Renal hyperfiltration, fatty liver index, and the hazard of all-cause and cardiovascular mortality

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Abstract

Background

Renal hyperfiltration (RHF) and fatty liver associate with negative health outcomes as separate conditions. This study investigates hazards of mortality when RHF and fatty liver coexist.

Methods

Middle-aged men belonging to the Kuopio Ischaemic Disease Risk Factor Study, \( n = 1552 \), were followed-up for a median of 29 years. The associations across RHF, fatty liver indexes (FLIs), age, Body Mass Index, smoking status, alcohol consumption, and the presence of hypertension were assessed with a logistic regression. We used Cox proportional hazards models to evaluate hazard ratios (HR) for all-cause and cardiovascular (CVD) mortality with respect to RHF and fatty liver.

Results

5% of the men had RHF (\( n = 73 \)), whereas more than half of them had fatty liver (\( n = 848 \)). RHF associated specifically to smoking, and fatty liver associated specifically to overweight. The hazard of all-cause mortality was highest (HR 2.0, 95% CI 1.3–3.0) among men with coexisting RHF and fatty liver (\( n = 33 \)). Among men with RHF but normal FLI (\( n = 40 \)), the HR of all-cause mortality was 1.7 (95% CI 1.2–2.4). Among men with fatty liver but normal eGFRs (\( n = 527 \)), the HR of all-cause mortality was 1.4 (95% CI 1.1–1.7). The hazard of CVD mortality associated evidently to RHF but not to fatty liver. We did not detect an interaction effect between RHF and fatty liver in relation to all-cause (synergy index 0.74, 95% CI 0.21–2.67) and CVD (0.94, 0.34–2.60) mortality.
Conclusion

RHF and fatty liver are independently associated with all-cause and CVD mortality.

Key Words

All-cause mortality, cardiovascular disease mortality, glomerular filtration rate, fatty liver, fatty liver index, renal hyperfiltration, biological interaction, synergy index
Introduction

Chronic kidney disease (CKD) and chronic liver disease (CLD) are increasingly prevalent diseases. With populations aging, the global prevalence of CKD has increased by nearly 30% since 1990 to affect over 9% of the world population and cause 4.6% of global deaths in 2017.\(^1\) Despite being a well-established risk factor for cardiovascular disease (CVD) mortality, even in its early stages,\(^2\) CKD remained an underdiagnosed condition, causing delays in treatment and worsening of outcomes.\(^3,4\) Typically, CKD refers to impaired kidney function and low glomerular filtration rates. However, also abnormally elevated glomerular filtration rates, known as renal hyperfiltration (RHF), appear to be an early sign of CKD and a predictor of mortality, cardiovascular diseases, and diabetes.\(^5\) 13 out of the 15 studies reviewed by Kanbay et al. suggested a strong association between RHF and mortality.\(^6\)

Among contributors to CLD, the fatty liver disease (FLD) is the fastest growing in terms of prevalence and attributed mortality.\(^7\) The incidence of FLD correlates with the worldwide spread of obesity and diabetes that play the main roles in the pathogenesis of the disease.\(^8,9\) The hepatic accumulation of lipids causes liver abnormalities, clinically classified as alcoholic and non-alcoholic FLD.\(^10\) The global prevalence of non-alcoholic FLD is 25% and growing.\(^11,12\) Despite the role of FLD in steatogenesis and hepatic cancer, the majority of deaths attributed to non-alcoholic FLD are due to CVD.\(^11\) As RHF, FLD is common and underdiagnosed.\(^13,14\)

RHF and FLD were presented as independent risk factors specifically for CVD\(^2,15\) but, as they share common pathogenesis pathways, notably the cardiometabolic syndrome\(^16\), they can coexist and may biologically interact with each other.\(^17,18\) Whether there is an interaction between RHF and FLD in respect to mortality risk has not been studied. In this study, we
investigate the combined effect of RHF and fatty liver on the hazard of all-cause and CVD mortality.

**Methods**

**Data source**

Middle-aged men belonging to the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) served as our study population. The KIHD study comprises 2682 randomly sampled Finnish men who lived in the city of Kuopio or its surrounding areas between March 1984 and December 1989. Since then, the KIHD study has followed the men’s health status via annual linkages to electronic health records including the Cause of Death registry administered by the Statistics Finland (License TK-53-1770-16) and the Care Register for Healthcare administered by the National Institute for Health and Welfare (License THL/93/5.05.00/2013). All KIHD study participants have given informed consent.

For this study we excluded men with diabetes \( (n = 162) \) as well as those who were abstainers from drinking alcohol at baseline \( (n = 366) \). In the KIHD study, men who informed at baseline that they have not consumed alcohol during the past 12 months differ from other study participants with respect to typical covariates, such as marital status, work status, the level of education, residential area, smoking status, and overall health. For statistical reasons we excluded two outliers and 600 men with missing values. After exclusions we included 1552 men to this study. Their median follow-up time was 29 years. The maximum follow-up time was 34 years. No participants were lost to follow-up.
Variables measurement

We calculated eGFRs in ml/min/1.73m² based on serum creatinine concentrations applying the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation which adjusts creatinine values for age, sex, and ethnicity. As the KIHD study used the Jaffe method to measure creatine concentrations, we multiplied the original creatinine values by 0.95 before eGFR calculations. We defined the cutoff value between normal and low eGFRs based on age-adjusted Finnish guidelines for the normal range of CKD-EPI eGFR. As a cutoff value for RHF, we used the 95th age-adjusted percentile of eGFRs.

We used the Bedogni et al. equation to calculate FLI. The equation considers the body mass index (BMI), waist circumference, and serum triglyceride and serum gamma-glutamyl-transferase concentrations to detect fatty liver. We considered FLI values <30 as normal and values ≥30 as an indicator of fatty liver.

Salonen et al. describe the KIHD study procedures for collecting, processing, and analyzing blood specimens.

As covariates, we included the following variables: age, BMI, smoking status (current smoker, previous smoker, or never smoker), alcohol consumption in grams per week, and the diagnosis of hypertension at baseline. These factors are associated both with RHF and negative cardiovascular outcomes. A KIHD research nurse measured men’s height, weight, and blood pressure. The men self-reported their smoking habits, alcohol consumption, illnesses, and medications using structured questionnaires. The men also had a physical examination by a physician. The examination included an interview regarding medical history.
The outcomes of interest were all-cause and CVD mortality. The Causes of Death Registry provided individual mortality data. ICD-10 codes I00–I99 as an underlying cause of death indicated a CVD death.28

Data Analysis

First, we used Kruskal-Wallis test by ranks and Chi-Square test for comparisons of baseline characteristics across six groups formed according to eGFR and FLI categories and Mann-Whitney U and Chi-Square tests for comparisons between survivors and non-survivors.

Second, we used a logistic regression analysis to study associations across RHF, fatty liver, and covariates. We reported the logistic regression results as odds ratios (ORs) with 95% confidence intervals (CIs).

Third, we used the Cox proportional hazards regression to analyze the associations of eGFR and FLI with all-cause and CVD mortality. We defined the periods at risk for each study participant in days from baseline until death or December 31, 2018. We reported the Cox regression results as hazard ratios (HRs) with 95% confidence intervals (CIs) and computed the area under the curve (AUC) and its related 95% CIs to assess the discriminative accuracy of the Cox models. Finally, we computed the synergy index to evaluate, on an additive scale, the relative excess hazard of mortality attributed to the interaction between RHF and fatty liver in the Cox proportional hazards models.31,32 We computed the 95% CIs of the synergy indices according to Hosmer and Lemeshow.33 A synergy index of 1 means no interaction.

In the analyses, the normal eGFR and normal FLI served as reference categories.

We used R programming language V4.0.2 in all computations and applied the R package: Survival Analysis V3.1–12 to build the models, test the proportional hazards assumptions with Schoenfeld residuals, and perform the analyses.
Results

Of the 1552 study participants, 919 (59.2%) died during the 34 years of follow-up, and 406 (44.2%) of these deaths were attributed to CVD. Men who died were older (54.5 vs. 48.9, median, \( p < 0.001 \)) had higher BMIs (26.7 vs. 25.8, median, \( p < 0.001 \)), included more current smokers (42.8% vs. 22.6%, \( p < 0.001 \)), consumed more alcohol (47 vs. 37 g/week, median, \( p = 0.001 \)), included more hypertension patients (32.4% vs. 22.6%, \( p < 0.001 \)), and had higher FLIs (38.2 vs. 28.7, median, \( p < 0.001 \)). The median eGFR did not differ between non-survivors and survivors (85.3 vs. 84.0 ml/min/1.73m\(^2\), \( p = 0.694 \)).

Less than 5% of the studied men belonged to the RHF category (\( n = 73 \)), whereas nearly 55% of them belonged to the fatty liver category (\( n = 848 \)). Only among 2% of the men RHF and fatty liver coexisted (\( n = 33 \)). All measured baseline characteristics differed across the groups formed according to the eGFR and FLI categories (Table 1).

In the logistic regression analysis, RHF associated specifically with current smoking (OR 3.44, 95% CI 1.75–7.42), whereas fatty liver associated specifically with overweight and obesity (Table 2). RHF and fatty liver did not associate with each other (Table 2).

In the Cox regression (Fig. 1), the hazard of all-cause mortality was highest among men with coexisting RHF and fatty liver (HR 1.96, 95% CI 1.27–3.01). Among men with RHF but normal FLIs, the HR for all-cause mortality was 1.67 (95% CI 1.15–2.42). Among men with fatty liver but normal eGFRs, the HR for all-cause mortality was 1.35 (1.09–1.66). Low eGFRs did not increase the hazard of all-cause mortality, and FLIs did not affect the association between low eGFRs and all-cause mortality (Table 3). The hazard of CVD mortality was highest among men with RHF irrespective of their FLIs (Fig. 1, Table 3).
With synergy indices of 0.74 (95% CI 0.21–2.67) for CVD mortality, and 0.94 (0.34–2.60) for all-cause mortality, the interaction between RHF and fatty liver did not associate with a change in mortality hazard.

Regarding covariates, being older, consuming more alcohol, being a current smoker, and having hypertension increased hazards of all-cause and CVD mortality in the Cox regression (Table 3). Overweight and obesity increased only the hazard of CVD mortality (Table 3).

The accuracy of the Cox regression model predicting the hazard of all-cause mortality was 75.1%, and that of the model predicting the hazard of CVD mortality was 74.5% (Supplementary figure 1).

**Discussion**

This study evaluated the hazard of long-term all-cause and CVD mortality in a cohort of middle-aged Finnish men in relation to different categories of eGFR and FLI. The study showed that the coexistence of RHF and fatty liver was associated with a higher HR for all-cause mortality than either of the conditions alone. However, we did not find an interaction between RHF and fatty liver and the coexistence of the two conditions did not associate with a synergic or an antagonist effect on mortality. Regarding the CVD mortality, a high HR was associated with RHF irrespective of fatty liver. Moreover, the study suggested that RHF and fatty liver do not associate with each other per se, but RHF relates specifically to smoking and fatty liver relates to obesity.

In general, there is evidence of the relationship between CKD and FLD; nonalcoholic FLD may increase the risk of CKD and other diseases typically related to health behaviors.\textsuperscript{15,36–39} Our study did not find an association between RHF and fatty liver, and it strengthened the view
that CKD and FLD may be completely independent of each other in their association with mortality. Previously, Paik et al. have demonstrated that CKD and nonalcoholic FLD are independently associated with increased mortality.\textsuperscript{38} Similar to the global figures,\textsuperscript{40} RHF and fatty liver coexisted only among a low percentage of the KIHD participants.

As Maeda et al.\textsuperscript{39}, we found a strong association between tobacco smoking and RHF. According to Park et al.\textsuperscript{44}, smoking is one of the most important covariates to be considered when analyzing the association between RHF and mortality. Our study underlines the recommendation by Park et al.\textsuperscript{44} In addition to smoking, controlling for BMI in RHF studies is of particular importance as obesity and low muscular mass tend to affect the accuracy of eGFR.\textsuperscript{6,41}

In our study, low eGFR category did not associate with mortality risk (Table 3). We speculate that a possible reason for this observation is that eGFRs of most of our participants in the low eGFR category were closer to normal values than to values defining chronic kidney disease (interquartile range 68-75 ml/min/1.73m\textsuperscript{2}).

As a limitation, we acknowledge that our findings represent only middle-aged men. While this fact hinders the generalizability of our findings, most chronic diseases start appearing in middle age,\textsuperscript{42} not earlier, and both RHF\textsuperscript{43} and FLD\textsuperscript{44} are more common in men than women. In addition to age and gender, the homogenous ethnicity and regional nature of our study population represent another limitation to the generalizability of our results.
Conclusion

Our findings propose that RHF and fatty liver are independently associated with all-cause and CVD mortality, and that tobacco smoking is the most important covariate to be considered when analyzing the relationship between RHF and mortality.

References


Fig. 1. Fully adjusted hazard ratios (HRs) with 95% CIs for all-cause and cardiovascular disease (CVD) mortality in respect of kidney (eGFR) and liver functions (FLI). eGFR denotes the estimated glomerular filtration rate, RHF denotes renal hyperfiltration, and FLI denotes the fatty liver index.

Supplementary figure 1. The area under the curve (AUC) for the discriminatory accuracy in the Cox regression models.
Table 1 Baseline characteristics of the study population by kidney (eGFR) and liver (FLI) functions.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Normal eGFR, normal FLI</th>
<th>Normal eGFR, fatty liver</th>
<th>Low eGFR, normal FLI</th>
<th>Low eGFR, fatty liver</th>
<th>RHF, normal FLI</th>
<th>RHF, fatty liver</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>1552</td>
<td>474 (31)</td>
<td>527 (34)</td>
<td>190 (12)</td>
<td>288 (19)</td>
<td>40 (3)</td>
<td>33 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deaths (column %)</td>
<td>919 (59)</td>
<td>254 (54)</td>
<td>351 (67)</td>
<td>81 (43)</td>
<td>177 (61)</td>
<td>32 (80)</td>
<td>24 (73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVD deaths (column %)</td>
<td>406 (26)</td>
<td>98 (21)</td>
<td>158 (30)</td>
<td>42 (22)</td>
<td>80 (28)</td>
<td>17 (42)</td>
<td>11 (33)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age in years</td>
<td>54 (48, 55)</td>
<td>54 (48, 54)</td>
<td>54 (49, 55)</td>
<td>54 (48, 55)</td>
<td>54 (48, 54)</td>
<td>54 (48, 55)</td>
<td>54 (48, 55)</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI</td>
<td>26 (25, 29)</td>
<td>25 (23, 26)</td>
<td>29 (27, 30)</td>
<td>24 (23, 26)</td>
<td>28 (27, 30)</td>
<td>24 (23, 26)</td>
<td>27 (25, 29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (column %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Never smokers</td>
<td>458 (30)</td>
<td>147 (31)</td>
<td>133 (25)</td>
<td>85 (45)</td>
<td>83 (29)</td>
<td>6 (15)</td>
<td>4 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous smokers</td>
<td>558 (36)</td>
<td>132 (28)</td>
<td>209 (40)</td>
<td>65 (34)</td>
<td>130 (45)</td>
<td>7 (18)</td>
<td>15 (45)</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>536 (35)</td>
<td>195 (41)</td>
<td>185 (35)</td>
<td>40 (21)</td>
<td>75 (26)</td>
<td>27 (68)</td>
<td>14 (42)</td>
<td></td>
</tr>
<tr>
<td>Alcohol (g/week)</td>
<td>43 (12, 105)</td>
<td>33 (10, 86)</td>
<td>51 (17, 139)</td>
<td>28 (10, 73)</td>
<td>55 (22, 125)</td>
<td>48 (12, 128)</td>
<td>76 (42, 197)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>441 (28)</td>
<td>87 (18)</td>
<td>193 (37)</td>
<td>39 (21)</td>
<td>106 (37)</td>
<td>10 (25)</td>
<td>6 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>85 (76, 95)</td>
<td>90 (84, 97)</td>
<td>89 (84, 97)</td>
<td>72 (68, 76)</td>
<td>72 (67, 75)</td>
<td>107 (105, 111)</td>
<td>109 (106, 114)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FLI</td>
<td>34 (17, 57)</td>
<td>16 (9, 23)</td>
<td>54 (42, 74)</td>
<td>16 (12, 23)</td>
<td>53 (40, 73)</td>
<td>15 (10, 24)</td>
<td>53 (36, 70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Follow-up in years</td>
<td>29 (20, 31)</td>
<td>30 (22, 32)</td>
<td>27 (18, 30)</td>
<td>30 (22, 31)</td>
<td>28 (21, 30)</td>
<td>23 (15, 30)</td>
<td>23 (12, 30)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note. Numbers indicate median (interquartile range) unless otherwise informed. * Kruskal-Wallis Ranks Sum test and Chi-square test for across groups comparison. BMI; body mass index; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; RHF, renal hyperfiltration.
Table 2 Fully adjusted odds ratios with 95% CIs for the renal hyperfiltration (RHF) and fatty liver in respect of baseline characteristics in the study population (n = 1552).

<table>
<thead>
<tr>
<th></th>
<th>RHF</th>
<th>Fatty liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>1.00 (0.96–1.04)</td>
<td>1.01 (0.98–1.03)</td>
</tr>
<tr>
<td>Normal weight (Ref.)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Slight overweight</td>
<td>0.71 (0.39–1.29)</td>
<td>7.14*** (5.18–9.95)</td>
</tr>
<tr>
<td>Overweight</td>
<td>0.46* (0.19–1.07)</td>
<td>57.45*** (36.79–92.31)</td>
</tr>
<tr>
<td>Obese</td>
<td>0.29** (0.09–0.81)</td>
<td>∞ (All obese)</td>
</tr>
<tr>
<td>Alcohol (100g/week)</td>
<td>1.05 (0.87–1.18)</td>
<td>1.46*** (1.27–1.69)</td>
</tr>
<tr>
<td>Never smoker (Ref.)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Previous smoker</td>
<td>2.00* (0.95–4.50)</td>
<td>1.50** (1.05–2.14)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>3.44*** (1.75–7.42)</td>
<td>1.41* (0.98–2.02)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.84 (0.45–1.47)</td>
<td>1.44** (1.05–1.98)</td>
</tr>
<tr>
<td>Normal FLI (Ref.)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fatty liver</td>
<td>1.10 (0.59–2.03)</td>
<td></td>
</tr>
<tr>
<td>Normal eGFR (Ref.)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Low eGFR</td>
<td>1.60*** (1.18–2.19)</td>
<td></td>
</tr>
<tr>
<td>RHF</td>
<td>1.24 (0.66–2.30)</td>
<td></td>
</tr>
</tbody>
</table>

Note. Ref., reference category; CIs, confidence intervals; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; *p <0.1; **p <0.05; ***p <0.01
Table 3 Hazard ratios for all-cause and cardiovascular disease mortality in the study population ($n = 1552$).

<table>
<thead>
<tr>
<th></th>
<th>Number of events ($n$)</th>
<th>All-cause mortality</th>
<th>Cardiovascular disease mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Crude HRs (95% CI)</td>
<td>Fully adjusted HRs (95% CI)</td>
</tr>
<tr>
<td>Normal weight (Ref.)</td>
<td>263 (504)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Slight overweight</td>
<td>285 (491)</td>
<td>1.01 (0.86-1.2)</td>
<td>1.19 (0.81–1.76)</td>
</tr>
<tr>
<td>Overweight</td>
<td>199 (308)</td>
<td>1.17 (0.97-1.4)</td>
<td>1.46 (0.95–2.24)</td>
</tr>
<tr>
<td>Obese</td>
<td>172 (249)</td>
<td>1.35 (1.12-1.64)</td>
<td>1.37 (0.86–2.18)</td>
</tr>
<tr>
<td>Never smoker (Ref.)</td>
<td>198 (458)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Previous smoker</td>
<td>328 (558)</td>
<td>1.45 (1.22-1.73)</td>
<td>1.63 (1.12–2.36)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>393 (536)</td>
<td>2.74 (2.31-3.25)</td>
<td>3.82 (2.74–5.33)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>298 (441)</td>
<td>1.28 (1.11-1.47)</td>
<td>1.32 (1.15–1.53)</td>
</tr>
<tr>
<td>Normal eGFR, normal FLI (Ref.)</td>
<td>254 (474)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Normal eGFR, fatty liver</td>
<td>351 (527)</td>
<td>1.43 (1.21-1.68)</td>
<td>1.35 (1.09–1.66)</td>
</tr>
<tr>
<td>Low eGFR, normal FLI</td>
<td>81 (190)</td>
<td>0.73 (0.57-0.94)</td>
<td>0.87 (0.67–1.12)</td>
</tr>
<tr>
<td>Low eGFR, fatty liver</td>
<td>177 (288)</td>
<td>1.06 (0.87-1.28)</td>
<td>1.06 (0.84–1.33)</td>
</tr>
<tr>
<td>RHF, normal FLI</td>
<td>32 (40)</td>
<td>2.07 (1.43-2.99)</td>
<td>1.67 (1.15–2.42)</td>
</tr>
<tr>
<td>RHF, fatty liver</td>
<td>24 (33)</td>
<td>2.06 (1.36-3.14)</td>
<td>1.96 (1.27–3.01)</td>
</tr>
</tbody>
</table>

*Note.* Crude HRs are hazard ratios adjusted for age only. Fully adjusted HRs are hazard ratios adjusted for age, body mass index, alcohol consumption, tobacco smoking, and hypertension. CI, confidence interval; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; Ref., reference category; RHF, renal hyperfiltration.
Fig. 1

All-cause mortality

CVD mortality

FLI  Normal FLI  Fatty liver

Low eGFR  Normal eGFR  RHF

Low eGFR  Normal eGFR  RHF

HRs