

# Association of aspartate aminotransferase in statin-induced rhabdomyolysis

Xu Cong Ruan BSc (Pharm)(Hons), MD;<sup>1</sup> Lian Leng Low MBBS, MMed (Fam Med);<sup>2</sup> Yu Heng Kwan BSc (Pharm)(Hons)<sup>3</sup>

<sup>1</sup> MD Candidate; Duke-NUS Medical School, Singapore

<sup>2</sup> Associate Consultant, Department of Family Medicine and Continuing Care, Singapore General Hospital, Singapore

<sup>3</sup> MD-PhD Candidate, Program in Health Services and Systems Research, Duke-NUS Medical School, Singapore

## ABSTRACT

**INTRODUCTION:** The risk of rhabdomyolysis in the general population is elevated by the increased prevalence of statin use. As the presentation of rhabdomyolysis is varied, there is a risk of delayed diagnosis leading to patient complications and increased healthcare costs. Creatine kinase (CK) alone is not sufficiently predictive for risk stratification. Beyond serum CK, other biomarkers such as transaminases may be used as surrogates to evaluate rhabdomyolysis severity and predict complication risks.

**AIM:** To assess if other biomarkers are associated with peak CK and severity of rhabdomyolysis to aid in clinical diagnosis of rhabdomyolysis.

**METHODS:** A retrospective study was conducted at an acute care hospital from 2008 to 2011. Inclusion criteria were: (1) patients diagnosed with statin-induced rhabdomyolysis; and (2) peak CK levels of  $\geq 1000$  IU/L. Patients with post-operational rhabdomyolysis, acute myocardial infarction and who had suffered from road traffic accidents were excluded. A total of 24,332 patients were screened, and 78 patients fulfilled our inclusion criteria.

**RESULTS:** Aspartate aminotransferase (AST) was found to be positively associated with peak CK levels in the multivariable linear regression model after adjusting for alanine aminotransferase (ALT) levels ( $P = 0.002$ ;  $\beta = 83.18$ ). Aspartate aminotransferase was found to be associated with severity of rhabdomyolysis in the multivariable logistics regression model after adjusting for ALT levels ( $P = 0.015$ ; OR = 1.01).

**DISCUSSION:** Aspartate transferase is associated with raised peak CK levels and severity of rhabdomyolysis. Clinicians may consider ordering AST to aid in the clinical diagnosis of rhabdomyolysis.

**KEYWORDS:** Rhabdomyolysis; statins; biomarkers

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## CORRESPONDENCE TO:

**Yu Heng Kwan**  
Duke-NUS Medical School,  
8 College Road, 169857,  
Singapore  
yuheng@u.duke.nus.edu

## Introduction

Rhabdomyolysis is precipitated by skeletal muscle breakdown leading to the release of creatine kinase (CK) into the bloodstream.<sup>1</sup> In addition to CK elevation, the breakdown of skeletal muscles also leads to leakage of intracellular contents such as potassium, aldolase, phosphate, myoglobin, lactate dehydrogenase (LDH) and aspartate aminotransferase (AST).<sup>1</sup> The presentation of rhabdomyolysis is varied, with some individuals

developing myalgia and muscle weakness while others are asymptomatic.<sup>2</sup> If untreated, patients may progress to acute kidney injury (AKI), compartment syndrome and eventual demise.<sup>1,2</sup>

The risk of rhabdomyolysis in the general population is further elevated as more patients are placed on statins to control cardiovascular disease risk factors.<sup>3</sup> Statin-induced rhabdomyolysis, resulting in hospital admission, is a concern and adds to healthcare costs.<sup>4</sup>

Given the potential for poor outcomes with delayed treatment in patients with rhabdomyolysis,<sup>1</sup> it is important for clinicians to stratify patients based on their risk of complications. Biomarkers, such as CK, that directly correlate with the degree of muscle injury, have been studied.<sup>1,2</sup> McMahon *et al.* showed that patients with high serum CK (>40,000 IU/L) are at high risk for AKI, and early hydration is vital to prevent complications.<sup>5</sup> However, CK levels alone are not sufficiently predictive to stratify risk.<sup>5</sup>

Beyond serum CK, other routine biomarkers, such as electrolytes, transaminases and urine myoglobin may be performed in patients with rhabdomyolysis. Potentially, these markers may be used as surrogates to evaluate the severity of rhabdomyolysis and predict the risk of complications. Our study objective was to find out which routinely performed biomarkers are associated with elevated serum CK, thereby facilitating clinicians in achieving an earlier diagnosis of rhabdomyolysis, stratifying patients with higher risk of complications and instituting early treatment of these patients to prevent disease progression.<sup>1</sup> Therefore, we aimed to find out which routinely performed biomarkers are associated with peak serum CK and severity of rhabdomyolysis. This knowledge will allow increased vigilance in anticipating rhabdomyolysis in statin users.

## Methods

### Study design

A retrospective study was conducted at an acute care hospital in Singapore. Based on the hospital's medical records, hospitalized patients from June 2008 to May 2011 were screened for incidences of statin-induced rhabdomyolysis. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for a primary diagnosis of other disorders of muscle, ligament and fascia (728.89, including rhabdomyolysis) was used to identify potential cases of rhabdomyolysis and myopathy. The study was approved by Institutional Review Board with a waiver for patient consent.

### WHAT GAP THIS FILLS

**What is already known:** Statin use is prevalent in an ageing population. Routine liver function tests are necessary to monitor liver function.

**What this study adds:** Aspartate aminotransferase (AST) is associated in statin-induced rhabdomyolysis patients. AST may be useful to look out for rhabdomyolysis.

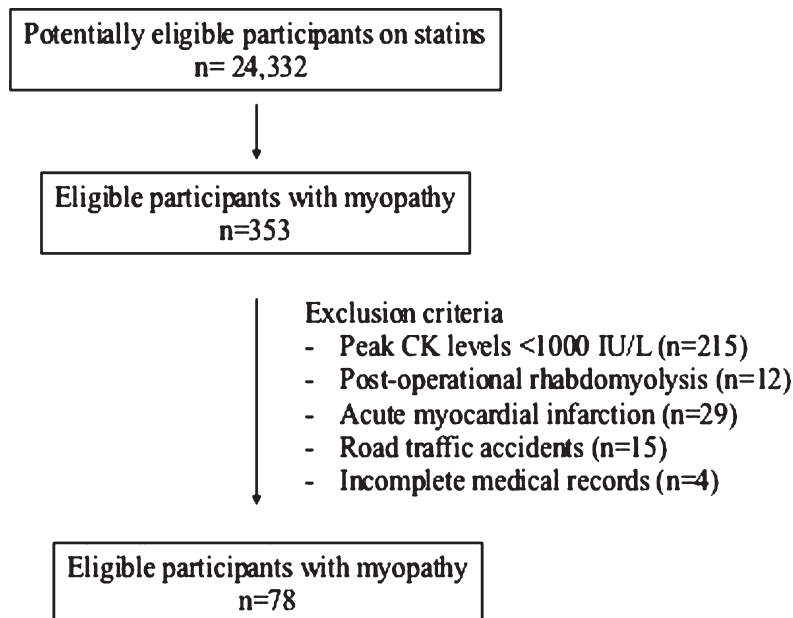
### Study group

The inclusion criteria were: (1) patients diagnosed clinically with statin-induced rhabdomyolysis; and (2) peak CK levels of  $\geq 1000$  IU/L.<sup>2</sup> Patients with post-operational rhabdomyolysis, acute myocardial infarction and who suffered from road traffic accidents were excluded. Figure 1 shows a flow diagram to illustrate patient selection into this study.<sup>6</sup>

### Data collection

Data were retrieved from the hospital's electronic clinical data monitoring system and patients' case-notes. Information extracted included demographics data and laboratory test results including peak CK levels, urine myoglobin,

Figure 1. Flow diagram of patient selection



electrolytes, liver, renal and lipid panels during hospitalization.

### Statistical analysis

Univariable linear regression analysis was performed to identify variables associated with an increase in peak CK in our study population. Variables found to have a *P* value of < 0.1 were subsequently included in a multivariable linear regression model. Variables with *P* values < 0.05 in the final model were considered statistically significant.

We defined severe rhabdomyolysis as peak CK  $\geq 5000$  IU/L, while mild rhabdomyolysis was

defined as peak CK of 1000–5000 IU/L.<sup>7</sup> To assess factors associated with severity of rhabdomyolysis, univariable logistics regression analysis was performed. Variables found to have a *P* value of < 0.1 were subsequently included in the multivariable logistics regression model. Variables with *P* values < 0.05 in the final model were considered statistically significant. We conducted further sensitivity analysis using both forward and backward stepwise regressions to assess if the estimates differed from the multivariable linear regression.

### Results

A total of 24,332 patients were screened and 78 patients fulfilled our inclusion criteria. The mean age of the study group was 69.0 years (standard deviation = 11.9 years) (Table 1). Most patients were male (79.5%) and Chinese (65.4%), 50% were diabetic and 21.9% had a history of renal impairment before hospitalization. Most patients (69.2%) were at high risk of coronary heart disease (CHD). Of the patients with statin-induced rhabdomyolysis, 60.3% were at the Third Report of the National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP III) low-density lipoprotein (LDL) goal.

#### Variables associated with an increase in peak CK

From the univariable linear regression model, alanine aminotransferase (ALT) (*P* < 0.001;  $\beta = 141.72$ ) and AST (*P* < 0.001;  $\beta = 76.52$ ) were selected for the multivariable linear regression model (Table 2). Creatinine, urea, potassium, calcium, phosphate and urine myoglobin were not considered for the multivariable model as their univariable *P* values were > 0.1. Only AST was found to be positively associated with peak CK levels in the multivariable linear regression model after adjusting for ALT levels (*P* = 0.002;  $\beta = 83.18$ ) (Table 2). The results were similar when the data were analysed with both forward and backward stepwise regression.

#### Variables associated with severity of rhabdomyolysis

Similar results were found when we binarised the peak CK values to define severity of rhabdo-

Table 1. Patient demographics

Characteristics	Total (%) (n = 78)
Mean age (years) $\pm$ s.d.	69.0 $\pm$ 11.9
Sex	
Male	62 (79.5)
Female	16 (20.5)
Ethnicity	
Chinese	51 (65.4)
Malay	25 (32.1)
Indian	2 (2.6)
Smoker	10 (12.8)
Type 2 diabetes	39 (50.0)
Renal impairment	17 (21.9)
Hepatic impairment	10 (12.8)
Treatment regimen	
Monotherapy	72 (92.3)
Combinational therapy	6 (7.7)
Ezetimibe	1
Fenofibrate	4
Fenofibrate + Nicotinic acid	1
Statin	
Simvastatin	69 (88.5)
Lovastatin	7 (9.0)
Rosuvastatin	2 (2.6)
10-year CHD risk	
High risk (>20%)	54 (69.2)
Intermediate risk (10–20%)	18 (23.1)
Low risk (<10%)	6 (7.7)
LDL level	
Reached ATP III goal	47 (60.3)
Not at goal	25 (32.1)
Unknown	6 (7.7)
Median peak CK level [IQR]	2730 [1734 – 6380]

IQR (interquartile range); s.d. (standard deviation); CHD (coronary heart disease); LDL (low-density lipoprotein); ATP (Adult Treatment Panel).

myolysis. From the univariable logistics regression model, ALT ( $P = 0.022$ ; OR = 1.01) and AST ( $P = 0.004$ ; OR = 1.01) were selected for the multivariable logistics regression model (Table 3). Creatinine, urea, potassium, calcium, phosphate and urine myoglobin were not considered for the multivariable model as their univariable  $P$ -values were  $>0.1$ . Only AST was found to be positively associated with severity of rhabdomyolysis in the multivariable logistics regression model after adjusting for ALT levels ( $P = 0.015$ ; OR = 1.01) (Table 3). The results were similar when the data were analysed with both forward and backward stepwise regression.

## Discussion

This is the first research report examining biomarkers associated with the peak CK values and severity of rhabdomyolysis in patients with statin-induced rhabdomyolysis, while adjusting with a comprehensive set of variables. We found AST to be associated with peak CK levels. This is congruent with the understanding that rhabdomyolysis leads to the leakage of intracellular contents from skeletal muscles, which precipitates AST elevation.<sup>1,2</sup> AST is an indirect surrogate for the level of muscle injury.<sup>8</sup> ALT, in contrast, is mainly released from liver cells, and is therefore less influenced by changes in muscle metabolism.<sup>7</sup>

Raurich *et al.* reported that the mortality rate of patients with rhabdomyolysis was higher in patients with elevated AST.<sup>9</sup> We postulate that AST levels may aid in the prediction of complication rates among rhabdomyolysis patients and could be used as a stratification tool in addition to peak CK.

There are several limitations in our study. Study participants were recruited from tertiary care, so our findings may not be generalisable to patients with myalgia or myositis who were followed up in primary care. In addition, given that this was a retrospective study, the lack of aldolase level measurements among our patient cohort meant we were unable to incorporate it as a study variable. This is a common issue faced by other studies relying on retrospective data.

## Conclusion

Elevated AST is associated with raised peak CK levels and severity of rhabdomyolysis. Clinicians may consider ordering an AST test to aid in the clinical diagnosis of rhabdomyolysis and allow for the early initiation of intravenous hydration for hospitalized rhabdomyolysis patients.

Table 2. Linear regression analysis using peak creatine kinase as the dependent variable

Parameter	Univariable analysis		Multivariable analysis	
	Beta coefficient (95% CI)	P value	Beta coefficient (95% CI)	P value
ALT	141.72 (71.39, 212.04)	<0.001	-18.74 (-136.14, 98.67)	0.751
AST	76.52 (48.46, 104.58)	<0.001	83.18 (32.78, 133.58)	0.002
Creatinine	7.15 (-36.39, 22.10)	0.628		
Urea	-198.23 (-758.37, 361.91)	0.483		
Potassium	-104.54 (-740.27, 531.18)	0.744		
Calcium	1143.89 (-13789.73, 16077.51)	0.879		
Phosphate	-1899.82 (-9400.04, 5600.40)	0.614		
Urine myoglobin	-1.05 (-9.61, 7.52)	0.789		

CI (confidence interval); ALT (alanine aminotransferase); AST (aspartate aminotransferase).

Table 3. Logistics linear regression analysis severity of rhabdomyolysis as the dependent variable

Parameter	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
ALT	1.01 (1.00, 1.02)	0.022	1.03 (0.96, 1.01)	0.399
AST	1.01 (1.00, 1.02)	0.004	1.01 (1.00, 1.03)	0.015
Creatinine	0.99 (0.99, 1.00)	0.720		
Urea	0.96 (0.91, 1.02)	0.298		
Potassium	0.72 (0.42, 1.21)	0.222		
Calcium	0.59 (0.08, 4.06)	0.594		
Phosphate	1.24 (0.47, 3.31)	0.655		
Urine myoglobin	0.99 (0.99, 1.00)	0.524		

Severe rhabdomyolysis was defined as a peak creatine kinase (CK) level of more than 5000 IU/L, whereas mild rhabdomyolysis was defined as peak CK level of more than 1000 to 5000 IU/L.

CI (confidence interval); ALT (alanine aminotransferase); AST (aspartate aminotransferase).

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**COMPETING INTERESTS**

None.