Limited Utility of Plasma M30 in Discriminating Non-Alcoholic Steatohepatitis from Steatosis – A Comparison with Routine Biochemical Markers

Wah-Kheong Chan1*, Pavai Sthaneswar2, Nik Raihan Nik Mustapha3, Sanjiv Mahadeva1

1 Gastroenterology and Hepatology Unit, Gastrointestinal Endoscopy Unit, Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, 2 Division of Laboratory Medicine, Department of Pathology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, 3 Department of Pathology, Hospital Alor Setar, Alor Setar, Kedah, Malaysia

Abstract

Introduction: The utility of Cytokeratin-18 fragment, namely CK18Asp396 (M30), for the diagnosis of non-alcoholic steatohepatitis (NASH) is currently uncertain. We aimed to provide further data in this area among multi-ethnic Asian subjects with NAFLD.

Materials and Methods: The accuracy of M30 for detecting NASH was compared with serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyl transpeptidase (GGT) levels in consecutive adult subjects with biopsy-proven non-alcoholic fatty liver disease (NAFLD).

Results: Data for 93 NAFLD subjects (mean age 51.0 ± 11.1 years old and 51.6% males) and 20 healthy controls (mean age 50.2 ± 16.4 years old and 33.3% males) were analyzed. There were 39 NASH subjects (41.9%) and 54 non-NASH subjects (58.1%) among the NAFLD subjects. Plasma M30 (349 U/L vs. 162 U/L), and serum ALT (70 IU/L vs. 26 IU/L), AST (41 IU/L vs. 20 IU/L) and GGT (75 IU/L vs. 33 IU/L) were significantly higher in NAFLD subjects than in healthy controls. Serum ALT (86 IU/L vs. 61 IU/L), AST (58 IU/L vs. 34 IU/L) and GGT (97 IU/L vs. 56 IU/L) were significantly higher in NASH subjects compared to non-NASH subjects, but no significant difference was observed with plasma M30 (435 U/L vs. 331 U/L). The accuracy of plasma M30, and serum ALT and GGT was good for predicting NAFLD (AUROC 0.91, 0.95, 0.87 and 0.85, respectively) but less so for NASH (AUROC 0.59, 0.64, 0.75 and 0.68, respectively). Serum ALT and AST, but not plasma M30 showed a significant trend with increasing grades of ballooning and lobular inflammation.

Conclusion: The utility of M30 in the detection of NASH in clinical practice appears limited, in comparison to routine biochemical markers.

Introduction

The prevalence of non-alcoholic fatty liver disease (NAFLD) has increased rapidly over the years, parallel to the increase in metabolic syndrome, and it is recognized as one of the most common causes of chronic liver disease worldwide [1]. NAFLD encompasses a spectrum of liver conditions, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) to fibrosis and cirrhosis. While simple steatosis is generally considered benign, NASH may lead to fibrosis and eventually cirrhosis, with an increased risk of morbidity and mortality [2,3].

The diagnosis of NASH is made by histopathological examination of a liver biopsy specimen. However, liver biopsy is invasive and it is associated with a small risk of serious complications [4]. It is not practical to subject all subjects with NAFLD to a liver biopsy to diagnose NASH. Furthermore, repeated liver biopsies to monitor disease progression in clinical practice is not acceptable either. A simple and reliable non-invasive test is needed for the diagnosis and follow-up of NASH.

Cytokeratin 18 (CK-18) is the major intermediate filament protein in liver cells and it is cleaved by caspases that are activated during apoptosis of liver cells, a process which plays an important role in NASH [5]. CK-18 fragment, namely CK18Asp396 (M30), has been studied for the diagnosis of NASH with varying results [6–13]. Whilst some studies have suggested that specific cut-off levels of CK-18 can reliably detect NASH in a cohort of NAFLD subjects [6–10], others have not shown such promising results [11–13]. These contrasting data may have been due to studies with a