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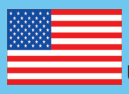

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Room 903, Building D, Ocean International Center,
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Telephone: +86-10-85381892
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World Journal of Hepatology
Room 903, Building D, Ocean International Center,
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Telephone: +86-10-85381892
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OBSERVATION

Overview of screening methods for fatty liver disease in children

Caroline Anitha Devadason, Ann O Scheimann

Caroline Anitha Devadason, Ann O Scheimann, Division of Pediatric Gastroenterology and Nutrition, Johns Hopkins University, Baltimore, MD 21287, United States
Author contributions: Devadason CA did research and wrote manuscript; Scheimann AO helped with manuscript development and writing/editing.
Correspondence to: Ann O Scheimann, MD, MBA, Division of Pediatric Gastroenterology and Nutrition, Johns Hopkins University, Baltimore, MD 21287, United States. ascheim1@jhmi.edu
Telephone: +1-410-9558769 Fax: +1-410-9551464
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Abstract

The prevalence of obesity and obesity related comorbidities including diabetes and nonalcoholic fatty liver disease (NAFLD) has been rising globally. Nonalcoholic fatty liver disease is emerging as a common liver disease among adults which can lead to the eventual development of complications including cirrhosis and hepatocellular carcinoma. With the rise of obesity in children, the development of detection methods for the presence of NAFLD is becoming imperative. Although the gold standard for diagnosis is liver biopsy, practical issues limit pediatric use and warrant development of noninvasive or minimally invasive screening tools for the detection and staging of NAFLD. A variety of diagnostic methods have been studied including use aminotransferases, imaging studies and serologic markers which have some population-based limitations. Additional factors such as gender and ethnicity may also play a role in the screening of NAFLD in pediatric population studies.

Key words: Nonalcoholic fatty liver disease; Children; Alanine aminotransferase; Ethnicity; Gender; Detection methods

Peer reviewers: Stephanie Abrams, MD, Texas Children's Hospital, 6621 Fannin, Suite 1010.00, Houston, TX 77030, United States; Jean Molleston, MD, Riley Hospital for Children, 702 Barnhill Drive, ROC 4210, Indianapolis, IN 46202, United States

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has emerged as the most common cause of liver disease among children, paralleling the rise in obesity over the past few decades. Fatty liver disease has a spectrum of clinical manifestations, ranging from simple steatosis to steatosis with inflammation and fibrosis nonalcoholic steatohepatitis (NASH)[1]. NAFLD was first described by Zelman[2] in 1952 among an inpatient population of thirty obese men with liver disease. In 1983, Moran *et al*[3] reported 3 children less than 14 years of age with severe hepatitis and fibrosis. Population studies also seem to suggest racial and gender variability regarding NAFLD[4,5]. Factors including obesity, gender and ethnicity may influence the development of NAFLD.

Development of safe and cost-effective methods for screening and detection of NAFLD is critical given the large number of patients. Frequently used screening methods for NAFLD include aminotransferases and ultrasonography. NAFLD is the most common etiology for transaminase elevation among adults[6]. Although the gold standard for diagnosis is a liver biopsy, the invasiveness and expense of the procedure limits the feasibility of this option in children. Available imaging modalities, including ultrasound, computed axial tomography and magnetic resonance imaging, have some limitations for broad use, including cost, radiation exposure, as well

as technical limitations due to body habitus. A literature search was performed, through PubMed, using the following and combination of the following terms: NAFLD, NASH, nonalcoholic fatty liver, steatohepatitis, infant, child and adolescent. The results were limited to human studies, and infant, child, adolescent and the English language. The utility of current screening methods for the detection of pediatric NAFLD will be reviewed.

ALANINE AMINOTRANSFERASE AS A SURROGATE OF NAFLD

Unexplained alanine aminotransferase (ALT) elevation is a frequently used surrogate for the presence of NAFLD in children and adults. ALT elevation (> 30 U/L) was reported in 6% of overweight adolescents and 10% of obese adolescents among 2450 children enrolled in the NHANES Ⅲ survey (National Health and Examination Survey cycle Ⅲ) by Strauss *et al*[7]. ALT elevation (>30 U/L) was an independent predictor for NAFLD among an Italian pediatric sample of 268 children between the ages of 6 and 20 years with a body mess index (BMI) of >90th percentile[8]. ALT elevation was present in 76 children with NAFLD (81% sensitivity of ALT for NAFLD prediction); in 49 children ALT values were > 40 U/L (89% sensitivity of ALT for NAFLD prediction)[8]. Louthan *et al*[5] noted that elevated ALT (ALT > 40 U/L) was four times more likely in obese children.

In several studies, ALT elevation has correlated with the presence of hepatic fat on imaging. Fishbein *et al*[9] reported a retrospective review of hepatic magnetic resonance imaging (MRI) findings of 39 obese Caucasian children, noting hepatic fat fraction correlated with serum ALT (ALT > 35; $r = 0.44$; $P < 0.05$) and age ($r = 0.54$; $P < 0.005$) but not with BMI z-score. In a prior study of obese children with hepatomegaly, he reported 21 of 22 (95%) subjects had elevated fat fraction on hepatic MRI and 12 of 20 (60%) had elevated serum ALT (ALT > 35)[10]. Correlation between ALT elevation (ALT > 58) and fatty liver on ultrasound ($P < 0.001$) was reported in a prospective study of 84 Chinese children seen in the obesity and lipid disorder clinic (ages 9.5-14 years); gamma-glutamyl-transpeptidase (GGT, abnormal GGT > 40) also correlated with fatty liver on imaging ($P < 0.001$)[11]. Tazawa *et al*[12] reported sensitivity, specificity and positive predictive values of 0.92, 0.62 and 0.83 respectively for ALT elevation (ALT > 30 U/L) and detection of evidence of fatty liver on ultrasound for a school-aged population in Japan.

PITFALLS OF ALT

There can be shortcomings with utilizing ALT as a screening method for NAFLD. Aminotransferase elevation is not universally encountered among patients with NAFLD. The Dallas Heart study conducted in Dallas County on 2287 adult subjects revealed that abnormal ALT was not a useful diagnosis of NAFLD as 79% of subjects with hepatic steatosis (determined by elevated hepatic triglycerides on imaging) had normal ALT levels[13]. In the study conducted by Franzese *et al*[14], 26 out of 38 (68%) obese children with fatty liver on imaging had normal aminotransaminases. Similar concerns were raised by Fishbein *et al*[10] upon demonstration that ALT (ALT > 35) did not detect low levels of hepatic fat fraction. In the study by Tazawa *et al*[12], 18% of Japanese schoolchildren with normal ALT levels (ALT < 30) had ultrasound findings of a fatty fibrotic pattern suggestive of nonalcoholic steatohepatitis. A study by Burgert *et al*[15] demonstrated that only 48% of obese children (42% Caucasian/25% African American/33% Hispanic) with intrahepatic fat accumulation on MRI had abnormal ALT levels (ALT > 35), concluding that use of serum ALT as a screening tool may not be effective. Of note, children with an absence of abnormal ALT levels are rarely investigated for NAFLD; evidence of insulin resistance and diabetes should heighten concern for possible NAFLD as it has been associated with liver disease in adults and children[16]. Upcoming imaging methods may enhance capacities for non-invasive detection and staging of NAFLD and NASH in children. Preliminary adult data suggest the FibroScan® probe as a potential noninvasive technique due to its non-specificity and potential to compensate for larger size. FibroScan® measures liver stiffness by transient elastography as a surrogate for fibrosis[17]. FibroScan® has been studied in adult mixed populations, including hepatitis and NAFLD. Prior probes were unable to measure liver stiffness in 2%-10% of patients due to inflammation and body size[18]. The XL® FibroScan probe has improved detection of NAFLD and fibrosis among adults through improved transducer sensitivity with greater measurement depth but still has suboptimal reliability among morbidly obese adults (BMI > 40) and diabetics[18-20]. However, the reproducibility of results is a drawback as well as concerns regarding specificity of findings.

GENDER IN NAFLD

Several studies have indicated a potential relationship between gender and the presence of NAFLD. In general, it has been noted that NAFLD is more prevalent in males than females. Several imaging studies using ultrasound and hepatic MRI have suggested male predominance[8,15]. In addition, a retrospective review, published in 2006 of pediatric autopsies by Schwimmer *et al*[4] in San Diego County, observed that children with fatty liver were older and more likely to be male with a higher BMI. An earlier study published by Schwimmer *et al*[21] published in 2003 observed that age and sex did not differ in patients with liver fibrosis, although the majority of patients in the study with NAFLD were male (70%). Similarly, male dominance was reported in a Japanese study by Tominaga *et al*[22] but the values were not statistically significant. In an Australian study of 500 adolescents, the prevalence of

transaminase elevation was increased in obese boys (40% in boys and 20% in girls), but there was no screening for the presence of underlying liver disease[16]. Likewise, in a study done in Taiwan (which included screening for hepatitis B and C), there was a higher prevalence of transaminase elevation in obese boys over girls[23]. A higher prevalence of transaminase elevation among obese boys has also been reported by Chan *et al*[11] and Schwimmer *et al*[24] (defined as ALT > 40 U/L), as well as Strauss *et al*[7], but with a note of caution as there was alcohol consumption reported among adolescent males. Using subjects from the ages of 12-19 years from the NHANES study (1999-2002) with exclusion of those with ethanol consumption, Graham *et al*[25] reported an interaction with male sex upon ALT elevation (ALT > 40).

Gender influences upon the prevalence of NAFLD in children have not been consistently substantiated by other investigators. Louthan *et al*[5] did not report an influence of gender upon ALT (ALT > 40) in her pediatric study population. Similarly, Fishbein *et al*[9] did not detect differences in ALT based upon gender.

ETHNICITY AND NAFLD

There has been a correlation between ethnicity and ALT levels. Normal ALT ranges vary between different ethnicities and differing ALT levels will have to be regarded for different ethnic groups.

In particular, African Americans have been noted to have the lowest percentage of elevated ALT levels, while those of Hispanic origin have been observed to have the highest. The prevalence of ALT elevation (ALT > 30) was 7.4% in Caucasian adolescents, 11.5% in Mexican Americans and 6.0% in African American adolescents in one study conducted utilizing the NHANES survey (1999-2004)[26]. Louthan *et al*[5] also observed that elevated ALT was four times less likely in African Americans than Caucasians, despite increased obesity and insulin resistance suggestive of potential ethnic differences in ALT norms[5].

Several studies have noticed the effect of ALT on the Hispanic population. A recent multicenter pediatric cross-sectional study by Schwimmer *et al*[24] reported a prevalence of elevated ALT (ALT > 40) levels as 36%, 22% and 14% among Hispanic, Caucasian and African American adolescents, respectively; other studies have reported similar findings[27]. Discrepancies may also exist among Asian subpopulations as children of Filipino descent had a prevalence of 20%, but only 4% in those of Vietnamese or Cambodian origin[4].

Similar ethnic influences upon NAFLD/NASH have been reported among adults, although higher percentages of African American patients were encountered. Likewise, out of 151 adults cared for at Brooke Army Medical Center and diagnosed with NAFLD (46% of cohort), the prevalence of NAFLD/NASH confirmed by biopsy was 58.3% among Hispanics, 44% among Caucasians and 35.1% among African Americans[28].

CONCLUSION

Paralleling the rise of obesity in children and adolescents has been a rise in the incidence of NAFLD in pediatric populations. Optimal methods for population-based screening for pediatric NAFLD remain undefined to date. As demographic factors such as gender and ethnicity may play a role in the prevalence of NAFLD/NASH, use of targeted screening methods may be feasible but consideration for ethnicity norms on markers, including ALT, may be necessary to enhance sensitivity. Data on influences of gender upon NAFLD/NASH prevalence/detection in children has been inconsistent to date, warranting additional investigation.

Utilizing ALT as a determinant of NAFLD may not be effective. Studies using ultrasonography indicated fibrotic patterns, yet subjects had normal ALT. Also, hepatic steatosis was noted in subjects with normal ALT in the Dallas Heart study. Therefore, further studies are needed to determine surrogate markers of NAFLD in varying pediatric populations.

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REVIEW

Liver transplantation for Wilson disease

Andreea M Catana, Valentina Medici

Andreea M Catana, Valentina Medici, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of California, Davis, Sacramento, CA 95817, United States

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Correspondence to: Valentina Medici, MD, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of California, Davis, 4150 V Street, Suite 3500, Sacramento, CA 95817,
United States. valentina.medici@ucdmc.ucdavis.edu
Telephone: +1-916-7343751 Fax: +1-916-7347908
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Abstract

The aim of this paper is to review the current status of liver transplantation (LT) for Wilson disease (WD), focusing on indications and controversies, especially in patients with neuropsychiatric disease, and on identification of acute liver failure (ALF) cases related to WD. LT remains the treatment of choice for patients with ALF, as initial presentation of WD or when anti-copper agents are stopped, and for patients with chronic liver disease progressed to cirrhosis, unresponsive to chelating medications or not timely treated with copper chelating agents. The indication for LT in WD remains highly debated in patients with progressive neurological deterioration and failure to improve with appropriate medical treatment. In case of Wilsonian ALF, early identification is key as mortality is 100% without emergency LT. As many of the copper metabolism parameters are believed to be less reliable in ALF, simple biochemical tests have been proposed for diagnosis of acute WD with good sensitivity and specificity. LT corrects copper metabolism and complications resulting from WD with excellent 1 and 5 year survival. Living related liver transplantation represents an alternative to deceased donor LT with excellent long-term survival, without disease recurrence. Future options may include hepatocyte transplantation and gene therapy. Although both of these have shown promising results in animal models of WD, prospective human studies are much needed to demonstrate their long-term beneficial effects and their potential to replace the need for medical therapy and LT in patients with WD.

Key words: Wilson disease; Liver transplantation; Copper; Indications; Contraindications

Peer reviewer: Krishnan Rajeshwari, Professor, Department of Pediatrics, Maulana Azad Medical College, New Delhi 110002, India

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INTRODUCTION

Over recent years, a burgeoning literature has attempted to describe indications and outcome of liver transplantation (LT) for Wilson disease (WD), a rare autosomal recessive disorder of copper metabolism with a prevalence of 1 in 30 000 in the general population. WD is an indication for LT in cases of acute liver failure or end stage liver disease when medical treatment options fail. LT will correct the underlying hepatic metabolic defect of WD, represented by impaired biliary copper excretion.

More than 300 mutations in the *ATP7B* gene, a gene that encodes a metal-transporting P-type adenosine triphosphatase, have been described in literature. These mutations can impair the protein function, leading to decreased hepatocellular excretion of copper into bile with its consequent accumulation in the liver and through the systemic circulation in the brain, cornea, heart, bones and kidney. The clinical manifestations are therefore heterogeneous, the most common being hepatic or neuro-

psychiatric signs and symptoms, for which the utility of LT is both poorly characterized and controversial. This review addresses the indications for and the controversies associated with LT for WD with a particular focus on the short and long term outcomes in terms of survival and clinical presentation. The authors also provide a future perspective on hepatocyte transplantation.

EPIDEMIOLOGY

Since the first successful LT in 1971[1], more than 500 transplants have been performed in the United States to date for WD, which is the primary indication for LT in 0.5% and 1.5 % of adults and children respectively[2].

These percentages are significantly lower than those initially reported by Gitlin[3] in 2003, who estimated that WD accounts for 5%-8% of all indications for LT. WD is a rare disease that can be medically managed, some cases are misdiagnosed as acute liver failure (ALF) or chronic liver disease (CLD) of unknown etiology and some of the WD patients die before being listed or while waiting for LT. All these factors could explain the relatively small number of LTs performed recently for WD. Due to lack of consensus regarding the indication for LT in patients with severe neurological deficits, a selection is usually done in most transplant centers according to the severity of the neurological manifestations[2]. The number of LTs for WD with neurological disease remains unknown, as there is no information in the United Network of Organ Sharing (UNOS) database regarding the neurological status of the recipients, other than encephalopathy. There are currently more than 16 000 patients waiting for LT in United States according to UNOS and 1.4% of the current listed adult patients are listed for "metabolic disease". The percentage of patients with WD waiting for LT remains unpublished. In children, metabolic liver diseases are the second indication for LT after biliary atresia. Fifteen percent of children enrolled in the studies in the pediatric liver transplantation (SPLIT) registry underwent LT for metabolic diseases[4] and 7.6% for WD. However, it should be noted that the enrollment in SPLIT was voluntary and therefore potentially biased.

Most patients with WD become symptomatic between the first and the fourth decade of life[5], although the age at presentation can vary from two[6] to seventy years old[7]. The average age at transplant is 15 years old (range 4-18 years) in children with WD and 30 years old (range 19-68 years) in adults[2,8].

The early onset (before 10 years old) is associated with more hepatic (83%) than neuro-psychiatric disorders (17%), compared with late age of onset when neuro-psychiatric symptoms are present in about 74% of cases compared with 24% cases with only liver manifestations[9,10]. The type of mutation may explain these findings, with missense mutation being associated with predominantly neurological and later presentation, while a deletion of the gene is associated with predominantly hepatic and earlier presentation[9,10]. A female predominance in the WD induced ALF has been described in the literature[2,11] with 78% and 64% of cases being females in children and adults, respectively[2]. The explanation for this remarkable finding remains unknown; however, data from an animal model of WD suggest that hormonal factors influence the development of early liver failure. The ovariectomy of female LEC rats delays the onset of liver failure[12].

INDICATIONS FOR LIVER TRANSPLANT

There are two main indications for LT in WD. The first is ALF that may be the initial presentation of WD or can occur when anti-copper agents are stopped. The second is CLD progressed to cirrhosis and portal hypertension and unresponsive to chelating medications, or is not timely treated with copper chelating agents. The indication for LT in WD is widely debated in patients with progressive neurological deterioration and failure to improve with correct medical treatment.

DIAGNOSIS OF WD IN CASES OF ACUTE LIVER FAILURE

Five percent of all WD patients present with ALF and they account for 4%-6% of all LTs performed in United States for ALF[13]. In these cases, early identification is key as mortality is 100% without emergency LT. The diagnosis of WD is based on a broad combination of laboratory tests and clinical features including: 24 h urine copper, hepatic copper concentration, ceruloplasmin, presence of *ATP7B* gene mutation, Kayser- Fleisher ring, neurological symptoms or brain magnetic resnane iamge findings and presence of hemolytic anemia. The diagnosis of WD in ALF is more difficult as many of the copper metabolism parameters, including serum and urinary copper and reduced serum ceruloplasmin, are believed to be less reliable and specific[14,15], whereas Kayser-Fleisher rings are only detectable in 50% of the cases[16] and many tests for copper metabolism parameters are not always available. Ceruloplasmin levels were reported to not be helpful with five cases of idiopathic liver failure[14]. Due to the difficulty in reaching the diagnosis of WD in the setting of ALF, there has been considerable interest in identifying simple biochemical tests for diagnosis. In 1991, Berman was the first to describe, in six patients, that the ratio of alkaline phosphatase to total serum bilirubin lower than 2 and aspartate aminotransferase (AST) to alanine aminotransferase (ALT) greater than 4 provided high sensitivity and specificity for fulminant WD[17]. A recent study done by Korman *et al*[18] in a cohort of 16 patients with ALF due to WD showed that a combined ratio of alkaline phosphatase to total serum bilirubin lower than 2 and AST to ALT greater than 2.2 had a sensitivity and specificity of 100% for fulminant WD. It is important to note that all the pa-

tients in this cohort had a very high model for end-stage liver disease (MELD) score and it is still unclear whether these screening tests apply in the early stages of clinical course of ALF secondary to WD. A prior study done by Eisenbach *et al*[19] found the ratio of alkaline phosphatase to serum bilirubin or AST to ALT to be unhelpful in a series of seven adults with a mean MELD score of 28. Furthermore, this ratio is not always helpful in children, likely because of the effect of bone-derived alkaline phosphatase. Small studies failed to confirm these correlations in the pediatric population[20-23]. Koppikar *et al*[24] showed that the Wilson Index, a score composed of bilirubin, international normalized ratio, AST, white blood cell and albumin, is helpful in identifying children with Wilsonian ALF in whom LT is indicated. All children with a score higher than 11 died without transplantation, whereas all those with a score less than 11 survived, the method having a 93% sensitivity and 98% specificity.

BRIDGE TO LIVER TRANSPLANT

Supportive measures for ALF due to WD which may help bridge patients to transplantation have been proposed over the years: exchange transfusion, plasmapheresis, the molecular adsorbent recycling system (MARS), fractionated plasma separation and absorption (FPSA), albumin dialysis and early institution of renal replacement therapy[25,26]. All these treatments are thought to lower circulating copper levels, to reduce hemolysis and secondary organ damage due to copper complexes accumulation. As reported by Jhang *et al*[27] and Asfaha *et al*[28], plasmapheresis is an effective method to reduce circulating copper and improve hemolysis and renal injury. MARS has been associated with improved renal and liver function, improved encephalopathy and short term survival[29,30] and used successfully in patients with ALF, allowing the removal of copper in the urine through chelation with penicillamine[31]. Sen *et al*[25] reported two patients successfully treated and bridged to transplant with MARS.

Although it has been shown that bio-artificial liver devices may improve encephalopathy and have considerable effects on acute or chronic liver failure, such as reduction of bilirubin, albumin-bound toxins or cardiovascular stabilization[32,33], a large randomized multicenter trial failed to show increased survival in these patients[34]. Unfortunately, the lack of information in UNOS database regarding the use of these modalities before LT prevents larger clinical trials. It is still believed that the use of aggressive plasmapheresis, FPSA or MARS to support patients with ALF related to WD waiting for transplant may improve future outcomes.

INDICATION FOR LIVER TRANSPLANT IN NEUROLOGICAL WD

Most of the data on LT for neurological WD come from case reports or case series describing patients who received LT because of liver function deterioration. The decision to perform LT was based on deteriorating neurological status, despite stable liver function only in a few cases[35,36]. Whether transplantation is indicated for progressive neurological disease due to WD without liver failure is highly debatable. LT reverses neurological deterioration in many WD patients; approximately 78% of patients improve or stabilize[37], as observed by Stracciari in a study that included 41 neurologically affected patients, while the remaining did not present any change in their neurological status[38]. Eghtesad *et al*[22] described total or partial neurological improvement in 10 of 17 patients (58.8%), advocating the benefit and importance of performing transplantation before neurological impairment becomes irreversible. Wang *et al*[39] showed neurological improvements in 8 of 9 patients (88.9%) who received living-related liver transplant (LRLT) for neurological complications. Marin *et al*[40] reported four patients with compensated cirrhosis and progressive neurological deterioration who underwent LT for WD. One of four died due to post LT infections while the other three experienced neurological improvement. To further the debate, Bax *et al*[36] reported the case of a 15 year old without significant liver disease, bedridden with severe incapacitating dysarthria despite maximal medical therapy, who returned almost to normal after LT. Geissler *et al*[41] reported that two of the six WD patients with mixed hepatic and neurological symptoms fully recovered after LT. He suggested that in such cases, an early decision for LT is justified because neurological deficits may become irreversible. However, the hypothesis that better results could be obtained in patients undergoing LT early after the onset of neurological symptoms has not been confirmed[37]. According to Cheng, the outcome was favorable in two patients in whom LRLT was performed because of severely disabling neurological symptoms. This finding substantiated the opinion of Mason *et al*[35] who suggested that, even though their patient died, LT should be considered for patients with severe, progressive neurological impairments. However, few data are available on the outcome of cognitive performance, long-term survival or predictors of outcome. These findings are in contrast with experience reported by Medici *et al*[20]. According to their retrospective multicenter Italian study in 2005 in 37 patients with WD who underwent LT, the combination of neuropsychiatric and hepatic symptoms was the only factor influencing survival after LT[20], with neuropsychiatric patients showing a significantly lower survival rate than the other WD patients. Patients with liver disease alone and those with both hepatic and neuropsychiatric conditions had a mean survival of 135 mo (range 118-152 mo) and 79 mo (range 46-113 mo), respectively ($P = 0.04$). The presence of neuropsychiatric symptoms was a negative prognostic factor, even with improvement or complete resolution of the neurological symptoms. According to Wang *et al*[42] who analyzed post transplant data (LRLT) in 15 patients

with mixed hepatic and mild or moderate neurological involvement, the survival of these patients was slightly lower than that of those without neurological involvement, but this decrease was not statistically significant. Among patients with severe neurological involvement, the survival decreased markedly compared with that of patients without neurological symptoms. These results are consistent with the prior reports from Medici *et al*[20], Ala *et al*[11] and Roberts *et al*[43], which advocated that patients with long standing neurological impairment from WD are unlikely to recover after LT transplantation, contraindicating transplant in such cases. Combined hepatic and neurological disease must be carefully assessed to determine the severity of neuropsychiatric disease. Some experts consider isolated neuropsychiatric symptoms a contraindication for LT because these patients may improve with medical therapy whereas many may worsen from post transplant care and they argue that the patients should not be exposed to the risk of LT when this may not improve symptoms.

POST LIVER TRANSPLANT SURVIVAL

Several reports show excellent post LT survival both at one year and long-term in most WD patients, with some differences depending on clinical presentation, ALF or CLD, age at transplant, the "era" at transplant and the center's experience.

Medical urgency reflected by the UNOS status (pre transplant intensive care unit-bound) and the severity of the underlying liver disease reflected by a MELD score above 20 are predictors of pre- transplantation mortality[44] and also independent factors predictive of patient post-transplantation survival[45]. In 2002, Schilsky reported 85% 1 year survival of all WD patients undergoing LT[46]. In a larger study, Arnon *et al*[2] reported higher 1 and 5 year survival rates for children and adults with WD for both graft and patient, regardless of the clinical presentation. There was a slightly higher survival for patient and graft in CLD compared with ALF presentation but the difference was not statistically significant. The overall 1 and 5 year patient and graft survival rates after transplantation for CLD in children were 100%, higher compared with transplantation for ALF which showed a 90% 1 year patient survival and 87.5% 5 year patient survival, compared with 87% 1 year graft survival and 82.5% 5 year graft survival. Similarly, the overall 1 and 5 year patient survival rates after transplantation for CLD in adults were 94.7% and 90.1%. One year graft survival was 89.5% compared with 85.5% at 5 years. The overall 1 and 5 year patient survival rates after transplantation for ALF were 90.3% compared with 89.7%. The graft survival rates were 87.1% at 1 year and 86.2% at 5 years[2]. The good outcome of these patients can be attributed to the relatively young age at transplant, low rate of comorbidities, lack of disease recurrence and low rate of hepatocellular carcinoma.

Data from the SPLIT registry between December 1995 and June 2008 shows the same results with excellent 1 and 5 year patient survival of 96% and 91.4%, respectively and 96% and 91.4% for graft survival. Children who underwent LT for metabolic disease had similarly excellent patient survival as, and better graft survival than, those who received a liver allograft for other indications[4].

However none of these studies looked at the subgroup of patients with mixed hepatic and neuropsychiatric disease. In the study published by Medici *at al*[20] in 2005, the overall patient survival rates at 3, 6 and 12 mo and at 3, 5 and 10 years after transplantation were similar to other publications.

LRLT AND AUXILIARY PARTIAL ORTHOTOPIC LIVER TRANSPLANT

As the scarcity of organs is a worldwide problem, LRLT represents an alternative to deceased donor LT. This is important especially in pediatric patients and in some countries where cadaveric transplantation is not allowed. Heterozygosity for the WD gene mutation is associated with abnormal serum copper and ceruloplasmin levels in 28%-35% of subjects[47]. Despite some unresolved problems with respect to screening for heterozygotes status and the risk of abnormal copper metabolism after transplantation, the use of a living related donor heterozygote for WD has been proven safe and there are multiple reports in literature showing improvement in copper metabolism without evidence of recurrence of WD after long-term follow-up[39,48]. Cheng showed an excellent patient survival at 1 and 5 years after LRLT: 91.7% and 75%, as well as graft survival 86.1% and 75%, respectively[45]. Similarly Yoshitoshi showed 1, 5, 10 year cumulative patient survival rates of 90.6%, 83.7%, 80%[49]. These results are compatible with the outcomes reported for deceased donor LT.

Auxiliary partial liver transplant has been performed with success, showing normalization of serum ceruloplasmin and liver tests, as well as improvement in neurological status[50]. However, according to Kasahara experience with auxiliary partial orthotopic liver transplant, patients had worse survival than those with classical LDLT, mainly due to post-transplant surgical complications, the most common being biliary strictures and graft failure due to stealing syndrome[51]. Another drawback of this technique as an indication for LT for CLD is the potential risk of carcinogenesis of the remnant native liver[50].

POST LIVER TRANSPLANT COPPER METABOLISM

Copper metabolism normalizes quickly after transplant. Copper overload slowly resolves in extrahepatic organs but it is still unclear whether de-coppering after LRLT from heterozygote donors is slower than de-coppering after cadaveric transplantation from non-related donors. Normalization of serum ceruloplasmin is usually seen in the first month post LT. Most patients have marked reduction in urinary copper excretion with normalization

between 6 to 9 mo after transplant and complete resolution of K-F rings is seen in more than 60% of cases with partial resolution in all of the post transplant patients[45,52].

FUTURE: LIVER CELL TRANSPLANTATION AND GENE THERAPY

Both approaches are potential exciting future treatments for WD and could offer cures for this disorder since current medical therapy is a lifelong commitment and patients often suffer from noncompliance-related complications. At present, only data from preclinical studies on animal models of WD are available. In the light of donor organ shortage, cell transplantation is emerging as an exciting alternative for whole liver transplantation with many advantages: it is less invasive, requires fewer organs and can be repeated several times if needed. But this leads to the question of the type and source of cells to be used. If human primary hepatocytes are not a realistic option due to the shortage of organ donors and inability to survive, expand and proliferate *in vitro* for prolonged periods of time, xenogenic hepatocytes cannot completely replace the synthesis of human plasma proteins and they are problematic from an immunological point of view. Hepatoma cell lines provide an endless support but often lack important metabolic and synthetic properties due to genetic alterations. Fetal hepatocytes and stem cells remain interesting candidates to establish hepatocyte-related cell lines[53,54]. Gene therapy for WD would be based on transfection of hepatocyte cells with normal *ATP7B* gene. Researchers in this field are currently seeking vectors that can transduce non-replicating cells, with long-term expression and proper cellular localization of *ATP7B*. The difficulties they are currently facing are transient expression of the transgene and low transfection efficiency, with need of repeat transfection due to inadequate cell numbers[55]. In most animal studies, cell proliferation was enhanced by preconditioning the host liver and nearly total repopulation with transplanted cells was achieved[56], but the methods used for preconditioning can hardly be translated to humans. Since the first use of LCT in human patients in 1992[52], less than 100 patients have been transplanted, mainly for inborn error or metabolism such as urea cycle disorder, Crigler-Najjar Syndrome or glycogen storage disease. LCT effect was transient in all studies with the longest duration of beneficial effects of 36 mo, reported in a 47 year old woman with glycogen storage disease[57], while the mean duration of positive effects in other cases was less than 10 mo. In most of the reported cases, LCT was used as a bridging method to LT. The small number of human studies with LCT is due to the technical difficulties that need to be overcome, including identifying the ideal cell line that can survive, expand and proliferate *in vitro*, develop safe techniques for expansion of cells *in vitro* and finding the ideal route of administration as portal vein administration is not realistic in patients with cirrhosis due to reversal of flow. Furthermore, LCT may require cells from multiple donors, lifelong immunosuppression and may need to be repeated if adequate cell survival or repopulation is not achieved. Prospective human studies are much needed to demonstrate the benefit of both these techniques, with the goal of achieving metabolic correction and replacing the need for medical therapy and LT in patients with WD.

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BRIEF ARTICLE

Elevation of the glycated albumin to glycated hemoglobin ratio during the progression of hepatitis C virus related liver fibrosis

Nobuhiro Aizawa, Hirayuki Enomoto, Hiroyasu Imanishi, Masaki Saito, Yoshinori Iwata, Hironori Tanaka, Naoto Ikeda, Yoshiyuki Sakai, Tomoyuki Takashima, Takashi Iwai, Ei-ichiro Moriwaki, Soji Shimomura, Hiroko Iijima, Hideji Nakamura, Shuhei Nishiguchi

Nobuhiro Aizawa, Hirayuki Enomoto, Hiroyasu Imanishi, Masaki Saito, Yoshinori Iwata, Hironori Tanaka, Naoto Ikeda, Yoshiyuki Sakai, Tomoyuki Takashima, Takashi Iwai, Ei-ichiro Moriwaki, Soji Shimomura, Hiroko Iijima, Hideji Nakamura, Shuhei Nishiguchi, Division of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo College of Medicine, Mukogawa-cho 1-1, Nishinomiya, Hyogo 663-8501, Japan

Hideji Nakamura, Department of Gasteroenterology, Nissay Hospital, Osaka 550-0012, Japan

Author contributions: Aizawa N and Enomoto H contributed equally to this work; Enomoto H and Nakamura H designed and proposed the research; all authors approved the analysis and participated in drafting the article; Aizawa N, Enomoto H, Saito M, Iwata Y, Tanaka H, Ikeda N, Sakai Y, Takashima T, Iwai T, Moriwaki E, Shimomura S and Iijima H treated the patients, performed the liver biopsies and collected the clinical data; all authors were involved in the histological evaluation and the final histopathological results were confirmed by Enomoto H and Imanishi H; Aizawa N, Enomoto H and Nishiguchi S performed the statistical analysis; Enomoto H, Imanishi H and Nakamura H wrote the manuscript; all authors were involved in the manuscript revision and approved the final version of the manuscript.

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Correspondence to: Hirayuki Enomoto, MD, PhD, Division of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo College of Medicine, Mukogawa-cho 1-1, Nishinomiya, Hyogo 663-8501, Japan. enomoto@hyo-med.ac.jp
Telephone: +81-798-456472 Fax: +81-798-456474

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Abstract

AIM: To analyze the relationship between the glycated albumin (GA) to glycated hemoglobin (HbA1c) ratio and the histological grading of liver fibrosis.

METHODS: The study retrospectively included consecutive hepatitis C virus positive chronic liver disease patients (n = 142) who had undergone percutaneous liver biopsy between January 2008 and March 2010 at our institution. The ratios of GA/HbA1c were calculated in all patients to investigate the relationship with the degree of the liver fibrosis. The values of the aspartate aminotransferase-to-platelet ratio index (APRI), an excellent marker for the evaluation of liver fibrosis, were also calculated. In addition, we combined the ratio of GA/HbA1c and the APRI in order to improve our ability to detect the presence of significant liver fibrosis.

RESULTS: Sixty-one (43%) patients had either no fibrosis or minimal fibrosis (METAVIR score: F0-F1), while 25 (17%) had intermediate fibrosis (F2). Fifty-six (39%) patients had severe fibrosis (F3-F4) and 27 of them had cirrhosis (F4). The mean values of the GA/HbA1c increased with the progression of the fibrosis (F0-1: 2.83 ± 0.24, F2: 2.85 ± 0.24, F3: 2.92 ± 0.35, F4: 3.14 ± 0.54). There was a significant difference between the F0-F1 *vs* F4, F2 *vs* F4, and F3 *vs* F4 groups ($P < 0.01$, $P < 0.01$, $P < 0.01$ and $P < 0.05$, respectively). The GA/HbA1c ratio was significantly higher in the patients with cirrhosis (F4) than in those without cirrhosis (F0-F3) (3.14 ± 0.54 *vs* 2.85 ± 0.28, $P < 0.0001$). The GA/HbA1c ratio was also significantly higher in the patients with severe fibrosis (F3-F4) than in those without severe liver fibrosis (F0-F2) (3.03 ± 0.41 *vs* 2.84 ± 0.24, $P < 0.001$). Furthermore, the GA/HbA1c ratio was also significantly higher in the patients with significant fibrosis (F2-F4) than in those without significant liver fibrosis (F0-F1) (2.98 ± 0.41 *vs* 2.83 ± 0.24, $P < 0.001$). The diagnostic performance of the increased GA/HbA1c ratio (> 3.0) was as follows: its sensitivity and specificity for the detection of liver cirrhosis (F4) were 59.3% and 70.4%, respectively and its sensitivity and specificity for the detection of severe liver fibrosis (F3-F4) were 50.0% and 74.4%,

respectively. With regard to the detection of significant fibrosis (F2-F4), its sensitivity was 44.4% and its specificity was 77.0%. Although even the excellent marker APRI shows low sensitivity (25.9%) for distinguishing patients with or without significant fibrosis, the combination of the APRI and GA/HbA1c ratio increased the sensitivity up to 42.0%, with only a modest decrease in the specificity (from 90.2% to 83.6%).

CONCLUSION: The GA/HbA1c ratio increased in line with the histological severity of liver fibrosis, thus suggesting that this ratio is useful as a supportive index of liver fibrosis.

Key words: Glycated albumin; Glycated hemoglobin; Liver fibrosis; Liver biopsy; Hepatitis C virus

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INTRODUCTION

Glycated proteins are known to reflect the plasma glucose level and glycated hemoglobin (HbA1c) is used as a standard index of glycemic control in patients with diabetes mellitus[1,2]. Since the lifespan of erythrocytes is about 120 d, HbA1c reflects the glycemia for the recent few months[3]. Glycated albumin (GA) is another index of glycemic control which correlates with the plasma glucose levels during the past few weeks because the turnover of albumin is about 20 d[4,5]. Although the ratio of GA/HbA1c is usually close to 3, the value changes based on the patient's condition[6]. In patients with chronic liver disease (CLD), hypersplenism causes a shortened lifespan of erythrocytes, leading to lower HbA1c levels relative to the plasma glucose level. In contrast, the turnover periods of serum albumin in CLD patients is prolonged in order to compensate for the reduced production of albumin. Therefore, the GA levels in CLD patients are higher relative to the degree of glycemia[6].

Since HbA1c shows lower and GA shows higher values in CLD patients, the GA/HbA1c ratio is thought to be high in patients with liver cirrhosis. Indeed, the GA/HbA1c ratio in patients with CLD has been reported to show an inverse correlation with some indicators of hepatic function (including the hepaplastin test, cholinesterase and bilirubin) independent of the mean plasma glucose levels, thus suggesting that the GA/HbA1c ratio increases as the liver cirrhosis progresses[7]. However, it has not been examined whether the GA/HbA1c ratio correlates with the histological fibrotic stage in CLD patients.

Hepatitis C virus (HCV) is one of the main causes of liver cirrhosis and hepatocellular carcinoma and knowledge about the progression of liver fibrosis is important. In the present study, we analyzed the relationship between the histological grading of liver fibrosis and the GA/HbA1c ratio in 142 patients with HCV-related CLD. Our findings suggest that the GA/HbA1c ratio is associated with the progression of liver fibrosis and cirrhosis in HCV-positive patients.

MATERIALS AND METHODS

Patients

We retrospectively studied HCV-positive CLD patients (n = 142) who had undergone percutaneous liver biopsy between January 2008 and March 2010 at our institution who met the following conditions: (1) HCV infection diagnosed by detectable HCV antibodies and HCV RNA in serum; and (2) blood samples were obtained on the same day of the liver biopsies. Patients with the following conditions were excluded from the study: the presence of other liver diseases, hepatocellular carcinoma, immunosuppressive therapy, hepatitis B virus co-infection and those with insufficient liver tissue for staging of fibrosis. The present study did not include patients whose GA/HbA1c ratios could have been influenced by poorly controlled diabetes.

The routine studies, including platelet counts, prothrombin time international normalized ratio (PT-INR), liver functional tests [alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase and total bilirubin] were performed. Since the index calculated by the combination of GA and HbA1c (CLD-HbA1c: defined as the average of the measured HbA1c and GA/3) was reported to be a good indicator for the evaluation of the mean plasma glucose level in patients with CLD[8], HbA1c and GA were also routinely measured in all patients. The values of GA and HbA1c were determined in the same sample and on the same day as the liver biopsies were performed. The AST-to-platelet ratio index (APRI), an excellent marker for the evaluation of liver fibrosis, was also calculated based on the formula proposed by Wai *et al*[9]: APRI = [(AST level/upper limit of normal)/platelet counts (10^9/L)] × 100. Written informed consent regarding the liver biopsy and retrospective use of clinical data was obtained from all patients on admission. This study was approved by the ethics committees of the institutional review board.

Liver biopsy

Liver biopsy examinations were performed using the

Table 1 Characteristics of the patients

Age (yr)	60 (19-78)
Gender (male/female)	60/82
AST (IU/L)	37.5 (14-328)
ALT (IU/L)	36 (10-388)
γ-GTP (IU/L)	29 (7-259)
ALP (IU/L)	217 (97-556)
Total bilirubin (mg/dL)	0.7 (0.1-2.1)
Albumin (g/dL)	3.96 ± 0.36
Hemoglobin (g/dL)	13.4 ± 1.8
Platelet (× 10^4/mm^3)	15.9 ± 5.5
PT-INR	1.04 ± 0.07

AST: Aspartate aminotransferase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; PT-INR: Prothrombin time international normalized ratio.

standard procedures and all liver specimens were evaluated by well-trained pathologists at our institute, with evaluation of the fibrosis stage and activity grade according to the METAVIR scoring system[10]. Fibrosis was staged on a scale of 0-4 (F0: no fibrosis, F1: portal fibrosis without septa, F2: portal fibrosis with rare septa, F3: numerous septa without cirrhosis, F4: liver cirrhosis). The histological evaluation of the biopsy samples was also routinely performed in our department. All authors participated in the conference about the histological evaluation and the final results were confirmed by two authors (Enomoto H and Imanishi H) who received training for histological studies.

Statistical analysis

In the present study, we attempted to clarify whether the GA/HbA1c ratio was associated with liver fibrosis and cirrhosis. The data for the comparisons among the groups "F0-1 *vs* F2 *vs* F3 *vs* F4" was analyzed by non-repeated measurements ANOVA and statistical significance was further examined by the Student-Newman-Keuls test. We compared the "F0-F3 (no cirrhosis) *vs* F4 (cirrhosis)", "F0-F2 (no - intermediate fibrosis) *vs* F3-F4 (severe fibrosis)" and "F0-F1 (no approximately minimal fibrosis) *vs* F2-F4 (significant fibrosis)" groups. The differences in the baseline characteristics and GA/HbA1c ratios of the groups were evaluated. Quantitative variables were expressed as the mean ± SD and those with an abnormal distribution were expressed as the median values (range). Statistical analysis was performed using Student's *t* test or the Mann-Whitney *U* test, as appropriate.

RESULTS

Characteristics of patients and clinical data

From January 2008 to March 2010, a total of 142 patients with HCV were consecutively included in the present study, based on the inclusion and exclusion criteria as described in the "Patients and Methods" section. The characteristics of the study population are summarized in Table 1. The population consisted of 60 (42%) males and 82 (58%) females, and the age of patients ranged from 19 to 78 years old (median 60). According to the METAVIR liver fibrosis staging[10], 56 (39%) patients had significant fibrosis (F3-F4) and 27 (19%) had cirrhosis (F4).

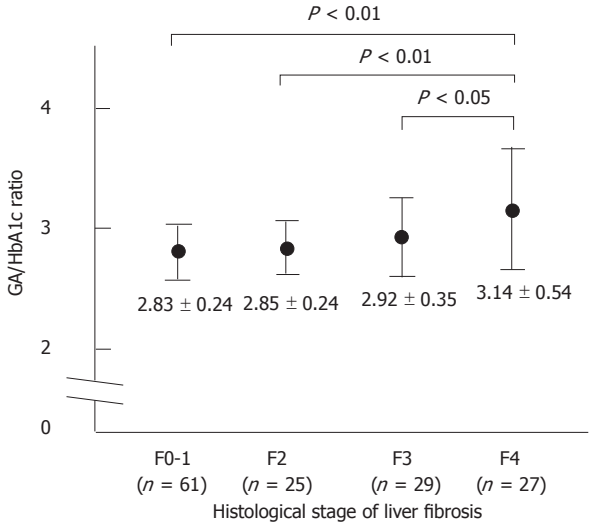

Figure 1 The glycated albumin/glycated hemoglobin ratio in relation to the METAVIR fibrosis score in patients with hepatitis C virus-related chronic liver disease. The glycated albumin (GA)/glycated hemoglobin (HbA1c) ratio increased as the fibrosis progressed. There was a significant difference between the F0-F1 *vs* F4, F2 *vs* F4, and F3 *vs* F4 groups.

The GA/HbA1c ratio in patients with HCV

The GA/HbA1c ratio in patients with CLD has been reported to show an inverse correlation with certain indicators of hepatic function. As shown in Figure 1, the mean values of the GA/HbA1c increased with the progression of the fibrosis stage, suggesting that the GA/HbA1c ratio was associated with the histological severity of liver fibrosis.

Comparing the F0-F3 (no cirrhosis) and F4 (cirrhosis) groups, we found that there was a significant difference in several parameters which correlated with hepatic function; that is, higher AST, ALT, γ-GTP alkaline phosphatase (ALP) and PT-INR levels and also a lower platelet count, and albumin values in the presence of cirrhosis (Table 2; left). However, no significant difference was observed in other parameters such as age and gender, which were not related to the hepatic function. Between the two groups, the GA/HbA1c ratio was significantly higher in patients with cirrhosis (Figure 2A), thus suggesting that the GA/HbA1c ratio is associated with the cirrhotic changes in the liver.

Next, we examined whether the GA/HbA1c ratio differed in patients with or without severe liver fibrosis. Comparing the F0-F2 (without severe fibrosis) and F3-F4 (with severe fibrosis) groups, we found significant differences, with higher AST, ALT, γ-GTP, ALP and PT-INR values and a lower platelet count, and albumin values in the presence of severe fibrosis (Table 2; middle). In patients with severe liver fibrosis, the GA/HbA1c ratio was significantly higher (Figure 2B) than that in patients without severe fibrosis, suggesting that the GA/HbA1c ratio

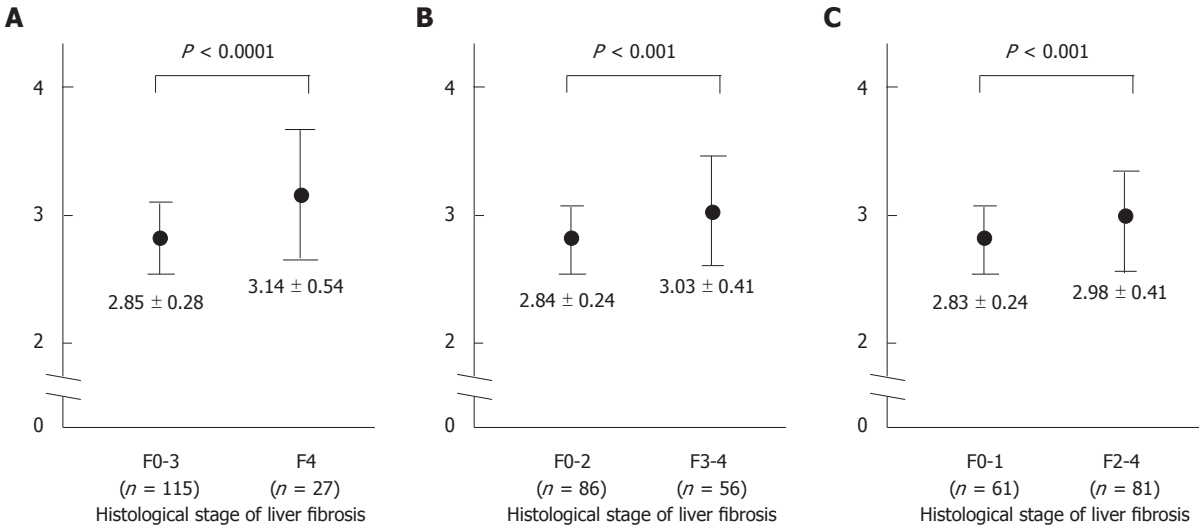

Figure 2 The glycated albumin/glycated hemoglobin ratio in patients with hepatitis C virus-related chronic liver disease. A: A comparison between the F0-F3 (no cirrhosis) group and F4 (cirrhosis) group. The glycated albumin (GA)/glycated hemoglobin (HbA1c) ratio was higher in patients with cirrhosis than that in non-cirrhotic patients; B: The comparison between the F0-F2 (no or intermediate fibrosis: without severe fibrosis) group and the F3-F4 (severe fibrosis) group. The GA/HbA1c ratio was higher in the patients with significant fibrosis than that in the patients with no or minimal fibrosis; C: A comparison between the F0-F1 (no or minimal fibrosis: without significant fibrosis) group and the F2-F4 (significant fibrosis) group. The GA/HbA1c ratio was higher in the patients with significant fibrosis than in those with either minimal fibrosis or none at all.

Table 2 Characteristics of the patients (F0-F3 *vs* F4), (F0-F2 *vs* F3-F4) and (F0-F1 *vs* F2-F4)

	F0-F3 (*n* = 115)	F4 (*n* = 27)	*P* value	F0-F2 (*n* = 86)	F3-F4 (*n* = 56)	*P* value	F0-F1 (*n* = 61)	F2-F4 (*n* = 81)	*P* value
Age (yr)	60 (19-78)	62 (23-78)	NS	60 (19-78)	62 (23-78)	NS	60 (19-78)	62 (23-78)	NS
Gender (male/female)	48/67	12/15	NS	31/55	29/37	NS	25/36	35/46	NS
AST (IU/L)	35 (14-195)	50 (20-328)	< 0.001	32 (14-175)	46 (20-328)	< 0.001	32 (14-104)	42 (18-328)	< 0.001
ALT (IU/L)	38 (10-388)	47 (10-310)	< 0.05	31.5 (10-388)	48 (10-310)	< 0.01	31 (11-388)	46 (10-310)	< 0.01
γ–GTP (IU/L)	25 (7-183)	50 (12-259)	< 0.001	22 (7-183)	42.5 (12-259)	< 0.0001	22 (8-183)	36 (7-259)	< 0.01
ALP (IU/L)	207 (97-490)	267 (133-556)	< 0.001	186 (97-465)	275 (133-556)	< 0.0001	207 (97-465)	258 (101-556)	< 0.001
Total bilirubin (mg/dL)	0.7 (0.1-1.6)	0.7 (0.3-2.1)	NS	0.7 (0.1-1.6)	0.8 (0.3-2.1)	NS	0.7 (0.1-1.6)	0.7 (0.3-2.1)	NS
Albumin (g/dL)	4.02 ± 0.31	3.70 ± 0.43	< 0.001	4.03 ± 0.32	3.84 ± 0.37	< 0.01	4.05 ± 0.31	3.89 ± 0.38	< 0.01
Hemoglobin (g/dL)	13.5 ± 1.7	12.8 ± 2.0	NS	13.5 ± 1.8	13.3 ± 1.7	NS	13.7 ± 1.7	13.2 ± 1.8	NS
Platelet ($\times 10^4$/mm^3)	16.5 ± 5.3	13.2 ± 5.9	< 0.001	17.2 ± 5.2	13.8 ± 5.5	< 0.001	17.2 ± 4.8	14.9 ± 5.9	< 0.05
PT-INR	1.03 ± 0.05	1.08 ± 0.06	< 0.001	1.02 ± 0.05	1.07 ± 0.06	< 0.001	1.02 ± 0.05	1.05 ± 0.08	< 0.05

AST: Aspartate aminotransferase; ALT: Alanine transaminase; ALP: alkaline phosphatase; PT-INR: Prothrombin time international normalized ratio.

also correlates with the progression of liver fibrosis.

We also examined whether the GA/HbA1c ratio differed in patients with or without significant liver fibrosis. When we compared the F0-F1 (no or minimal fibrosis: without significant fibrosis) and F2-F4 (with significant fibrosis) groups, we also found significant differences, with higher AST, ALT, γ-GTP ALP and PT-INR values and a lower platelet count and albumin values in the presence of significant fibrosis (Table 2; right). In patients with significant liver fibrosis, the GA/HbA1c ratio was significantly higher than that in patients without significant fibrosis (Figure 2C).

Although the GA/HbA1c ratio is usually about 3, we found that the ratio increased in line with the progression of liver fibrosis (Figure 2). We therefore evaluated the diagnostic performance of the increased GA/HbA1c ratio (> 3.0) for the detection of patients with cirrhosis (F4), severe fibrosis (F3-F4) and significant fibrosis (F2-F4) (Table 3). Its sensitivity for the detection of liver cirrhosis was 16/27 (59.3%) and the specificity was 81/115 (70.4%). With regard to the detection of severe fibrosis, the sensitivity of the increased GA/HbA1c ratio (> 3.0) was 28/56 (50.0%) and its specificity was 64/86 (74.4%). With regard to the detection of significant fibrosis, the sensitivity of the increased GA/HbA1c ratio (> 3.0) was 36/81 (44.4%) and its specificity was 47/61 (77.0%).

Combination of the GA/HbA1c ratio and APRI for the detection of significant liver fibrosis

As described above, the GA/HbA1c ratio in patients with significant liver fibrosis was higher than that in patients without significant fibrosis. However, the differences were small and the GA/HbA1c ratio had difficulty in distinguishing between F1 and F2.

Several biomarkers for the evaluation of fibrosis have

Table 3 Glycated albumin/glycated hemoglobin ratio for the detection of cirrhosis (F4), severe fibrosis (F3-F4) and significant fibrosis (F2-F4) (%)

	F4	F0-F3	F3-F4	F0-F2	F2-F4	F0-F1
GA/HbA1c > 3.0	16/27 (59.3)	34/115 (29.6)	28/56 (50.0)	22/86 (25.6)	36/81 (44.4)	14/61 (23.0)
GA/HbA1c ≤ 3.0	11/27 (40.7)	81/115 (70.4)	28/56 (50.0)	64/86 (74.4)	45/81 (55.6)	47/61 (77.0)

GA/HbA1c: Glycated albumin/glycated hemoglobin.

Table 4 Aspartate aminotransferase-to-platelet ratio index for the detection of significant liver fibrosis (F2-F4)

	F2-F4 (%)	F0-F1 (%)		F2-F4 (%)	F0-F1 (%)
APRI > 0.5	68/81 (84.0)	32/61 (52.5)	APRI > 1.5	21/81 (25.9)	6/61 (9.8)
APRI ≤ 0.5	13/81 (16.0)	29/61 (47.5)	APRI ≤ 1.5	60/81 (74.1)	55/61 (90.2)

APRI: Aspartate aminotransferase-to-platelet ratio index.

Table 5 Combination of aspartate aminotransferase-to-platelet ratio index and glycated albumin/glycated hemoglobin ratio for the detection of significant liver fibrosis (F2-F4)

	F2-F4 (%)	F0-F1 (%)		F2-F4 (%)	F0-F1 (%)
APRI > 1.5 or GA/HbA1c > 3.0	43/81 (53.1)	18/61 (29.5)	APRI > 1.5 or GA/HbA1c > 3.2	34/81 (42.0)	10/61 (16.4)
Others	38/81 (46.9)	43/61 (70.5)	Others	47/81 (58.0)	51/61 (83.6)

GA/HbA1c: Glycated albumin/glycated hemoglobin; APRI: Aspartate aminotransferase-to-platelet ratio index.

been reported previously and the APRI is a simple and useful marker for the prediction of significant fibrosis. We combined the GA/HbA1c ratio and the APRI in order to examine their utility for the detection of patients with significant liver fibrosis. At first, based on prior studies[9,11,12], we assessed two cut-off points (0.50 and 1.50) of the APRI to predict the absence or presence of significant fibrosis (Table 4). When we used the cut-off point as 0.5 (Table 4; left), the sensitivity was 68/81 (84.0%) and the specificity was 29/61 (47.5%). When we used the cut-off value of 1.5 (Table 4; right), the sensitivity was 21/81 (25.9%) and the specificity was 55/61 (90.2%). Therefore, as previously reported, the cut-off point of 1.50 had a high specificity but a low sensitivity to detect significant fibrosis.

We next asked whether a combination of the GA/HbA1c and the APRI could improve the sensitivity to detect the presence of significant fibrosis and help distinguish between the two groups (F0-F1 and F2-F4). When we examined the criteria "APRI >1.5 or GA/HbA1c ratio > 3.0", the sensitivity and the specificity for the detection of significant liver fibrosis was 43/81 (53.1%) and 43/61 (70.5%), respectively (Table 5; left). In addition, when we used the criteria "APRI >1.5 or GA/HbA1c ratio > 3.2", the sensitivity was 34/81 (42.0%) and the specificity was 51/61 (83.6%) (Table 5; right). Therefore, compared with the detection of significant liver fibrosis by using the APRI alone, the combination of GA/HbA1c and the APRI (APRI >1.5 or GA/HbA1c ratio > 3.2) improved the sensitivity from 25.9% to 42.0% without a major decrease in the specificity (only a modest reduction from 90.2% to 83.6% was observed).

DISCUSSION

Liver biopsy is the gold standard method for histological evaluation of liver fibrosis[13]. Although a liver biopsy is generally a safe procedure, it is costly, invasive and has a small risk of complications. In addition, only 1/50 000 of the organ is removed and there can be sampling errors[13]. Furthermore, it has also been reported that there are inter- and intra-observer discrepancies of 10% to 20%[14,15]. Therefore, many noninvasive biomarkers readily available via laboratory tests have been proposed to predict the presence of significant fibrosis or cirrhosis in patients with HCV.

The Fibro-Test score is computed using the patient's age, sex and results of the analyses of serum haptoglobin, α2-macroglobulin, apolipoprotein A1, γ-GTP and bilirubin levels[16]. Forns *et al*[17] developed the Forns score, which is an algorithm including the platelet count, γ-GTP, age and cholesterol level. Wai *et al*[8] reported the APRI for fibrosis and cirrhosis prediction. In addition, some models such as the Hepascore[18], FibroMeter[19], FibroIndex[20] and FIB-4[21] have also been proposed for the evaluation of liver fibrosis. In addition, there are several noninvasive methods for the evaluation of liver fibrosis using ultrasound waves[22-26] such as Transient Elastography (FibroScan)[22,26]; SonoElastography (Real-Time Tissue Elastography)[23] and Acoustic Radiation Force Impulse[24-26]. Although each noninvasive tool has

an excellent positive predictive value for the diagnosis of moderate or significant fibrosis, none of the available methods completely meets the criteria of an ideal (simple, inexpensive and easily reproducible) method.

The Fibro-Test[16] is a combination of 6 markers and the Forns score[17] contains a complicated formula, indicating that while these markers are excellent, they lack simplicity. Recently introduced markers including APRI, FIB-4 and the FibroIndex are well-established, simple and inexpensive tools to assess liver fibrosis[9,20,21]. However, the values of these markers in one patient can vary within a short period, since the levels of AST or ALT or platelet count in the same patient often change daily. In addition, regarding APRI and FIB-4, the appropriate definition of the upper limit of normal (ULN) of the AST level remains uncertain, since each laboratory uses a different value for the ULN. With regard to the methods using special ultrasound tools, they are costly and cannot be routinely evaluated in all medical institutes.

In the present study, we have shown that the GA/HbA1c ratio of HCV-positive patients increases with the progression of liver fibrosis. Unlike the other previously established methods, the GA/HbA1c ratio is a simple and unique tool which is calculated based on the two glycated proteins and correlates with the degree of liver fibrosis. Since GA and HbA1c are stable over several weeks, the GA/HbA1c ratio does not change in a short period, resulting in a high reproducibility of its value. The stability of the two glycated proteins over weeks is a unique point, different from other biomarkers.

Bando *et al*[7] previously reported that the GA/HbA1c ratio in patients with CLD have an inverse correlation with the some indicators of hepatic function, regardless of the mean plasma glucose levels, thus suggesting that the increase of GA/HbA1c ratio indicates a reduction in the liver function caused by the progression of liver cirrhosis. Consistent with that report, our current histological evaluation revealed that the GA/HbA1c ratios of the cirrhotic patients were significantly higher than those of the patients without cirrhosis (Figure 2A). Furthermore, as shown in Figure 2B, the GA/HbA1c ratios increased in patients with severe fibrosis (F3-F4) compared to those in patients without severe fibrosis (F0-F2), thus suggesting that the GA/HbA1c ratio increased in correlation with the progression of fibrosis.

Since the GA/HbA1c ratio is usually about 3, we examined the diagnostic performance of the elevated GA/HbA1c ratio (GA/HbA1c > 3.0) and determined the sensitivity and specificity (Table 3). As described in the "Results" section, its solo diagnostic performance did not achieve satisfactory levels. However, when we combined the GA/HbA1c ratio with the APRI, the sensitivity to distinguish patients with significant fibrosis (F2-F4) from those without significant fibrosis was improved, with only a modest reduction in the specificity (Table 5). These findings suggest that the GA/HbA1c ratio can be used as a supportive index for the evaluation of liver fibrosis. Since only a small number of patients were investigated in the present study, we will therefore need to rigorously investigate the ratios in both larger and different populations.

In summary, we have shown that the GA/HbA1c ratio increases with the progression of the histological findings of liver fibrosis. However, its rate of change is relatively small. Although we have shown that the GA/HbA1c ratio improves the diagnostic performance of the APRI for the detection of significant fibrosis, it will be necessary to establish a new and better biomarker using a combination of the GA/HbA1c ratio and other parameter(s).

COMMENTS

Background

Hepatitis C virus (HCV) is one of the main causes of liver cirrhosis and hepatocellular carcinoma, and knowledge about the progression of liver fibrosis is important. Many noninvasive biomarkers readily available *via* laboratory tests have been proposed to predict the presence of significant fibrosis or cirrhosis in patients with HCV. The glycated albumin (GA)/glycated hemoglobin (HbA1c) ratio in patients with chronic liver disease (CLD) has been reported to show an inverse correlation with some indicators of hepatic function independent of the mean plasma glucose levels, thus suggesting that the GA/HbA1c ratio increases as the liver cirrhosis progresses. However, it has not been examined whether the GA/HbA1c ratio correlates with the histological fibrotic stage in CLD patients.

Research frontiers

Liver biopsy is the gold standard method for histological evaluation of liver fibrosis. Although a liver biopsy is generally a safe procedure, it is costly, invasive and has a small risk of complications. It is very important to establish a simple, inexpensive and easily reproducible method for the evaluation of liver fibrosis.

Innovations and breakthroughs

In the previous studies, many excellent noninvasive methods for the evaluation of liver fibrosis have been proposed. However, none of the available methods completely meets the criteria of an ideal (simple, inexpensive and easily reproducible) method. The present study has shown that the GA/HbA1c ratio of HCV-positive patients increases with the progression of liver fibrosis. Unlike the other previously established methods, the GA/HbA1c ratio is a simple and unique tool which is calculated based on the two glycated proteins and correlates with the degree of liver fibrosis.

Applications

The study showed that the GA/HbA1c ratio increased in line with the histological severity of liver fibrosis, thus suggesting that this ratio is useful as a supportive index of liver fibrosis.

Terminology

HbA1c is used as a standard index of glycemic control in patients with diabetes mellitus. Since the lifespan of erythrocytes is about 120 d, HbA1c reflects the glycemia for the recent few months; GA is another index of glycemic control which correlates with the plasma glucose levels during the past few weeks because the turnover of albumin is about 20 d.

Peer review

The study focuses on the power of the GA/HbA1c ratio in estimation of liver fibrosis in people with HCV infection. Previously defined noninvasive fibrosis markers exist but none of them have proved to be equal to liver biopsy. Therefore, research on defining new but more effective fibrosis markers should be encouraged. People with HCV are always a good research base in this context. Therefore, the present study may be interesting for the readers.

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MEETING

Events Calendar 2012

January 18, 2012
AHPBA Sponsored Consensus Conference on the Multidisciplinary Treatment of Colorectal Cancer Liver Metastases
San Francisco, CA, United States

January 20-21, 2012
AGA Clinical Congress of Gastroenterology and Hepatology: Practice, Evidence and Quality in 2012
Miami, FL, United States

January 27-28, 2012
28th Annual Meeting of the German Association for the Study of the Liver
Hamburg, Germany

January 30-31, 2012
5th International Conference on the Management of Patients with Viral Hepatitis
Paris, France

February 8-10, 2012
Stockholm Liver Week 2012
Stockholm, Sweden

February 16-19, 2012
22nd Conference of the Asian Pacific Association for the Study of the Liver
Taipei, Taiwan, China

March 16 -17, 2012
Hepatitis Single Topic Conference
Atlanta, GA, United States

March 16-17, 2012
ESGE - Workshop on Advanced Endoscopy with Live Demonstrations
Vienna, Austria

March 31-April 1, 2012
27th Annual New Treatments in Chronic Liver Disease
San Diego, CA, United States

April 18-22, 2012
The International Liver Congress by EASL
Barcelona, Spain

April 27-28, 2012
The European Society for Paediatric Gastroenterology, Hepatology and Nutrition
Stockholm, Sweden

May 16-19, 2012
International Liver Transplant Society 18th Annual International Congress 2012
San Francisco, CA, United States

May 19-22, 2012
Digestive Disease Week 2012
San Diego, CA, United States

June 22-23, 2012
EASL Monothematic Conference: Vascular Liver Diseases
Tallin, Estonia

July 1-5, 2012
10th World Congress of the International Hepato-Pancreato-Biliary Association 2012
Paris, France

September 5-8, 2012
International Congress of Pediatric Hepatology, Gastroenterology and Nutrition
Sharm El-Sheikh, Egypt

September 7-9, 2012
Viral Hepatitis Congress 2012
Macclesfield, United Kingdom

September 7-9, 2012
The Viral Hepatitis Congress
Frankfurt, Germany

September 14-16, 2012
The International Liver Cancer Association's 6th Annual Conference
Berlin, Germany

September 20-22, 2012
Prague Hepatology Meeting 2012
Prague, Czech Republic

September 20-22, 2012
1st World Congress on Controversies in the Management of Viral Hepatitis
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World Journal of Hepatology

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INSTRUCTIONS TO AUTHORS

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Ocean International Center,
No. 62 Dongsihuan Zhonglu,

Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381892
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Acknowledgments

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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