Association of Baseline Concentrations of Liver Function Tests and Full Blood Count Indices with Annual eGFR Decline and Renal Outcomes in Aboriginal and Torres Strait Islander People: The eGFR Follow- Up Study

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Abstract

Background:

Determination of risks for progression in chronic kidney disease (CKD) would improve strategies to reduce progression to ESKD. The eGFR study recruited and followed a cohort of adult Aboriginal and Torres Strait Islander people (Indigenous Australians) from Northern Queensland, Northern Territory and Western Australia, with the aim to address the heavy CKD burden experienced within these communities.

Methods:

Using data from the eGFR study, we explored the association of baseline liver function tests (LFTs) (alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), bilirubin and albumin) and full blood count (FBC) indices (white blood cell and red blood cell counts and haemoglobin) with annual eGFR decline and renal outcomes (first of 30% decline in eGFR with a follow-up eGFR <60 mL/min/1.73 m^2, initiation of renal replacement therapy, or renal death). Comparisons of baseline variables across eGFR categories were calculated using analysis of variance and logistic regression as appropriate. Linear and multivariable regression models were used to estimate the annual change in eGFR for changes in FBC indices and LFTs. Cox proportional hazard models were used to estimate the hazard ratio for developing renal outcome for changes in baseline FBC indices and LFTs.

Results:

Of 547 participants, 540 had at least one baseline measure of LFTs and FBC indices. The mean age was 46.1 (14.7) years and 63.6% were female. The median follow-up was 3.1 (IQR 2.8-3.6) years. Annual decline in eGFR was associated with low serum albumin ($p<0.001$) and haemoglobin ($p=0.007$). After adjustment for age, gender, urine albumin/creatinine ratio, diabetes and cardiometabolic markers, low serum albumin ($p<0.001$), haemoglobin ($p=0.012$) and bilirubin ($p=0.011$) were associated with annual decline in eGFR

Renal outcomes were inversely associated with serum albumin ($p<0.001$), bilirubin ($p=0.012$) and haemoglobin ($p<0.001$) and directly with GGT ($p=0.007$) and ALP ($p<0.001$). Other FBC indices and LFTs were not associated with annual decline in eGFR or renal outcomes.

Conclusions:

GGT, ALP, bilirubin, albumin and haemoglobin independently associate with renal outcomes. Contrary to findings from other studies, no association was found between renal outcomes and other FBC indices. These findings may help focus strategies to prevent disease progression in this high-risk population.

Background

Aboriginal and Torres Strait Islander people (the First Nation people of Australia/ Indigenous Australians) suffer some of the highest rates of end stage kidney disease (ESKD) requiring dialysis [1]. Clear determination of the potential risks for decline in estimated glomerular filtration rate (eGFR) would increase understanding and improve the ability to implement targeted strategies to reduce the progression to ESKD. The association of biomarkers of inflammation with kidney function decline has been documented in several studies [2, 3] and also

reported in the eGFR Study, a longitudinal study of adult Indigenous Australians [4]. Some recent studies have shown a possible association of elevated concentrations of white blood cells with kidney function decline [5, 6] and others have shown that the neutrophil/lymphocyte ratio, a marker of systemic inflammation, may be associated with poor renal outcomes [7, 8]. Furthermore, there is also emerging evidence of an association of abnormal liver function tests with decline in eGFR and increasing albuminuria [9]

The eGFR study was a longitudinal study of 654 Indigenous Australian adults from more than 20 sites in urban, regional, and remote Australian regions known to have high incidence of dialysis requiring ESKD, and participants were selected across five strata of health, diabetes status, and kidney function [10–12]. This study confirmed the accuracy of the CKD-EPI equation in estimating GFR in Indigenous Australians [12]. In a longitudinal follow-up, progression of CKD occurred rapidly, with loss of kidney function at approximately three times higher rate than expected through healthy ageing [13, 14]. Predictors of progression of CKD included elevated baseline urine albumin/creatinine ratio (UACR) and C-reactive protein (CRP) concentrations [9, 14, 15]. The inflammatory marker, soluble tumour necrosis factor receptor 1 (sTNFR1), was also associated with CKD progression, where this outcome was independent of albuminuria and eGFR in participants with diabetes [4]. Serum bilirubin concentration was positively associated with haemoglobin and total cholesterol; however there was an inverse association with UACR [9]. Cardiometabolic risk factors were not strong predictors for eGFR decline in Indigenous Australians who had normoalbuminuria at baseline [16].

An assessment of the potential association of abnormal liver function tests (LFTs) and full blood count (FBC) indices with annual eGFR decline in the eGFR Study will therefore increase our understanding of their potential role as predictors of eGFR decline in Indigenous Australians. We therefore undertook an exploratory study of whether abnormal baseline concentrations of liver function tests (LFTS- i.e. high alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), and bilirubin and low albumin) and FBC indices (high white blood cell (WBC) counts and red blood cell (RBC) counts and low haemoglobin (Hb)), were associated with annual decline in eGFR and renal outcomes.

Methods

Study design, participants, and data source

The eGFR study is a longitudinal study of Indigenous Australian adults. Participants were recruited from 20 community sites within five large geographic regions: Top End of the Northern Territory of Australia, Central Australia, Far North Queensland (North Queensland and the Torres Strait), and the Kimberley and Goldfields regions in Western Australia. The details of the eGFR study protocol have been described elsewhere[11].

Using an existing data set from the eGFR study, an analysis was performed to explore the association of baseline concentrations of LFTs and FBC indices with annual eGFR decline and renal outcomes.

Definitions of outcomes

The follow-up was the time from the date of baseline to the follow-up serum creatinine measurements (range 0.52–5.75 years). Outcomes were defined, as in previous published work from the eGFR study [4, 14, 16, 17], as follows; 1) the annual eGFR decline as annual change in CKD-EPI eGFR ([CKD-EPI eGFR at follow up-CKD-EPI eGFR at baseline]/follow up period) and 2) the combined renal outcome defined as the first of the following: an

absolute 30% decline in eGFR with a follow-up eGFR < 60 mL/min/1.73 m^2, death from renal causes, or initiation of renal replacement therapy. All deaths occurring when eGFR declined to < 15 mL/min/1.73 m^2 were defined as renal deaths. Participants were censored at the time the first end point was reached.

Laboratory and clinical measurements

At baseline and follow-up, non-fasting venous blood samples were collected, and pathology and clinical records were reviewed. Serum creatinine, LFTs, FBC, CRP, UACR and other metabolite assays were performed at each centre as part of standard clinical care. The creatinine assay at each centre was performed in an accredited laboratory using an assay with claimed traceability to the Isotope Dilution Mass Spectrometry reference method. In addition, serum creatinine was measured in all samples at a central laboratory, using Roche enzymatic method on a Beckman- Coulter DxC 800 analyser (Fullerton, CA, USA).

Statistical analysis

A descriptive analysis of the demographic, clinical, biochemical and outcome data summarising the data as mean and standard deviation (SD) for continuous normally distributed variables and median and inter-quartile range (IQR) for continuous variables with skewed distributions was performed. Comparisons of baseline variables across eGFR categories were carried out using analysis of variance for continuous variables and Chi-Squared tests for categorical variables Univariable linear regression models were used to regress the annual change in eGFR on FBC indices and on LFTs. Multivariable regression models were used to examine the potential confounding effect on FBC indices and on LFTs of other factors shown to be associated with eGFR decline including age and gender, urine ACR, diabetes, CRP, cholesterol and triglycerides. Univariable and multivariable Cox proportional hazard models were used to estimate the hazard ratio (HR) for developing a combined renal outcome for changes in baseline FBC indices and concentrations of LFTs (AST, ALT, ALP, GGT, bilirubin and albumin).

Transformation of independent variables was performed where indicated by the distribution of the variable. Potential effect modifications of CRP and diabetes were investigated with linear regression models and Cox proportional hazard models that included the interaction terms between CRP and measures of LFTs and FBC and between diabetes and measures of LFTs and FBC indices respectively. We excluded UACR in the adjustment for models examination the association between the outcomes and serum albumin concentrations due the correlation between serum albumin concentrations and UACR.

Sensitivity analyses were carried out where the regression analyses were performed with each of the predictor variables divided into quintiles.

Two-sided tests were used for all the analyses and the level of significance was set at $p < 0.05$. All analyses were performed using STATA software version 15.1 (StataCorp 2017©1985–2017 StataCorp LP).

Results

Available data on baseline concentrations of LFTs and FBC indices and baseline characteristics

Of the 654 Indigenous Australian participants in the baseline eGFR study [15], data were available on 547 participants for the purposes of this study. Of these, 540 participants had at least one measure of LFTs concentrations and FBC indices at baseline. There were no data on AST, differential WBC (for determination of neutrophil/lymphocyte ratio) and red blood cell distribution width in the dataset so analysis on these could not be performed.

The mean age was 46.1 (14.7) years and 348 (63.6%) participants were female. The median follow-up was 3.1 years (IQR 2.8 to 3.6 years). The baseline clinical characteristics, including concentrations of LFTs, FBC indices and cardiometabolic risk markers stratified by eGFR are summarised in Table 1. At baseline, older age, the presence of diabetes, gender, low concentrations of ALT, albumin, bilirubin and haemoglobin and high concentrations of ALP and adiponectin as well as high UACR, systolic blood pressure, WHR and HbA1c were significantly associated with lower eGFR categories. There was no significant association between each of baseline concentrations of GGT and FBC indices and eGFR categories. (Table 1).

Table 1
Baseline clinical characteristics, measures of liver function, FBC and cardiometabolic markers stratified by eGFR

Baseline variable	eGFR (CKD EPI) < 60 ml/min per 1.73 m^2 (n = 83)	eGFR (CKD EPI) 60–89 ml/min per 1.73 m^2 (n = 110)	eGFR (CKD EPI) > 90 ml/min per 1.73 m^2 (n = 354)	P Value*	Total (N=-547)
Age(years)	58.5 (12.6)	51.1 (13.6)	41.6 (13.1)	< 0.001	46.1 (14.6)
Female n (%)	49 (59)	60 (54.5)	239 (67.1)	0.533	348 (63.6)
Diabetes n (%)	54 (65.1)	50 (45.6)	135 (38.1)	0.007	239 (43.7)
ALT (U/L)	23 (17.5–29.5))	27(19–36)	26(19–38)	0.005	26 (19–36)
GGT (U/L)	32 (23–77)	33(22–50)	34(25–58)	0.391	34 (24–61)
ALP (U/L)	121.5 (96-156.5)	95(76–112)	93 (77–119)	< 0.001	96 (78–122)
ACR (mg/mmol)	53.7(12.4-220.9)	1.6(0.8–13.1)	1.5(0.7-7.0)	< 0.001	2.1 (0.7–17.7)
CRP (mg/L)	5.0 (3.0–13.0)	5.0 (2.5-9.0)	6.0 (3.0–11.0)	0.646	5.8 (3–11)
Albumin (g/L)	39.4(4.6)	42.3(3.98)	42.6(4.1)	< 0.001	42.1 (4.3)
Bilirubin (µmol/L)	5(3–8)	7 (5–10)	7 (5–9)	0.002	6.5 (7.9–9.6)
WBC ($X10^9$)	8.1 (3.5)	7.78 (3.3)	7.8 (3.2)	0.650	7.9 (3.2)
Hb (g/L)	124.1 (18.8)	135.5(16.7)	139.3 (16.4)	< 0.001	136.3 (17.6)
RBC ($X10^{12}$)	4.1 (1.7)	4.7(1.0)	4.6 (1.5)	0.060	4.6 (1.4)
SBP (mmHg)	123.0(17.4)	120.2 (21.0)	116.5 (16.1)	0.002	118.2 (17.5)
DBP (mmHg)	74.5 (9.8)	74.5 (9.8)	74.8 (10.5)	0.712	74.7 (10.2)
WHR (0.1 unit)	1.0 (0.08)	0.9 (0.1)	0.9 (0.1)	< 0.001	0.9 (0.1)
HbA1c (%)	6.5 (5.9–8.4)	6.1 (5.7–7.2)	6.0 (5.6-7.0)	0.012	6.1 (5.6–7.3)

Baseline variable	eGFR (CKD EPI) < 60 ml/min per 1.73 m^2 (n = 83)	eGFR (CKD EPI) 60–89 ml/min per 1.73 m^2 (n = 110)	eGFR (CKD EPI) > 90 ml/min per 1.73 m^2 (n = 354)	P Value*	Total (N=-547)
HbA1c (mmol/L)	47.5 (41.0-68.3)	43.2 (38.8–55.2)	42.1(37.7–53.0)	0.012	43.2 (37.7–56.3)
Adiponectin (pg/L) (X 10^6)	4.4 (3.2-6.0)	3.5 (2.2–4.6)	3.0 (2.2-4.0)	< 0.001	3.2 (2.3–4.4)
Adiponectin(ng/L)	4367.6 (3202.7–5975.0)	3491.2 (2237.6-4569.4)	2989.5 (2247.6-4029.3)	< 0.001	3282.4 (2332-4429.3)
Cholesterol (mmol/L)	4.5 (1.1)	4.8(1.1)	4.9(1.1)	0.012	4.8 (1.1)
Triglycerides (mmol/L)	2.2 (1.6–3.4)	1.8 (1.2–2.4)	1.8 (1.3–2.5)	0.069	1.8 (1.3–2.5)

Data are mean (SD) or median (25th, 75th percentile) unless otherwise specified. CKD-EPI, CKD-Epidemiology Collaboration; ALT, Alanine Aminotransferase; GGT, Gamma-glutamyl transferase; ALP, Alkaline phosphatase; ACR, Albumin to creatinine ratio; CRP, C-reactive protein; FBC, Full Blood Count; WBC, white blood cell count; Hb, haemoglobin; RBC, red blood cell count; SBP, Systolic blood pressure; DBP, diastolic blood pressure; WHR, waist-hip ratio; HbA1c, glycated haemoglobin; U/L, units per litre; g/mol, grams per mol; g/L, grams per litre; mmHg, millimetres of mercury; mmol/L, millimoles per litre; ng/L, nanograms per litre; pg/L, picograms per litres. *p-value of comparisons across eGFR categories and was calculated using ANOVA for continuous variables and logistic regression for categorical variables

Associations of baseline concentrations of LFTs and measures of FBC indices with annual decline in eGFR

Univariable analyses results show no relationship between annual decline in eGFR and the following; log ALT (p = 0.315), log GGT (p = 0.224), log ALP (p = 0.226), log bilirubin (p = 0.599), WBC (p = 0.720), RBC (p = 0.483) and CRP (p = 0.827). A strong association was demonstrated between annual decline in eGFR and low concentrations of serum albumin (P < 0.001) and haemoglobin (p = 0.007). (Table 2)

Table 2
Regression models of the relationship between annual decline in eGFR and baseline concentrations of measures of liver function tests and full blood count indices

Baseline factor	unadjusted		Adjusted for age and gender		Adjusted for age, gender and UACR		Adjusted for age gender, UACR and diabetes		Adjusted for age, gender, UACR and [a]other cardiometabolic markers	
	β (95% CI)	p-value	β (95%CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
Log ALT (U/L)	0.55 (-0.52-1.62)	0.315	0.66 (-0.45-1.77)	0.245	0.56 (-0.54-1.67)	0.315	0.55 (-0.57-1.67)	0.336	-0.06 (-1.16-1.04)	0.912
Log GGT (U/L)	-0.45 (-1.17-0.27)	0.224	-0.39 (-1.13-0.34)	0.295	-0.18 (-0.92-0.56)	0.636	-0.07 (-0.83-0.69)	0.857	-0.18 (-0.94-0.59)	0.650
Log ALP (U/L)	-0.98 (-2.58-0.61)	0.226	-1.05 (-2.65-0.56)	0.200	-0.04 (-1.67-0.60)	0.966	0.12 (-1.55-1.77)	0.897	0.38 (-1.26-2.02)	0.649
Log Bilirubin (μmol/L)	-0.27 (-1.28-0.74)	0.599	-0.17 (-1.21-0.86)	0.742	-1.00 (-2.07-0.07)	0.067	-1.04 (-2.13-0.06)	0.063	-1.43 (-2.52--0.33)	0.011
Serum albumin (g/L)	0.34 (0.22–0.46)	< 0.001	0.36 (0.24–0.49)	< 0.001	N/A	N/A	0.34 (0.21–0.47)[b]	< 0.001	0.31 (0.18–0.44)[b]	< 0.001
Hb (g/L)	0.04 (0.01–0.07)	0.007	0.06 (0.03–0.10)	0.001	0.05 (0.01–0.08)	0.014	0.04 (0.01–0.08)	0.018	0.013 (-0.02-0.05)	0.012
WBC ($x10^9$/L)	0.03 (-0.14-0.20)	0.720	0.03 (-0.14-0.20)	0.739	0.08 (-0.09-0.25)	0.354	0.07 (-0.10-0.24)	0.404	0.02 (-0.15-0.19)	0.796
RBC ($x10^{12}$/L)	0.14 (-0.24-0.51)	0.483	0.17 (-0.22-0.56)	0.391	0.15 (-0.24-0.54)	0.456	0.14 (-0.26-0.53)	0.493	-0.04 (-0.45-0.36)	0.830

β, β-coefficient; CI, Confidence Intervals; ALT; Alanine Aminotransferase; GGT; Gamma-glutamyl transferase; ALP; Alkaline phosphatase; UACR, Urine Albumin/creatinine ratio; U/L; units per litre; g/L; grams per litre; μmol/L; micromoles per litre; [a]cholesterol mmol/L, triglycerides mmol/L, C-reactive protein mg/L, [b]UACR no included in the model.

After adjustment for age, gender, UACR, diabetes and other cardiometabolic markers, only low concentrations of serum albumin ($p < 0.001$) and haemoglobin ($p = 0.012$), and high concentrations of bilirubin ($p = 0.011$) were significantly associated with annual decline in eGFR. However, with this adjustment, there was no significant association between annual decline in eGFR and concentrations of the rest of measures of LFTs and FBC indices. (Table 2).

When divided into quintiles and adjusted for age, gender, UACR, diabetes and other cardiometabolic markers, there was a positive linear association with more preserved eGFR across the five quintiles of concentrations of serum albumin, RBC, haemoglobin, relative to lowest (first quintile). (Tables S1 and S2).

Association of baseline concentrations of measures of LFTs and FBC indices with the renal outcomes

Table 3 details the associations between baseline concentration of measures of LFTs and FBC indices with the combined renal outcome. 12.4% (n = 68) of the 540 participants experienced the outcome over the follow-up period of a median of 3.1 (IQR 2.8–3.6) years The following baseline measures were associated with reduced crude hazard ratio of the renal outcome; concentrations of serum ALT, serum albumin and haemoglobin. These associations were independent of age, gender, UACR, diabetes and other cardiometabolic markers for serum bilirubin, albumin, and haemoglobin but not for concentration of ALT. Concentrations of GGT and ALP were associated with increased crude hazard ratio of renal outcomes. This increased hazard ratio persisted after adjustment for age, gender and UACR, diabetes and other cardiometabolic markers

Table 3
Cox regression models of association of measures of concentrations of liver function tests and full blood count indices with renal outcomes

Baseline measure	Crude		Adjusted for age and gender		Adjusted for age, gender and UACR		Adjusted for age gender, UACR and diabetes		Adjusted for age, gender, UACR, diabetes and [a]other cardiometabolic markers	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Log ALT (U/L)	0.58 (0.35–0.94)	0.027	0.67 (0.40–1.12)	0.129	0.64 (0.37–1.10)	0.109	0.54 (0.31–0.98)	0.041	0.64 (0.35–1.17)	0.147
Log GTT (U/L)	1.48 (1.10-2.00)	0.012	1.49 (1.10–2.02)	0.011	1.53 (1.10–2.13)	0.011	1.54 (1.08–2.16)	0.017	1.55 (1.13–2.14)	0.007
Log ALP (U/L)	11.38 (5.88–22.01)	< 0.001	13.40 (6.68–27.23)	< 0.001	9.35 (4.40-19.86)	< 0.001	7.56 (3.55–16.08)	< 0.001	4.94 (2.32–10.52)	< 0.001
Log Bilirubin (µmol/L)	0.42 (0.26–0.68)	< 0.001	0.35 (0.21–0.57)	< 0.001	0.52 (0.31–0.89)	0.016	0.49 (0.28–0.87)	0.015	0.61 (0.35–1.07)	0.012
Albumin (g/l)	0.87 (0.84–0.90)	< 0.001	0.88 (0.84–0.91)	< 0.001	N/A	N/A	0.86 (0.81–0.91)[b]	< 0.001	0.84 (0.79–0.90)[b]	< 0.001
WBC ($x10^9$/L)	1.07 (0.99–1.15)	0.108	1.07 (1.00-1.15)	0.044	1.05 (0.97–1.14)	0.219	1.05 (0.97–1.13)	0.245	1.05 (0.96–1.13)	0.283
RBC ($x10^{12}$/L)	0.93 (0.82–1.05)	0.237	0.94 (0.82–1.08)	0.392	0.96 (0.83–1.10)	0.545	0.96 (0.83–1.10)	0.535	0.96 (0.82–1.13)	0.622
Haemoglobin (g/L)	0.96 (0.95–0.97)	< 0.001	0.95 (0.94–0.97)	< 0.001	0.95 (0.94–0.97)	< 0.001	0.95 (0.94–0.97)	< 0.001	0.96 (0.94–0.98)	< 0.001

HR, Hazard Ratio; 95% CI, 95% Confidence Intervals;, ALT, Alanine Aminotransferase; GGT, Gamma-glutamyl transferase; ALP, Alkaline phosphatase' UACR, Urine albumin/creatinine ratio; U/L, units per litre; g/L, grams per litre; µmol/L, micromoles per litre; [a]cholesterol mmol/L, triglycerides mmol/L, C-reactive protein mg/L, [b]UACR not include in the model.

RBC and WBC were not associated with crude hazard ratio of renal outcomes. This lack of relationship with hazard ratio of renal outcomes remained on multivariable analyses.

There was no significant interaction between CRP and measures of LFTs and FBC indices and between diabetes and measures of LFTs and FBC indices with annual eGFR decline and renal outcomes, respectively.

Discussion

In this analysis of the longitudinal eGFR study, in a population at high risk of renal disease and progression to ESKD, we explored the association of measures of liver function and full blood count indices with annual decline in eGFR and combined renal outcomes.

For the first outcome, the annual decline in eGFR, we report an association with low concentrations of serum albumin, haemoglobin, and high concentrations of serum bilirubin.

For the second outcome, defined as the incidence of a combined renal end point, which was the first of the following: a 30% decline in eGFR with a follow-up eGFR < 60 mL/min/1.73 m^2, death from renal causes, or initiation of renal replacement therapy, we report an inverse association with concentrations of serum albumin, serum bilirubin and haemoglobin and a positive association with concentrations of GGT and ALP

Our study supports the emerging evidence that high bilirubin concentrations may be protective against decline in kidney function and poor renal outcomes. We have previously reported from the eGFR study the inverse association of log-bilirubin with UACR [9].Several other studies suggest a protective role of high serum bilirubin against progression of chronic kidney and poor renal outcomes and this may be related to delaying progression of fibrosis-related kidney disease [18–23]

In our study of participants with high risk of CKD, there was a statistically significant decrease in the baseline concentrations of serum ALT across categories of decreasing eGFR. However, there was no significant relationship between baseline concentration of serum ALT and the annual decline in eGFR. The inverse association of ALT with the crude hazard of renal outcomes disappeared after adjustment for other covariates. To our knowledge, there are no previous studies exploring the association of serum concentrations of ALT and AST with renal outcomes. AST was not measured in this study. However, observational studies have described lower serum concentrations of serum aminotransferases over time in adults with CKD [24, 25], with multifactorial causes postulated. The same studies have suggested that new reference ranges may need to be set for these enzymes in people with CKD although the rationale for this is not clear from the current evidence [24, 25].

Our analysis has shown a statistically significant association between increased concentrations of serum GGT and poor renal outcomes although an association with annual decline in eGFR was lacking. Other studies have also suggested that GGT is an independent predictor of mortality in patients with stage 4–5 chronic kidney disease [26]. Some previous studies have suggested an association of serum GGT with development and progression of CKD [27–29] although some studies have suggested that in some ethnic groups this association is confounded by other factors such as body mass index, life style factors, lipids, smoking and heavy alcohol intake [28, 30]. This positive association of high baseline concentrations of GGT with poor renal outcomes may indicate that the serum levels of this enzyme can be used as a surrogate marker of risk for poor renal outcomes. The mechanism linking GGT and progression of CKD is unclear and will need to be further studied although oxidative stress and inflammation in synergy with serum ferritin have been suggested [27].

In this study, there was a positive association between serum ALP concentrations and increased risk of poor renal outcomes. Serum ALP concentrations increased with progression in CKD. However, this is likely to be the bone isoenzyme of the ALP (not liver) which increases with the onset and severity of renal bone disease [31–33].

Although this supports the potential use of serum ALP as predictor of poor outcomes in people with CKD [26, 32, 33], the liver isoenzyme and association with decline in eGFR and renal outcomes would need further studies.

As expected, and found in many studies, serum albumin concentrations were inversely associated with decline in eGFR and high risk of adverse renal outcomes [34–37]. Similarly, the inverse relationship between haemoglobin and decline in eGFR and poor renal outcomes is expected.

Our current study showed no association of concentrations of WBC and RBC with annual decline in eGFR and renal outcomes. The potential role of the neutrophil/lymphocyte ratio could not be assessed because these variables were not available among the data. Recent studies have demonstrated mixed results on the predictive role of WBC on decline of eGFR in the people with CKD. Some studies have showed that elevated WBC count was a strong predictor of kidney function decline [5], high monocyte count was significantly associated with risks of incident CKD and CKD progression to ESKD [6] and low WBC count was independently associated with CKD progression in the elderly [38]. Other studies have demonstrated the potential role of the high neutrophil/lymphocyte ratio as a predictor of poor renal outcomes [7, 8]. However, in a study of inflammatory markers including hsCRP, WBC count and ferritin, hsCRP and ferritin stratified by albumin associated with RRT and rapid renal progression, but WBC count was not associated with renal outcomes [39]. These mixed results suggest the need for further studies on this potential association of WBC with renal outcomes.

Our analysis showed no association between RBC counts and annual decline in eGFR and renal outcomes after adjusting for other covariates. In our study, we did not have data on red blood cell distribution width (RDW), a measure of the range of variation of RBC volume. The association of red blood cell count and progression of renal disease remains poorly understood. Most studies have demonstrated the shortened life span of red blood cells with progression of CKD [40–42]. Studies have also suggested the predictive value of RDW, for cardiovascular and risk of CKD and renal outcomes [43, 44]. Therefore, further studies of the association between renal outcomes and RBC counts and RDW are needed.

Limitations

There were some limitations to our study. There was no data on AST, viral hepatitis, history of liver disease, which would need to be used in the adjustment for the potential role of the liver function tests (ALT, GGT, ALP, Albumin and bilirubin) in the Cox model. This will need further exploration as studies have indicated the association of liver disease with progressing of CKD [45–47]. The absence of other parameters of the FBC indices, such as the differential WBC and red RDW, meant that we were unable to corroborate the details of the association of these indices with eGFR decline and renal outcomes.

The small number of participants in the study who reached the renal outcomes potentially limited the power to detect the associations and increased the lack of precision of estimates for the associations. The median follow-up of 3.1 years was relatively short, and the ongoing long-term follow-up will provide more robust assessment of these associations.

Conclusion

Our findings show that measures of liver function (GGT, ALP, bilirubin and albumin) and haemoglobin, routinely measured in clinical practice, are independently associated with poor renal outcomes. Contrary to results from other studies, we did not find any association of FBC indices (WBC count and RBC count) with progression of CKD and renal outcomes. Noting the need for further studies for clarity, our findings may help focus strategies to prevent disease progression in this high-risk population.

List Of Abbreviations

ALT, alanine aminotransferase

GGT, Gamma-glutamyl transferase

ALP, Alkaline phosphatase

WBC, white blood cell count

RBC, red blood cell count

CKD, chronic kidney disease

ESKD, end stage kidney disease

HR, Hazard ratio

FBC, Full Blood Count

UACR, Urine albumin to Creatinine ratio

CRP, C-Reactive protein

hsCRP, highly sensitive C-Reactive protein

Declarations

Ethics approval and consent to participate

All participants provided written informed consent. The ethics committees of each region approved the study. These included the Human Research Ethics Committees (HREC) of the Menzies School of Health Research and Northern Territory Department of Health including the Aboriginal subcommittee; Central Australian Human Research Ethics Committee; Western Australian Aboriginal Health Information and Ethics Committee, Royal Perth Measurements Hospital Ethics Committee and Cairns and Hinterland Health Services District Human Research Ethics Committee.

Consent for publication

Not applicable

Availability of data and materials

All data supporting the study are presented in the manuscript and available on a request to the eGFR study editorial committee.

Competing interests

None of the authors have any disclosures.

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Authors' contributions

All authors are members of the eGFR study investigators and contributed to the design and follow up of the study. LJMB, RJM and JTH are members of the study editorial committee. SWM and FB performed the analysis. SWM wrote the first draft of the manuscript. All authors discussed the results and approved the manuscript as submitted. All authors approved the final version of the manuscript.

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