LETTER TO THE EDITOR

'Liver: an alarm for the heart?'

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I read with interest the paper by Mirbagheri *et al.* (1) on the association between sonographic fatty liver (FL) and angiographic coronary artery disease (CAD). The authors recruited a group of patients with angiographic CAD and another group of patients with cardiac symptoms necessitating coronary angiography (CAG) but with negative results. All patients underwent liver sonography, the result of which was thereafter compared along with other relevant variables between the groups in both uni- and multivariate analyses. The authors concluded that FL was an independent correlate of CAD.

The association between FL and CAD is an important issue and has not been studied well. While I appreciate the attempt made by Mirbagheri *et al.* (1) I would like to make a number of comments on their study:

1. Family history of premature CAD is missing in the paper.
2. The diagnosis of diabetes was made according to fasting blood sugar and use of oral agents/insulin. The lack of 2-h post-prandial glucose in patients' profile results in under-estimation of the prevalence of diabetes.
3. Plasma insulin level, by which homeostasis model assessment-insulin resistance (HOMA-IR) and therefore IR could be determined, was not measured. IR seems to be the mediator of all components of the metabolic syndrome (MS) including both FL (2) and CAD (3, 4).
4. IR has been shown to accompany (and possibly cause) coronary artery stenosis even in very early stages, i.e. microscopic CAD (3). I believe relying solely on conventional CAG underestimates the prevalence of CAD.
5. Existence of MS should have been determined, included in analysis and compared between the groups. I guess MS would be a variable with significant difference between the groups even after controlling for confounding variables.
6. Liver function test was not performed. Therefore, the authors failed to distinguish between FL and steatohepatitis (5).
7. Liver sonography is a qualitative measure of liver status and does not reflect histopathological severity in the broad spectrum of nonalcoholic steatohepatitis (6). Lack of data on the degree of liver inflammation adds to this problem in the mentioned study.

In summary, the study by Mirbagheri *et al.* is a considerable progress towards understanding the link between the components of MS. Also, it is the first study on the subject in our region and helps fill the prevailing evidence gap. Considering the above points, in future, studies will shed more light on the complex pathophysiology of MS.

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Reply:

We thank Dr Alavian for his thoughtful comments on our paper (1). This study was conducted in a setting with limited facilities and we fully agree that it had a number of limitations, including lack of data on the following: (i) family history of premature coronary artery disease (CAD), (ii) 2-h post-prandial glucose, to avoid under-estimation of the frequency of diabetes (DM), (iii) insulin levels which could provide a measure to evaluate insulin resistance (IR) by use of homeostasis model assessment (HOMA)-IR and (iv) liver enzymes, which could help discriminate between fatty liver (FL) and steatohepatitis.

Insulin resistance accompanies microscopic CAD (2). This is true but does not introduce a flaw in our analysis. We classified the subjects according to their coronary angiography (CAG) results. Analysis was performed and results were interpreted accordingly. We concluded that FL alarms for the presence of clinically significant CAD. The group with normal or mildly abnormal CAG almost surely included some individuals with angiographically undetectable microscopic CAD (possibly accompanying IR), but the association between FL and microscopic CAD (due to IR as a potential cause of both) cannot be investigated by our methodology.

Liver biopsy, which could not be performed on our patients for obvious reasons, is the only definitive way to discriminate steatohepatitis from fatty liver and to determine the histopathological severity of the condition. Studies on alternative (noninvasive) methods have shown that the differences between nonalcoholic steatohepatitis and simple liver steatosis (FL) are not apparent with any radiological modalities (3–5). Specifically, only the severity of steatosis is reflected in ultrasonography and magnetic resonance imaging (4). Attenuation of the liver seems to be correlated with histopathological grade but not with histopathological stage (3).

While the manuscript was under review we recruited 103 more individuals and achieved a sample size of 420 (normal or mildly abnormal CAG: 302; clinically relevant CAD: 118). The analysis of the new dataset robustly reproduced the results we had originally obtained on 317 subjects with gender, fasting blood sugar (FBS), low-density lipoproteins (LDL), DM, hypertension and FL being the variables with statistically significant difference between the groups. We evaluated all subjects for the presence of metabolic syndrome (MS) based on the adult treatment panel III (ATPIII) criteria (6). Because FBS and blood pressure are elements of the ATP criteria, we did not include them in multivariate analysis. Therefore, binary logistic regression was performed with CAD as the dependent variable and gender, LDL, FL and MS as covariates (Table 1). As predicted by Dr Alavian, MS turned out to be a statistically significant correlate of CAD [$P = 0.023$, odds ratio (OR) = 1.94, 95% confidence interval (CI) = 1.10–3.43] and this association was not confounded by other variables. Interestingly, the odds ratio for FL was much larger than the one we had obtained previously (OR = 14.47, 95% CI = 7.89–26.54 vs. OR = 8.48, 95% CI = 4.39–16.40 respectively). However, there existed a considerable overlap between the corresponding 95% CIs.

Table 1. Binary logistic regression (dependent: CAD; independent: gender, LDL, FL, metabolic syndrome)

Variable	*P*-value	OR (95% CI)
FL	$< 0.001^{**}$	14.47 (7.89–26.54)
Male sex	0.017^{*}	2.04 (1.14–3.66)
Metabolic syndrome	0.023^{*}	1.94 (1.10–3.43)
LDL	0.034^{*}	0.993 (0.986–0.999)

$^{*}P < 0.05$.
$^{**}P < 0.01$.
CAD, coronary artery disease; CI, confidence intervals; FL, fatty liver; LDL, low-density lipoproteins; OR, odds ratio.

Despite limitations, our study sheds more light on the complex pathophysiology of MS. According to results, both FL and MS are strong independent correlates of significant CAD. This is consistent with the syndromic trend to consider nonalcoholic fatty liver disease as an additional feature of MS with specific hepatic IR and then use MS as a risk factor for CAD (7).

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LETTER TO THE EDITOR

Comparison of health-related quality of life between populations

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To the Editor:

In a recent issue of *Liver International*, Bondini *et al*. (1) compared health-related quality of life (HRQoL) between patients with chronic hepatitis B virus (HBV) infection, chronic hepatitis C and primary biliary cirrhosis (PBC). We are writing to express a general concern about this approach of comparing dissimilar conditions using a standardized HRQoL measure.

Generic HRQoL questionnaires, such as the Medical Outcomes Study Short Form 36 (SF-36), are validated instruments developed for use in general populations for a broad assessment of a wide range of diseases (2, 3). However, a scale that claims to measure differences is valid only if it can be externally verified by someone or something in a position to assess the differences between the items it measures.

As a simple 'mind experiment', consider a non-cirrhotic patient with compensated, uncomplicated chronic HBV. Assume for a moment that this patient rated his HRQoL poorly – as poorly as another patient with PBC. Let us now assume that this patient with HBV spontaneously develops comorbid PBC. When asked to reconsider the severity of his hepatitis B in isolation from the PBC, he might now be less inclined to attribute the same HRQoL decrement of HBV to that of PBC. Now that he is burdened with PBC, the HBV might be perceived as relatively less severe than before. This is a well-described 'frameshift bias' that tends to lessen the argument of comparing unlike conditions with a standard instrument. We believe it borders on non-informative to rank-order dissimilar conditions using a standard measurement tool.

Consider another example: Patient A has dialysis-requiring end-stage renal disease, and scores a 50 on the SF-36 physical health summary (PCS). Patient B has isolated knee osteoarthritis and also scores a 50 on the SF-36 PCS. Can we therefore conclude that end-stage renal disease engenders the same HRQoL decrement as osteoarthritis. After all, the SF-36 is a valid and reproducible measure of HRQoL, and Patients A and B report the same HRQoL when using the 'exchange currency' of the SF-36. Yet, there is something unsatisfactory about this conclusion, because patients on dialysis suffer from a wide range of physical, psychological and social symptoms that can dramatically impact HRQoL, possibly beyond the HRQoL decrement from isolated knee osteoarthritis. However, until each patient has experienced *both* end-stage renal disease *and* knee osteoarthritis, neither is in a meaningful position to judge the other's condition *relative* to their own. We would like to emphasize that HRQoL remains an important instrument to measure the impact of disease severity. However, one should be cautious when comparing HRQoL between different populations – a manoeuvre we admit to having performed ourselves (4), but in retrospect, consider potentially non-informative for the reasons expressed above.

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