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Combination of alpha-1-acid glycoprotein and alpha-fetoprotein as an improved diagnostic tool for hepatocellular carcinoma

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ABSTRACT

Background: To evaluate the diagnostic value of α-1-acid glycoprotein (AAG) and the combination with alpha-fetoprotein (AFP) in hepatocellular carcinoma (HCC) patients.
Methods: AAG was measured in serum of 65 HCC patients and 54 chronic liver diseases (CLD) patients by using proteomic approach. Sensitivity and specificity of AAG and its combination with AFP were determined and compared with AFP alone for the diagnosis of HCC.
Results: The expression concentration of AAG was significantly higher in HCC patients than chronic liver disease with sensitivity (77%) and accuracy (83%). Receiver operating characteristic analysis yielded the following AUC: AFP 0.750 (CI 95% 0.663–0.837), AAG 0.907 (CI 95% 0.855–0.960) and AFP+AAG 0.943 (CI 95% 0.897–0.988). At a specificity of 90%, the combination of AFP+AAG had sensitivity 89% and accuracy 90%, which was higher than sensitivity (52.3%) and accuracy (70%) when using AFP alone.
Conclusion: The combination of AAG and AFP shows high sensitivity and improves the accuracy of HCC diagnosis.

1. Introduction

α-1-acid glycoprotein (AAG) is a member of the lipocalins, a family that shares at least 2 structurally conserved sequence motifs [1]. AAG is synthesized predominantly in the liver as a single polypeptide of 41–43 kDa, made up of 183 amino acids, with a hydrophobic prosthetic group, and a high content of sialic acid [2]. The biological functions of AAG are poorly understood; it is an acute phase protein, and its plasma concentration increase as a response to inflammation is triggered by cytokines [3,4]. As a consequence, AAG concentrations vary in many physiological states (age and pregnancy) and pathological conditions such as liver cirrhosis, renal disease, and cancer [5–7]. Significant increases of AAG have been found in patients with active lung and gastrointestinal cancers compared with patients with inactive disease. Moreover, in patients with colorectal cancer treated with 5-fluorouracil, AAG correlates with a response to therapy, with lower AAG concentrations seen in responding patients and higher AAG concentrations found in patients with progressive disease [8,9]. Recently, AAG serum concentrations has been suggested as a potential marker for cirrhosis and hepatocellular carcinoma (HCC) [10,11].

Prognosis and survival of patients with HCC is heavily affected by the disease stage at the time of diagnosis. The availability of reliable markers would greatly improve the chances of detecting early stage HCC. Imaging modalities, such as ultrasonography, are currently limited by their low positive predictive values (11). It has been widely reported that α-fetoprotein (AFP), the only serological marker currently available in clinical practice, is not a sufficiently reliable marker to identity HCC patients, mainly because of its poor sensitivity [12]. Several studies indicate that high concentrations of AFP are related to poor prognosis as well as the histologic grade of malignancy. Those with high serum AFP concentrations at the time of HCC diagnosis have more unfavourable outcomes compared patients with low AFP concentrations [13,14]. Moreover, equivocal AFP concentrations are common in *non*-malignant chronic liver diseases (CLD) and the sensitivity of the AFP test for HCC in this setting thus tends to be low [15]. This observation leads to a critical need to review how AFP can be utilized to improve its utility in the detection of HCC. This may be in combination with newer markers such as AAG.

The absence of correlation between AAG and AFP suggests that each marker is related to a different aspect of HCC. The use of these markers in combination however may improve the diagnostic accuracy of HCC diagnosis. By undertaking a proteomic approach, we measured (i) the concentration of AAG in the sera from HCC patients in comparison with CLD, (ii) the diagnostic value of serum AAG compared with AFP (AFP≤200 ng/ml and AFP>200 ng/ml), and

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