b	2.44	1.62–3.67	< 0.0001	2.9	1.8–4.69	< 0.0001
Increasing baseline D. bilirubin ^b	2.86	1.66–4.91	< 0.0001	–		
Low baseline s. albumin ^c	2.05	1.27–3.3	0.003	–		
Increasing s. creatinine ^b	1.01	0.92–1.11	0.7	–		
Increasing random sugar ^b	1.003	1–1.7	0.029	–		
Low EF ^d	1.008	0.98–1.03	0.51	–		
CPR	3.02	1.12–8.13	0.028	–		
DC shock	6.27	1.75–22.3	0.005	5.83	1.4–24.2	0.015
Increasing dose of amiodarone ^e	1.001	1–1.003	0.087	1.002	1–1.003	0.014

OR: Odds ratio, CI: Confidence interval, CM: Cardiomyopathy, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, T. bilirubin: Total bilirubin, D. bilirubin: Direct bilirubin, EF: Ejection fraction, CPR: Cardiopulmonary resuscitation and DC: Direct current.

^a In increment of 1 IU/L.

^b In increment of 1 mg/dl.

^c In decrement of 1 g/dl.

^d In decrement of 1%.

^e In increment of 1 mg.

ROC curve analysis (Fig. 1B) showed that a total bilirubin > 1.6 mg/dl can predict severe AILI with a sensitivity and specificity of 52.9% and 77.3% respectively (AUC: 0.67, 95% CI: 0.6–0.74, *P* < 0.0001). Regarding dose of amiodarone, ROC curve analysis did not show a significant cutoff value (AUC: 0.55, 95% CI: 0.47–0.64, *P* = 0.2).

3.5. Correlations with post-amiodarone aminotransferases among cases

Among patients with AILI (90 cases), post-amiodarone ALT and AST were significantly correlated with each of baseline ALT, AST, total bilirubin, direct bilirubin, and EF (Table 5,

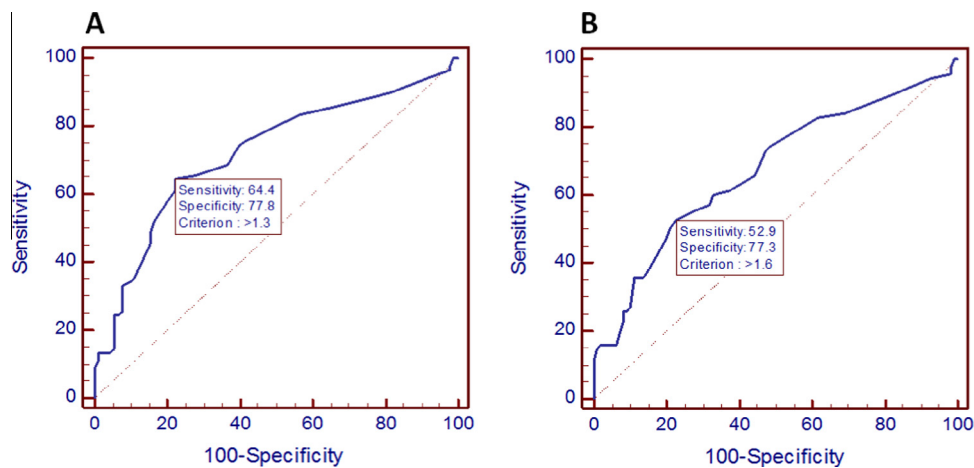


Figure 1 A: ROC curve showing predictive effect of total bilirubin on amiodarone induced liver injury (AUC 0.72, 95% CI: 0.64–0.79, $P < 0.0001$). A value of > 1.3 mg/dl was the best cutoff value that is likely associated with amiodarone induced liver injury. B: ROC curve showing predictive effect of total bilirubin on severe (grade 4) amiodarone induced liver injury (AUC: 0.67, 95% CI: 0.6–0.74, $P < 0.0001$). A value of > 1.6 mg/dl was the best cutoff value that is likely associated with severe amiodarone induced liver injury.

Table 4 Predictors of severe (grade 4) amiodarone induced liver injury on univariate and multivariate logistic regression analyses.

	Univariate			Multivariate		
	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value
Male gender	1.48	0.81–2.71	0.19	–	–	–
CM	1.36	0.74–2.4	0.31	–	–	–
Inotropic support	4.94	1.5–16.2	0.008	4.03	1.11–14.6	0.034
Congestive hepatomegaly	3.19	1.6–6.35	0.001	2.69	1.24–5.83	0.012
+ve viral markers	1.95	0.98–3.87	0.054	–	–	–
Increasing baseline ALT ^a	1.01	0.99–1.02	0.24	–	–	–
Increasing baseline AST ^a	1.006	0.99–1.02	0.41	–	–	–
Increasing baseline T. bilirubin ^b	1.87	1.33–2.64	< 0.0001	2.02	1.35–3.006	0.001
Increasing baseline D. bilirubin ^b	2.03	1.28–3.2	0.002	–	–	–
Low baseline s. albumin ^c	2.12	1.3–3.44	0.002	–	–	–
Increasing s. creatinine ^b	1.03	0.93–1.12	0.52	–	–	–
Increasing random sugar ^b	1.003	1–1.006	0.069	–	–	–
Low EF ^d	1.01	0.98–1.03	0.33	–	–	–
CPR	2.06	0.84–5.08	0.11	–	–	–
DC shock	2.37	0.9–6.24	0.079	–	–	–
Increasing dose of amiodarone ^e	1.001	1–1.003	0.027	1.002	1.001–1.003	0.002

OR: Odds ratio, CI: Confidence interval, CM: Cardiomyopathy, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, T. bilirubin: Total bilirubin, D. bilirubin: Direct bilirubin, EF: Ejection fraction, CPR: Cardiopulmonary resuscitation and DC: Direct current.

^a In increment of 1 IU/l.

^b In increment of 1 mg/dl.

^c In decrement of 1 g/dl.

^d In decrement of 1%.

^e In increment of 1 mg.

Fig. 2). Post-amiodarone AST, but not ALT, was significantly correlated with LVEDD and LVESD.

Stepwise linear regression analysis with post-amiodarone ALT and AST as dependant outcomes and baseline ALT, AST, total and direct bilirubins, and EF as independent variables showed that baseline ALT was the only significant independent predictor of post-amiodarone ALT ($P < 0.0001$), while baseline AST ($P < 0.0001$) and EF ($P = 0.012$) were the only significant independent predictors of post-amiodarone AST.

4. Discussion

Identifying the predictors of IV amiodarone induced liver injury (AILI) may help close patient monitoring or the choice of other measures alternative to amiodarone in high risk patients. While risk factors of liver injury with oral amiodarone were previously characterized,²² little is known regarding IV amiodarone.

In the current study, the presence of CM, congestive hepatomegaly, increasing baseline total bilirubin, DC

Table 5 Variables correlated with post-amiodarone aminotransferases.

	Post-amiodarone ALT	Post-amiodarone AST
Age		
Correlation coefficient*	-0.12	-0.17
P value	0.25	0.1
Baseline ALT		
Correlation coefficient	0.62	0.48
P value	< 0.0001	< 0.0001
Baseline AST		
Correlation coefficient	0.41	0.53
P value	< 0.0001	< 0.0001
Baseline T. bilirubin		
Correlation coefficient	0.34	0.29
P value	0.001	0.005
Baseline D. bilirubin		
Correlation coefficient	0.31	0.29
P value	0.003	0.005
Baseline s. albumin		
Correlation coefficient	-0.12	-0.09
P value	0.23	0.39
S. creatinine		
Correlation coefficient	-0.05	0.005
P value	0.58	0.96
Random sugar		
Correlation coefficient	0.05	0.15
P value	0.64	0.13
Hemoglobin		
Correlation coefficient	0.07	0.02
P value	0.49	0.81
EF		
Correlation coefficient	-0.22	-0.36
P value	0.037	< 0.0001
LVEDD		
Correlation coefficient	0.15	0.28
P value	0.15	0.007
LVESD		
Correlation coefficient	0.13	0.24
P value	0.2	0.022
Dose of amiodarone		
Correlation coefficient	-0.09	-0.14
P value	0.35	0.16

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, T. bilirubin: Total bilirubin, D. bilirubin: Direct bilirubin, EF: Ejection fraction, LVEDD: Left ventricular end diastolic diameter and LVESD: Left ventricular end systolic diameter.

* All correlations were done using Spearman's rho.

cardioversion, and increasing dose of amiodarone were found to be independent predictors for AILI on multivariate analysis. We demonstrated that underlying CM, congestive hepatomegaly, and DC cardioversion increased the possibility (or odds) of having AILI by 2, 4, and 5 folds respectively, and every 1 mg/dl increase in baseline total bilirubin raised the possibility of having AILI by about 3 folds. We also demonstrated that every 1 mg increase in amiodarone dose raised the odds of having AILI by 1.002 fold (i.e. 1.9 folds with a dose of 450 mg) which means that the possibility of liver injury almost doubles with every 12 hours of IV amiodarone therapy. Similarly, heart failure, congestive liver disease, high

dose of IV amiodarone, and hypotension from ventricular arrhythmias were observed in patients with AILI among case reports.^{4,18,19}

Liver injury was found to be severe in the majority (77.8%) of our cases as well as most of the case reports, indicating that injury might follow "all or none" phenomenon. This can also explain that the predictors of severe AILI in our study were similar to those of AILI. However, in a retrospective study, Huang et al.²³ reported that liver injury was mild in 92 out of 101 patients with IV amiodarone induced hepatotoxicity. Two reasons were likely behind this discrepancy; the first is the difference in defining the severity of liver injury (they

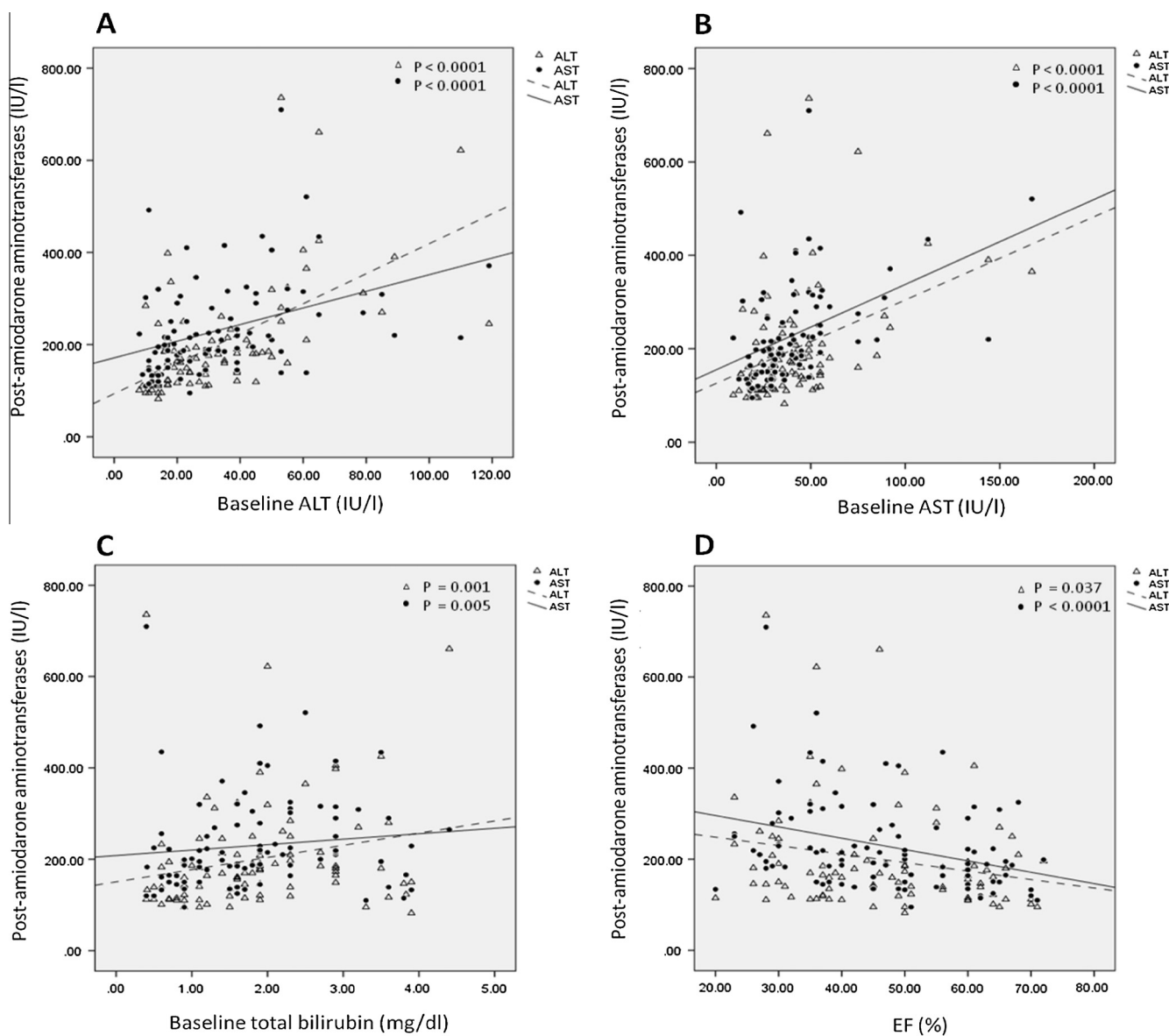


Figure 2 Correlations with post-amiodarone aminotransferases, showing significant correlations with each of baseline ALT (A), AST (B), total bilirubin (C), and ejection fraction (D).

defined severe injury as ALT > 10 folds of ULN in their study). The second reason is the incomplete amiodarone dosing regimen given in 55.7% of their study population in the form of either loading without maintenance or maintenance without loading. Furthermore, the loading dose in their study was much lower than that recommended by guidelines. Although they studied a large number of patients, they did not include baseline liver functions, abdominal ultrasound, or echocardiographic measures in their analysis. However, they found that male gender was a risk factor for IV amiodarone induced hepatotoxicity which was similar to what we observed on univariate analysis. The same was also reported with oral amiodarone.²⁴

In the present study, baseline total bilirubin was a highly significant predictor for AILI and severe AILI. A total bilirubin > 1.3 mg/dl could predict AILI, while a serum level > 1.6 mg could predict severe AILI with low sensitivity but

higher specificity. In a similar context, total bilirubin was found to be a significant predictor for drug induced liver injury (DILI) in general, and a cutoff level ≥ 1.0 mg/dL was associated with high risk of acute liver failure.²⁵ High serum bilirubin is associated with hepatic decompensation and was solely found to be a prognostic marker in patients with chronic liver disease in which aminotransferases may be mildly elevated.²⁶ We observed that baseline ALT and AST were significant predictors for severity of liver injury on linear regression analysis. High baseline aminotransferases were also associated with high risk of acute liver failure in patients with DILI.²⁵

We demonstrated that hemodynamic state might predispose liver to AILI. While the presence of cardiomyopathy and the need for DC cardioversion due to VAs could predict AILI, the need for inotropic support was associated with severe AILI. The debate around liver hypoperfusion whether or not to be the actual cause of injury associated with IV

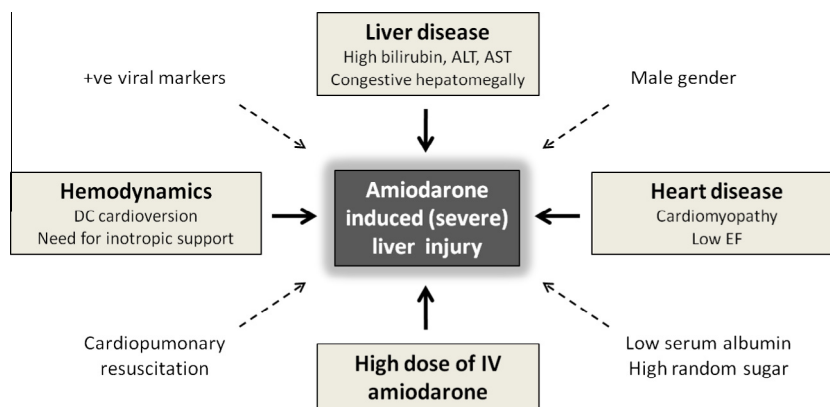


Figure 3 Illustrative summary of our findings, showing predictors of the occurrence and severity of IV amiodarone induced liver injury in the present study. Solid arrows indicate multivariate predictors. Dashed arrows indicate univariate predictors. ALT: Alanine aminotransferase. EF: Ejection fraction.

amiodarone^{5,6,16} demanded a case control study with multivariate analysis. Since we found other factors to be independently associated with AILI, the link between liver hypoperfusion and AILI is likely to be a predisposition rather than a causal relationship.

Underlying cardiac condition was related to AILI in the present study in two aspects. The presence of CM was a significant predictor for its occurrence on logistic regression, and the EF was a significant predictor for its severity on linear regression. This was in accordance with several case studies in which LV dysfunction was observed.^{4,7,12,18,19} The same was also found with oral amiodarone.²² If direct drug toxicity is assumed, LV dysfunction delays amiodarone elimination by prolonging the half life of its metabolites, and therefore might predispose to liver injury.⁷

We summarized the predictors of AILI and its severity in Fig. 3 based on our findings. In high risk patients, we recommend that benefit of IV amiodarone should be weighed against its possible hazard, especially in non-life threatening conditions such as atrial fibrillation.

5. Conclusions

Parenteral amiodarone induced liver injury (AILI) and its severity could be predicted by underlying heart disease (cardiomyopathy, low EF), liver disease (congestive hepatomegaly, elevated bilirubin and aminotransferases), hemodynamic instability (DC cardioversion, inotropic support), and increasing dose of amiodarone.

Conflict of interests

The authors have no conflict of interests to disclose.

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