Title
Authors
Journal
Year publication
Country
Funding
Population source
Demographics
Period follow up
Years of study
Study size
Intervention'
NAFLD definition
CKD definition
Quality (Newcastle-Ottawa Score)
Inclusion criteria
Exclusion criteria
Study design
Subgroup analysis
Adjustments for confounding factors
Longitudinal f/u
Outcome examined & definition
Statistical analysis
NAFLD prevalence
Cases
Primary outcome results
Secondary outcome results
OUTCOME

Non-alcoholic fatty liver disease and clinical outcomes in chronic kidney disease
Rajkumar Chinnadurai, James Ritchie, Darren Green and Philip A. Kalra
Nephrol Dial Transplant
2019
UK
?
Salford Kidney Study (SKS) - extension of the Chronic Renal Insufficiency Standards Implementations Study (CRISIS)
Mean age 66 years, males 60.7%, mean BMI 28, DM 34%, HTN 78%, hyperlipidaemia 49%, median eGFR 33.5 mL/min/1.73 m^2
Median 65 months
Liver USS (01/01/2000 - 31/12/2014), end of analysis period 31/12/2015
1148 CKD patients (205 NAFLD, 752 normal liver, 191 had other hepatic abnormalities on USS) 852 CKD patients (183 NAFLD, 669 normal liver) after excluding patients with incomplete follow-up data sets 276 CKD patients (138 NAFLD, 138 normal liver) with 1:1 propensity score matching
NAFLD vs no NAFLD
Liver USS (hyperechogenicity or echobright liver consistent with fatty infiltration)
eGFR <60 mL/min/ 1.73 m^2 using CKD-EPI formula
(1) Mortality NOS = 8, (2) non-fatal CVE NOS = 8, (3) CKD progression NOS = 9
Patients ≥ 18 years old referred to Salford renal service (tertiary centre); eGFR <60 mL/min/ 1.73 m^2, not needing immediate RRT
Maintenance RRT at time of liver USS , drinking above 21 units men / 14 units women, history of chronic hepatitis B & C or other chronic liver diseases
Retrospective observational longitudinal cohort study
NFCVE outcomes subgroup analysis: cardiac event, cerebrovascular event, PVD CCF Deaths analysed according to: cardiac, non-cardiac No subgroup analysis according to severity of NAFLD / severity CKD at baseline
Propensity matching for: age, gender, BMI, SBP, DBP, baseline hypertension, diabetes, hypercholesterolaemia, IHD, MI, CCF, CVA, PVD, malignancy, use of statin and renin–angiotensin blocking agents, eGFR (NB age difference, NAFLD 66 yrs, normal liver 68 yrs p=0.04)
Annual review: comorbidities, hospital admissions, cardiovascular events, medications, blood results
(1) ESRD: commencement of RRT or eGFR of <10 mL/min/1.73 m^2 (2) Rate of change of eGFR (eGFR slope) from baseline to study end-point (3) NFCVE: composite of ACS, non-fatal MIs, non-fatal cardiac arrest, coronary revascularizations, new diagnosis cardiac failure / admissions with exacerbations of cardiac failure, new diagnosis of PVD, CVAs (4) All-cause mortality
Univariate & multivariate Cox proportional hazards models to determine HRs & 95% CI (outcomes 1,3,4) Linear regression slope generated using serial serum creatinine measurements (outcome 2)
17.9% (205 / 1148)
(1) ESRD: NAFLD 26 (14.2%), normal 134 (19.1%), p=0.07 (2) CKD progression (rate of decline of eGFR slope): NAFLD -2.54 [-7.61 - 0.31] mL/min/1.73 m^2, normal -2.09 [-6.14 - 1.06] mL/min/1.73 m^2 (3) NFCVE: NAFLD 46 (25.1%), normal 82 (12.3%), p<0.001 (4) All cause mortality: NAFLD 50 (27.3%), normal 22 (33.0%), p=0.14
(1) ESRD: total sample HR 0.99 [0.65–1.52], p=0.90; matched HR 0.64 [0.35-1.16], p=0.145 (2) CKD progression (rate of decline of eGFR slope): total sample p<0.09; matched p=0.58 (3) NFCVE: total sample HR 2.07 [1.39-3.09], p<0.001; matched HR 1.85 [1.04-3.30], p<0.04 (multivariate: total sample HR 2.03 [1.33-3.13], p<0.001; matched HR 2.00 [1.10-3.66], p=0.02) (4) All-cause mortality: total sample HR 0.79 [0.58-1.08], p=0.14; matched HR 0.88 [0.57–1.34], p=0.54
N/A
INCLUDE

Nonalcoholic fatty liver disease accelerates kidney function decline in patients with chronic kidney disease: a cohort study
Hye Ryoun Jang, Danbee Kang, Dong Hyun Sinn, Seonhye Gu, Soo Jin Cho, Jung Eun Lee, Wooseong Huh, Seung Woon Paik, Seungho Ryu, Yoosoo Chang, Tariq Shafi, Mariana Lazo, Eliseo Guallar, Juhee Cho, Geum-Youn Gwak
Scientific reports
2018
South Korea
?
Individuals who underwent a comprehensive health screening examination at the Samsung Medical Centre Health Promotion Centre, Seoul, South Korea
Mean age 60.8 years, males 70%, mean BMI 24.8, DM 24%, HTN 60%, hyperlipidaemia 41%, median eGFR 59.1 mL/min/1.73 m^2
Average 6.5 years
January 2003 through December 2013
1,525 CKD patients
NAFLD vs no NAFLD
USS based on standard criteria, including parenchymal brightness, liver-to-kidney contrast, deep beam attenuation and bright vessel walls
eGFR < 60 ml/min/1.73 m^2 using CKD-EPI formula, or proteinuria ≥2+ on urinalysis
NOS = 7
Patients ≥ 18 years old who underwent a comprehensive health screening examination at the Samsung Medical Centre Health Promotion Centre and were found to have CKD with at least 1 additional follow up serum creatinine
History of cancer, liver cirrhosis, positive hepatitis B surface antigen, or hepatitis C virus antibodies, alcohol intake ≥ 30 g/day in men or ≥20 g/day in women, previous kidney transplant or started dialysis within 1 year after baseline examination, missing information on alcohol intake, NFS, or less than 6 months follow up
Retrospective observational longitudinal cohort study
(1) Severity NAFLD assessed via NFS: −1.675 + 0.037 × age (years) + 0.094 × BMI + 1.13 × impaired fasting glucose/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet count (×10^9/l) − 0.66 × albumin (g/dl). Based on NFS, patients were classified as high-intermediate (NFS ≥ −1.455) and low probability (NFS < −1.455) of advanced fibrosis. (2) Severity of CKD at baseline: cut-off value eGFR ≥45 ml/min/1.73 m^2 vs. <45 ml/min/1.73 m^2 (dividing G3a and G3b)
Stratified analyses to evaluate if association of NAFLD with CKD progression differed in pre-specified subgroups: age (<60 vs. ≥ 60 years), sex, smoking (never or former vs. current), alcohol drinking (none vs. moderate), BMI ≥ 25 kg/m2, hypertension (SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or use of antihypertensives), diabetes (fasting serum glucose ≥ 126 mg/dl, HbA1c ≥ 6.5%, or use of antidiabetic medication), hyperlipidaemia (HDL < 40 mg/dl in men or < 50 mg/dl in women, TG ≥ 150 mg/dl, or use of lipid-lowering medication), or baseline eGFR (<45 vs. ≥ 45 ml/min/1.73 m^2).
At each visit demographic characteristics, smoking status, alcohol consumption, medical history and medication use were collected through standardized, self-administered questionnaires along with blood results
CKD progression: average annual percent change in eGFR from baseline eGFR
Compared serial changes in eGFR among CKD patients with or without NAFLD at baseline using linear mixed models for longitudinal data with random intercepts and random slopes. Used loge-transformed eGFR as outcome and estimated the average difference in annual % change in eGFR (with 95% CI).
40.9% (902/1525)
Average annual percent change in eGFR from baseline: NAFLD -0.79% [-1.31 - -0.27], no NAFLD 0.30% [-0.14 - 0.76] Average difference in % decline of eGFR per year NAFLD vs no NAFLD: (i) Adjusted for age, sex, year of visit: -1.09% [-1.77 - -0.41] (ii) Adjusted for all confounders: -1.06% [-1.73 - -0.38]
Average difference in % decline of eGFR per year NAFLD vs no NAFLD: (i) Adjusted for age, sex, year of visit: p=0.002 (ii) Adjusted for all confounders: p=0.002
(1) Multivariable adjusted average difference in annual % changes in eGFR for low NFS (≤ 1.455) or intermediate to high NFS (≥ −1.455) & those without NAFLD: 0.01% [−0.74 - 0.99) & −2.12% (−2.93 - −1.31) respectively (2) Multivariable adjusted average difference in annual % changes in eGFR among patients with eGFR < 45 ml/min/1.73 m^2 at baseline -6.27% [-12.08 - - 0.08] (n=168) vs -0.76 [-1.32 - -0.19] (n=1357) for baseline eGFR ≥ 45
INCLUDE

Chronic kidney disease is independently associated with increased mortality in patients with nonalcoholic fatty liver disease.
James Paik, Pegah Golabi, Zahra Younoszai, Alita Mishra, Gregory Trimble, Zobair M. Younossi
Liver International
2019
USA
None
NHANES-III & linked mortality files
Mean age 43.3 years, males 48.4%, DM 6.5%, HTN 40.7% (total cohort)
Average 19.2 years
NHANES-III 1988 - 1994; linked mortality files up to 2011 or date of death
11,695 adult participants 'NAFLD- CKD-' 74.6%, 'NAFLD+ CKD-' 16.1%, 'NAFLD- CKD+' 6.8%, 'NAFLD+ CKD+' 2.5%
CKD vs no CKD in NAFLD cohort (main results reported in paper) NAFLD in CKD cohort (some data)
Liver USS (moderate/severe hepatic steatosis in absence of any other possible cause CLD)
eGFR < 60 ml/min/1.73 m2 using CKD-EPI formula +/- albuminuria
NOS = 9
Persons aged 20-74 at time of examination with complete data on ultrasound video images for hepatic steatosis assessment and serum creatinine measurements
Patients with other causes of chronic liver disease were excluded
Retrospective analysis of data collected from cross-sectional study
Presence of fat within hepatic parenchyma graded as normal, mild, moderate, or severe hepatic steatosis. NAFLD-associated advanced fibrosis was defined with ultrasound diagnosed NAFLD and at least one of the following fibrosis markers: APRI> 1, FIB-4 index >2.67, or NFS>0.676. Cardiovascular mortality was defined as death due to heart diseases (ICD-10: I00-I09, I11, I13, and I20-I51) and cerebrovascular diseases (ICD-10: I60-I69).
Age, gender, race, smoker, metabolic syndrome
Data linked with mortality files
(1) All-cause mortality (2) Cardiovascular-related mortality: death due to heart diseases (ICD-10: I00-I09, I11, I13, I20-I51) & cerebrovascular diseases (ICD-10: I60-I69)
Logistic regression & cox proportional hazards model
29% (410/1,413)
(1) All-cause mortality: NAFLD 54.7% (SE 3.6), no NAFLD 46.5% (SE 2.4), p<0.05 (age adjusted: NAFLD 31.0% [25.0-37.0], no NAFLD 25.9% [22.0-29.7], p=ns) (2) Cardiovascular-related mortality: NAFLD 16.0% (SE 2.5), no NAFLD 16.2% (SE 1.7), p=ns (age adjusted: NAFLD 7.8% [3.7-11.9], no NAFLD 8.2% [5.6-10.9], p=ns)
(1) All-cause mortality: adjusted HR NAFLD 2.34 [1.91-2.87], no NAFLD 2.08 [1.80-2.40], p=ns (2) Cardiovascular-related mortality: adjusted HR NAFLD 2.12 [1.44-3.13], no NAFLD 2.43 [1.8-3.2], p=ns
(1) CKD + NAFLD + advanced fibrosis (n=60) All-cause mortality: 73.1% [50.7-95.5], p=ns vs no advanced fibrosis; adjusted HR 3.49 [2.25-5.43], p=ns vs no advanced fibrosis Cardiovascular-related mortality: 14.6% [1.6-27.7], p=ns vs no advanced fibrosis; adjusted HR 2.83 [0.69-11.51], p=ns vs no advanced fibrosis (2) CKD + NAFLD + no advanced fibrosis (n=97) All-cause mortality: 52.1% [44.8-59.3]; adjusted HR 2.51 [1.98-3.18] Cardiovascular-related mortality: 16.5% [11.1-21.9]; adjusted HR 2.45 [1.61-3.73]
INCLUDE

Increased Risk for Cardiovascular Events in Patients with Diabetic Kidney Disease and Non-Alcoholic Fatty Liver Disease.
Rajkumar Chinnadurai, Constantina Chrysochou, Philip A. Kalra
Nephron
2018
UK
?
Salford Kidney Study (SKS) - extension of the Chronic Renal Insufficiency Standards Implementations Study (CRISIS)
Mean age 65 years, males 66%, mean BMI 30, DM 100%, HTN 87%, median eGFR 31.6 mL/min/1.73 m^2, hyperlipidaemia 79%
Median 69 months
Liver USS (01/01/2000 - 31/12/2014), end of analysis period 31/12/2015
192 patients with DKD (55 NAFLD, 113 normal liver, 24 had other hepatic abnormalities on USS) 149 patients with DKD (183 NAFLD, 669 normal liver) after excluding patients with incomplete follow-up data sets
NAFLD vs no NAFLD
Liver USS (hyperechogenicity or echobright liver consistent with fatty infiltration)
eGFR <60 mL/min/ 1.73 m^2 using CKD-EPI formula
Patients ≥ 18 years old referred to Salford renal service (tertiary centre); eGFR <60 mL/min/ 1.73 m^2, not needing immediate RRT
Maintenance RRT at time of liver USS , drinking above 21 units men / 14 units women, history of chronic hepatitis B & C or other chronic liver diseases
Retrospective observational longitudinal cohort study
NFCVE outcomes subgroup analysis: cardiac event, cerebrovascular event, PVD CCF Deaths analysed according to: cardiac, non-cardiac No subgroup analysis according to severity of NAFLD / severity CKD at baseline
Propensity matching for: age, gender, BMI, SBP, DBP, baseline hypertension, diabetes, hypercholesterolaemia, IHD, MI, CCF, CVA, PVD, malignancy, use of statin and renin–angiotensin blocking agents, eGFR (NB age difference, p=0.04)
Annual review: comorbidities, hospital admissions, cardiovascular events, medications, blood results
(1) ESRD: commencement of RRT or eGFR of <10 mL/min/1.73 m^2 (2) Rate of change of eGFR (eGFR slope) from baseline to study end-point (3) NFCVE: composite of ACS, non-fatal MIs, non-fatal cardiac arrest, coronary revascularizations, new diagnosis cardiac failure / admissions with exacerbations of cardiac failure, new diagnosis of PVD, CVAs (4) All-cause mortality
Univariate & multivariate Cox proportional hazards models to determine HRs & 95% CI (outcomes 1,3,4) Linear regression slope generated using serial serum creatinine measurements (outcome 2)
28.6% (55/192)
(1) ESRD: NAFLD 7 (14.6%), normal 17 (16.8%), p=0.73 (2) CKD progression (rate of decline of eGFR slope): NAFLD -3.97 [-7.2 - 0.12] mL/min/1.73 m^2, -2.95 [-9.07 - 0.407] normal mL/min/1.73 m^2 (3) NFCVE: NAFLD 20 (41.7%), normal 14 (13.9%), p<0.001 (4) All cause mortality: NAFLD 16 (33.3%), normal 36 (35.6%), p=0.78
(1) ESRD: not reported (2) CKD progression (rate of decline of eGFR slope): p=0.65 (3) NFCVE: HR 3.48 [1.59-7.6], p=0.002 (multivariate: HR 2.95 [1.31-6.60], p=0.01) (4) All-cause mortality: HR 0.72 [0.40-1.31], p=0.28
N/A
Sub group of previous paper by Chinnadurai

Nonalcoholic Fatty Liver Disease and Renal Function Impairment: A Cross-Sectional Population-Based Study on Its Relationship From 1999 to 2016
Michael H. Le, Yee Hui Yeo, Linda Henry, and Mindie H. Nguyen
Hepatology Communications
2019
USA
?
National Health and Nutrition Examination Survey (NHANES): cross-sectional survey conducted in US by the National Centre for Health Statistics of the Centres for Disease Control and Prevention (CDC)
Mean age 53 years, males 56%, mean BMI 34, DM 24%, HTN 52.3%, median eGFR 90.5 mL/min/1.73 m^2, dyslipidaemia 61%
1999 - 31 Dec 2015
14,255 adults (not all had renal insufficiency); 4680 NAFLD patients (population of interest for this study)
Renal insufficiency vs no renal insufficiency
U.S. Fatty Liver Index (USFLI) ≥30 to rule in fatty liver
eGFR determined CKD-EPI & ACR. Unable to determine if renal insufficiency was acute or chronic. Renal insufficiency divided into 4 stages: no RI, mild, moderate & severe
People aged 18 years and older, who participated in a medical examination at a mobile centre, and underwent fasting blood work during their examination.
Participants <18 years old, missing laboratory data needed to calculate the non-invasive indices (age, race/ethnicity, waist circumference, GGT, fasting insulin, fasting glucose, serum creatinine, urine creatinine, and urine albumin), those who had a diagnosis of viral hepatitis, and those with heavy alcohol use.
Cross-sectional study
Severity of liver fibrosis assessed using NAFLD Fibrosis Score (NFS). NFS >0.676 rule in stage 3-4 fibrosis, NFS <–1.455 rule out stage 3-4 fibrosis.
2 yearly cross-sectional interviews, examinations and laboratory data
(1) Trends in NAFLD +/- renal insufficiency prevalence over time in US (2) Predictors of RI in NAFLD patients (3) Health literacy levels for kidney & liver disease (4) Mortality (national death index): all-cause mortality, cause-specific mortality from diseases of heart and malignant neoplasms: compared NAFLD + renal insufficiency vs NAFLD without renal insufficiency (5) Risk factors predicting mortality in NAFLD cohort with & without renal insufficiency
Univariate & multivariate logistic regression; Kaplein Meier curves; cox regression
31.2% (not all patients had renal insufficiency)
(1) Prevalence 1999-2000: NAFLD without RI 23.5% [20.2-27.1], NAFLD-RI 5.7% [4.3-7.6]; prevalence 2015- 2016, NAFLD without RI 27.3% [23.7-31.1], NAFLD-RI 7.7% [6.2-9.5]. Trend analysis 1999-2016: prevalence of overall NAFLD, NAFLD without RI & NAFLD-RI all significantly increased over time (p=0.007, p=0.048, p=0.006 respectively). Among those with NAFLD, RI prevalence did not increase significantly 1999-2016 (p=0.221). No significant increases were observed in mild, moderate, or severe RI in those with NAFLD (p=0.448, p=0.222, p=0.478 respectively) (2) Significant independent predictors of RI in NAFLD: age > 65, HTN, DM, dyslipidaemia, CVD, high probability of fibrosis stage 3 and 4 (multivariate analysis) (3) Among those with NAFLD-RI, awareness of kidney disease was 8.56% [6.69-10.89], awareness of liver disease among all NAFLD was 4.49% [3.17-6.33] (4) 5 yr cumulative mortality incidence: NAFLD alone 4.5%; mild RI 14.2%, moderate 21.2%, and severe 36.0% RI (p<0.001). 15 yr cumulative mortality incidence: NAFLD alone 19.9%, mild RI 42.4%, moderate RI 80.6%, and severe RI 85.5% (p<0.001). 5 yr cumulative incidence CV-related mortality highest in NAFLD + severe RI at 10.5% (36.7% at 15 years). Independent risk factors for all-cause mortality in NAFLD: age, mild/mod/sever RI, high probability of fibrosis; former/current smoker; history of CVD. Independent risk factors for CV mortality in NAFLD: older age, moderate & severe RI, history of CVD.
Intervention is CKD in NAFLD cohort rather than NAFLD in CKD cohort.

Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate.
Grams ME1, Sang Y2, Ballew SH2, Carrero JJ3, Djurdjev O4, Heerspink HJL5, Ho K6, Ito S7, Marks A8, Naimark D9, Nash DM10, Navaneethan SD11, Sarnak M12, Stengel B13, Visseren FLJ14, Wang AY15, Köttgen A16, Levey AS12, Woodward M17, Eckardt KU18, Hemmelgarn B19, Coresh J20
Kidney Int.
2018
30 countries
Participants in International Chronic Kidney Disease Prognosis Consortium
Median eGFR 24 mL/min/1.73 m2
264,296 individuals
Age, sex, race, eGFR, ACR, SBP, smoking status, DM, history of CVD.
eGFR < 30 ml/min/1.73m2
Aim to develop 2 & 4 year models of the probability & timing of kidney failure requiring RRT, a non-fatal CVD event & death
Competing-risk regression, random-effect meta-analysis, and Markov processes with Monte Carlo simulations
NAFLD was not examined in this study