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ORIGINAL ARTICLE

Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios: associations with mortality in a haemodialysis cohort

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ABSTRACT

Background. Lymphocyte ratios reflect inflammation and have been associated with adverse outcomes in a range of diseases. We sought to determine any association between neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) and mortality in a haemodialysis cohort, including a coronavirus disease 2019 (COVID-19) infection subpopulation.

Methods. A retrospective analysis was performed of adults commencing hospital haemodialysis in the West of Scotland during 2010–21. NLR and PLR were calculated from routine samples around haemodialysis initiation. Kaplan–Meier and Cox proportional hazards analyses were used to assess mortality associations.

Results. In 1720 haemodialysis patients over a median of 21.9 (interquartile range 9.1–42.9) months, there were 840 all-cause deaths. NLR but not PLR was associated with all-cause mortality after multivariable adjustment [adjusted hazard ratio (aHR) for in participants with baseline NLR in quartile 4 (NLR ≥8.23) versus quartile 1 (NLR <3.12) 1.63, 95% confidence interval (CI) 1.32–2.00]. The association was stronger for cardiovascular death (NLR quartile 4 versus 1 aHR 3.06, 95% CI 1.53–6.09) than for non-cardiovascular death (NLR quartile 4 versus 1 aHR 1.85, 95% CI 1.34–2.56). In the COVID-19 subpopulation, both NLR and PLR at haemodialysis initiation were associated with risk of COVID-19-related death after adjustment for age and sex (NLR: aHR 4.69, 95% CI 1.48–14.92 and PLR: aHR 3.40, 95% CI 1.02–11.36; for highest vs lowest quartiles).

Conclusions. NLR is strongly associated with mortality in haemodialysis patients while the association between PLR and adverse outcomes is weaker. NLR is an inexpensive, readily available biomarker with potential utility in risk stratification of haemodialysis patients.

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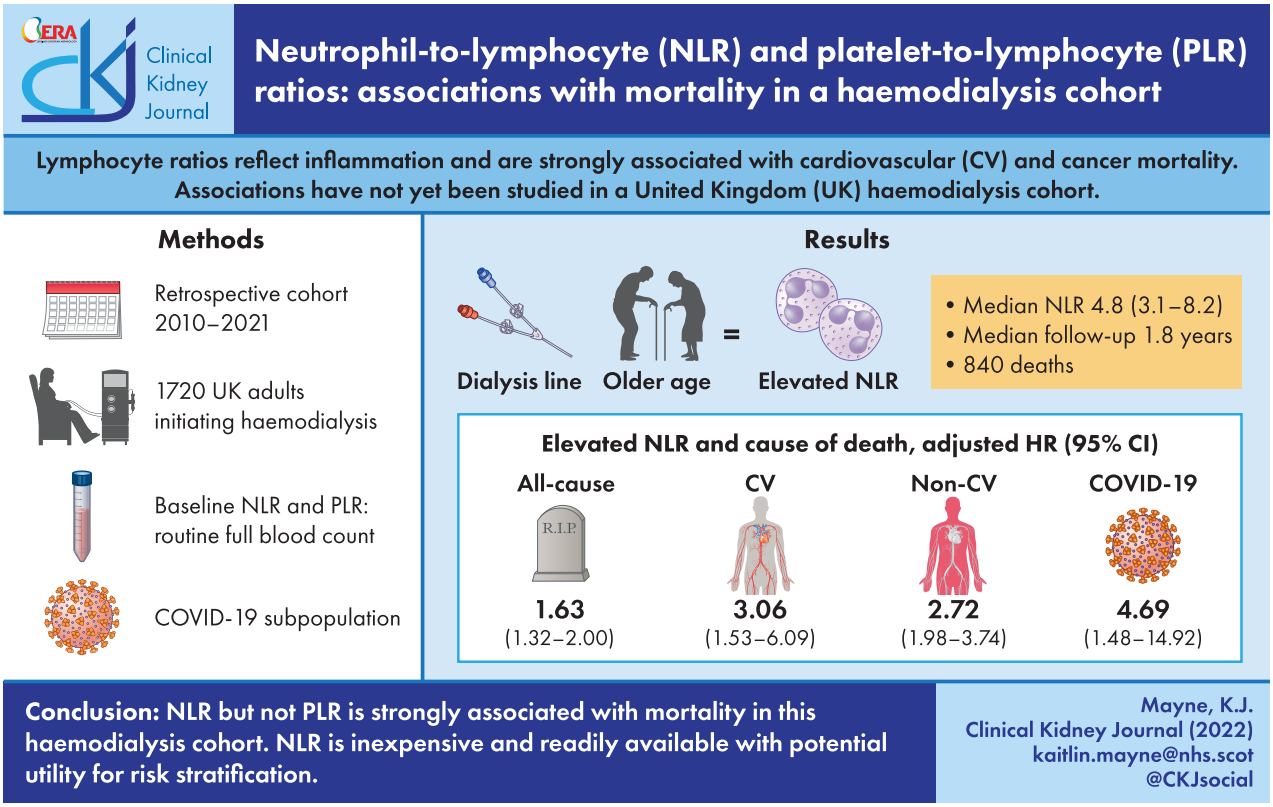
GRAPHICAL ABSTRACT



Keywords: COVID-19, haemodialysis, inflammation, lymphocyte, mortality

INTRODUCTION

Neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte ratios (PLR) are simple ratios of neutrophil count or platelet count divided by lymphocyte count. They can be calculated from the inexpensive and commonly collected full blood count, and are surrogate markers of systemic inflammation and endothelial damage [1]. Where the NLR or PLR is raised, pro-inflammatory cells outnumber anti-inflammatory lymphocytes indicating a state of inflammatory imbalance [1].

Inflammation is a key pathophysiological process in chronic kidney disease (CKD) due to several contributing factors including uraemia, reduced clearance of inflammatory mediators, volume overload, increased susceptibility to infection, oxidative stress and technical factors relating to dialysis [2–5]. In advanced CKD and kidney failure, inflammation is evident and quantifiable using established markers of inflammation. These markers—which include C-reactive protein (CRP) as well as more sophisticated biomarkers of inflammation such as interleukin-6 and tumour necrosis factor-α (TNF-α)—can be expensive and many are not measured routinely in clinical practice [6]. By comparison, lymphocyte ratios such as NLR and PLR are inexpensive and readily available.

In part due to chronic inflammation, kidney failure is strongly associated with mortality and cardiovascular disease [7–10]. NLR and PLR are established as markers of inflammation and poor prognosis from cancer and cardiovascular disease [1]. More recently, NLR and PLR have been shown to be associated with adverse prognosis specifically in CKD populations [1]. Interest in lymphocyte ratios has also grown in the context of the coronavirus disease 2019 (COVID-19) pandemic and meta-analyses have demonstrated positive associations between NLR at COVID-19 presentation and COVID-19 disease severity and mortality in general adult COVID-19 populations [11–13]. Similar findings have been reported in smaller studies in dedicated CKD populations with COVID-19 disease [14–17].

Lymphocyte ratios might represent a clinically useful and cost-effective tool for risk stratification of cardiovascular disease and mortality in kidney failure. Existing studies in European haemodialysis populations are small and, to our knowledge, associations between lymphocyte ratios and adverse outcomes in haemodialysis patients have not been characterized in a UK cohort. We sought to determine the association between lymphocyte ratios and all-cause and cardiovascular mortality in a large cohort of consecutive, incident haemodialysis patients in the UK and to study these associations in a subpopulation of haemodialysis patients who developed COVID-19 infection.

MATERIALS AND METHODS

Study design and participants

We performed a retrospective analysis of all patients aged over 16 years with kidney failure commencing haemodialysis (i.e. incident haemodialysis patients) in National Health Service (NHS) Greater Glasgow & Clyde (GGC) and Forth Valley health boards between 1 January 2010 and 31 December 2021 ($n = 1735$). Participants were identified using the Strathclyde Electronic Renal Patient Record (SERPR) which is used to deliver renal care across the West of Scotland (supported by Vitalpulse, UK). Participants missing baseline differential white blood cell count (WCC) ($n = 14$) or missing data on follow-up time were excluded ($n = 1$); therefore, 1720 participants were included in the analysis cohort. We did not apply additional exclusion criteria based on comorbidity or other treatment modalities in order to assess a representative sample of haemodialysis patients.

Formal ethical approval was not required as analyses used routinely collected pseudonymized data. However, Caldicott Guardian approval was applied for and granted for the use of these data by the information governance manager for both NHS GGC & NHS Forth Valley.

Baseline measurements

Baseline variables were measured at haemodialysis initiation. Age was calculated from date of birth. Data were recorded on sex, primary renal diagnosis and haemodialysis access. Primary renal diagnosis was coded in accordance with the Scottish Renal Registry (SRR) analysis method which is based upon the European Renal Association's (ERA) groupings [18]. Haemodialysis access was described as arteriovenous fistula or graft central venous catheter (CVC; tunnelled, non-tunnelled or not otherwise specified) or not recorded. History of diabetes mellitus and cardiovascular disease were obtained from the electronic patient record. Pre-existing cardiovascular disease was defined as any of ischaemic heart disease, heart failure, cerebrovascular disease or peripheral vascular disease, according to coded diagnoses within the electronic patient record.

Baseline laboratory measurements were defined as the first result within 30 days of dialysis initiation for total and differential WCC, haemoglobin, platelet count, serum albumin, adjusted calcium and phosphate. Routine practice in our services is to monitor bloods on a monthly basis during maintenance haemodialysis treatment; therefore, 30 days was chosen to capture the first result closest to haemodialysis initiation. In the majority of cases, we expect participants to have results available from the day of haemodialysis initiation but in isolated cases where these are not available, the earliest result within 30 days was used. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios were calculated by dividing neutrophil count ($\times 10^9$/L) and platelet count ($\times 10^9$/L) by lymphocyte count ($\times 10^9$/L), respectively, and expressing these as ratios.

Outcome measurements

Primary cause of death was obtained from the electronic patient record. The primary outcome was all-cause death during follow-up. Cardiovascular death and non-cardiovascular death, as defined by SRR/ERA groupings [18] (see Supplementary Methods) were studied as secondary outcomes. Participants were censored at the time of renal transplant, dialysis modality change, recovery of native renal function or transfer to another facility. Additionally, in the analysis of cardiovascular death, participants were censored at the time of non-cardiovascular death, and vice versa.

COVID-19 subpopulation analysis

Participants who had at least one positive COVID-19 laboratory [polymerase chain reaction (PCR)] test result recorded in the electronic patient record since haemodialysis initiation were included in a subpopulation analysis. PCR was performed in patients with possible COVID-19 symptoms only. Participants with an interval of 90 days or more between episodes of COVID-19 infection were considered to have possible reinfection in accordance with Public Health Scotland's definition [19] (see Supplementary Methods). Mortality data recorded within the electronic patient record using SRR/ERA cause of death codes do not capture death due to COVID-19 and death certificates were not available. Deaths within 28 days of a positive COVID-19 test were considered COVID-19-related deaths and documented causes of death were reviewed in these cases (see Supplementary Methods).

Statistical analysis

Normality was assessed by visual inspection of histograms and quantile–quantile plots. Data were summarized using mean [standard deviation (SD)] for normally distributed variables and median [interquartile range (IQR)] if non-normally distributed. Numbers and percentages were used to summarize categorical variables. NLR, PLR and total WCC were non-normally distributed and therefore log-transformed. Prior to transformation, NLR and PLR were also categorized into quartiles. Baseline characteristics and laboratory measurements were presented by NLR quartile. Tests for trends across categories were assessed using ANOVA, Pearson chi-squared or Kruskal–Wallis tests as appropriate.

Missing values in other variables were handled by imputing the mean value, assuming data were missing at random and missing in $<10\%$ of the cohort.

Kaplan–Meier analysis and log-rank tests were used to compare cumulative survival across NLR and PLR quartiles in unadjusted analyses. Univariable Cox regression models were used to assess the relationship between baseline variables and outcomes. NLR and PLR were included in Cox regression models as categorical variables (quartiles) and were analysed in separate models due to potential collinearity. To address the potential concern of loss of information and statistical power by categorizing NLR/PLR, the final models were repeated replacing NLR/PLR quartiles with NLR/PLR as a continuous log-transformed variable to test the validity of conclusions drawn based upon categorized data. Variables which were assumed clinically relevant and/or significantly associated with the outcome on univariable analysis were entered into the multivariable Cox proportional hazards model (age, sex, diabetes, cardiovascular disease, albumin and initial mode of haemodialysis access). The proportional hazards assumption was tested by fitting each covariate as a time-varying covariate in the fully adjusted model. Where violation occurred, the variable was included in the final model as a time-varying covariate. Due to significant interaction with time, serum albumin was modelled as a time-varying covariate in all analyses. NLR quartile also interacted with time only in the survival analysis for cardiovascular mortality and so was modelled as a time-varying covariate in this analysis. Evidence of multiplicative interaction effects were sought between NLR, PLR and

Table 1: Baseline characteristics and serum laboratory markers by NLR quartile.

	Total	NLR Q1 <3.12	NLR Q2 ≥3.12 to <4.85	NLR Q3 ≥4.85 to <8.23	NLR Q4 ≥8.23	
	N = 1720	n = 430	n = 433	n = 429	n = 428	P
Age, mean (SD), years	62.2 (14.6)	57.9 (15.7)	60.9 (14.6)	64.6 (13.4)	65.6 (13.2)	<.001
Sex, n (%)						.39
Male	1042 (60.6)	251 (58.4)	265 (61.2)	273 (63.6)	253 (59.1)	
Female	678 (39.4)	179 (41.6)	168 (38.8)	156 (36.4)	175 (40.9)	
Primary renal diagnosis, n (%)						<.001
Glomerulonephritis	252 (14.7)	75 (17.4)	72 (16.6)	62 (14.5)	43 (10.0)	
Interstitial	334 (19.4)	110 (25.6)	81 (18.7)	75 (17.5)	68 (15.9)	
Multisystem	325 (18.9)	63 (14.7)	78 (18.0)	75 (17.5)	109 (25.5)	
Diabetic nephropathy	538 (31.3)	107 (24.9)	139 (32.1)	149 (34.7)	143 (33.4)	
Not known/other	271 (15.8)	75 (17.4)	63 (14.5)	68 (15.9)	65 (15.2)	
Cardiovascular disease, n (%)	377 (21.9)	79 (18.4)	88 (20.3)	107 (24.9)	103 (24.1)	.064
Diabetes, n (%)	749 (43.5)	149 (34.7)	189 (43.6)	211 (49.2)	200 (46.7)	<.001
Dialysis access, n (%)						<.001
Arteriovenous fistula	652 (37.9)	203 (47.2)	177 (40.9)	155 (36.1)	117 (27.3)	
Arteriovenous graft	83 (4.8)	36 (8.4)	22 (5.1)	16 (3.7)	9 (2.1)	
CVC	924 (53.7)	171 (39.8)	215 (49.7)	246 (57.3)	292 (68.2)	
Not recorded	61 (3.5)	20 (4.7)	19 (4.4)	12 (2.8)	10 (2.3)	
NLR, median (IQR)	4.8 (3.1–8.2)	2.4 (1.9–2.8)	3.9 (3.6–4.3)	6.3 (5.4–7.2)	13.4 (10.3–19.4)	<.001
PLR, median (IQR)	188.5 (132.1–281.4)	120.1 (95.9–155.3)	163.4 (134.7–210.0)	215.6 (162.3–281.1)	350.0 (260.6–511.5)	<.001
Total WCC, median (IQR), $\times 10^9$/L	7.9 (6.1–10.0)	6.5 (5.2–8.2)	7.5 (6.0–9.3)	8.4 (6.6–10.0)	10.2 (7.6–14.0)	<.001
Haemoglobin, mean (SD), g/L	91.7 (15.2)	95.7 (14.5)	92.7 (14.9)	89.3 (15.1)	89.0 (15.4)	<.001
Albumin, mean (SD), g/L	28.1 (6.2)	29.7 (6.2)	29.6 (5.8)	27.3 (5.8)	25.9 (6.1)	<.001
Adjusted calcium, mean (SD), mmol/L	2.3 (0.2)	2.3 (0.2)	2.3 (0.2)	2.3 (0.2)	2.2 (0.2)	<.001
Phosphate, mean (SD), mmol/L	1.9 (0.7)	1.7 (0.6)	1.8 (0.7)	2.0 (0.7)	2.2 (0.8)	<.001

all covariates. Effect modification by COVID-19 infection on the relationship between NLR, PLR and outcomes was also tested in the complete cohort using multiplicative interactions terms. Model fit was assessed for each covariate using likelihood ratio test chi-squared statistics. All analyses were conducted using Stata: Release 17 (StataCorp, 2021, College Station, TX, USA).

Table 2: Baseline neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio by access type at haemodialysis initiation.

	NLR [median (IQR)]	PLR [median (IQR)]
CVC	5.6 (3.6–10.0)	204.3 (139.2–313.3)
Arteriovenous fistula	4.3 (2.8–7.1)	172.9 (123.6–248.9)
Arteriovenous graft	3.5 (2.5–5.5)	165.3 (131.2–251.1)

RESULTS

Participant characteristics

The complete cohort included 1720 incident HD patients who were followed for a median of 21.9 (IQR 9.1–42.9) months. Table 1 displays the baseline characteristics by baseline NLR quartile. Overall, mean age was 62.2 (SD 14.6) years and 1042 participants (60.6%) were male. Primary renal diagnosis was in keeping with national prevalence data, i.e. diabetes was the most common cause of kidney failure. Pre-existing cardiovascular disease was noted in 377 participants (21.9%) and 749 (43.5%) had pre-existing diabetes. More than half commenced haemodialysis via a CVC (924, 53.7%), 735 (42.7%) had arteriovenous access at initiation [fistula: 652 (37.9%) versus graft: 83 (4.8%)] and access type was not recorded in a further 61 participants (3.5%). Across increasing NLR and PLR quartiles (indicating increased inflammation), there was an increase in age and use of CVCs as initial mode of haemodialysis access (Table 1). NLR and PLR were both highest in patients with a CVC as first dialysis access and lowest in those with arteriovenous grafts (Table 2; $P < .001$).

Outcomes

At the end of the observation period, 954 participants (55.5%) had died, 302 (17.6%) had a functioning renal transplant, 2 (0.1%) had switched to peritoneal dialysis, 12 (0.7%) had been censored for other reasons (no longer receiving haemodialysis in the region due to recovery or relocation) and 450 (26.2%) remained on haemodialysis. Around one-quarter of participants died within 2 years of starting haemodialysis (450 participants, 26.2%) and almost half died within 5 years (791, 46.0%). There were 840 deaths from any cause included in the primary survival analysis with a median time-to-event of 23.6 (IQR 8.5–45.9) months. Cause of death was recorded for 75% of participants reaching the primary endpoint and there were 213 (12.4%) cardiovascular deaths occurring at a median of 23.6 (IQR 9.2–40.7) months; and 362 non-cardiovascular deaths with a median time-to-death of 22.7 (IQR 7.6–44.5) months. Participants who died were older at haemodialysis initiation and more likely to have pre-existing diabetes and cardiovascular disease (Supplementary data, Table S1).

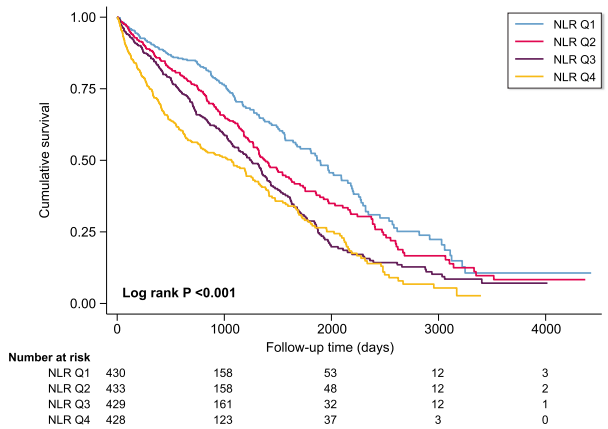


Figure 1: Kaplan–Meier cumulative survival plots for all-cause mortality by baseline NLR.

All-cause mortality

NLR and PLR were significantly higher in those who died compared with survivors (Supplementary data, Table S1) but did not differ significantly by cause of death (NLR: $P = .396$, PLR: $P = .998$). Cumulatively worse unadjusted survival was observed across NLR (log rank χ^2 for trend 66.28, $P < .001$; Fig. 1) and PLR (log rank χ^2 for trend 22.26, $P < .001$) quartiles. On univariable analysis, a one log unit increase in NLR and PLR were associated with all-cause mortality. Following multivariable adjustment, NLR (but not PLR) remained significantly associated with all-cause mortality. Among those with the highest levels of NLR (quartile 4: ≥8.23), there were 63% increased adjusted hazards of death from any cause compared with those in NLR quartile 1 (NLR <3.12) [hazard ratio (HR) 1.63, 95% confidence interval (CI) 1.32–2.00; Table 3].

Cardiovascular mortality

A one log unit increase in NLR (but not PLR) was associated with cardiovascular mortality on univariable analysis, and the association persisted after multivariable adjustment (Table 3). Adjusted hazards of cardiovascular death for participants in NLR quartile 4 were three-fold higher than those in NLR quartile 1 (HR 3.06, 95% CI 1.53–6.09; Table 3).

Non-cardiovascular mortality

NLR (but not PLR) was also associated with non-cardiovascular death on multivariable analysis, but to a lesser extent than cardiovascular death (Table 3). Participants in NLR quartile 4 had 85% increased hazards of death compared with NLR quartile 1 after adjustment for age, sex, serum albumin and first haemodialysis access modality (HR 1.85, 95% CI 1.34–2.56; Table 3). There was no evidence of statistical interaction between NLR and any covariate, including COVID-19 infection, for all-cause, cardiovascular or non-cardiovascular mortality outcomes.

COVID-19 subpopulation analysis

After initiation of haemodialysis, 309 participants (18.0%) recorded positive tests for COVID-19 between 20 March 2020 until 31 March 2022. Of these, 117 had either undergone kidney transplantation (105/309, 34.0%), switched to peritoneal dialysis (11/309, 3.6%) or withdrawn and relocated (1/309, 0.3%) prior to COVID-19 infection and were therefore excluded, leaving 192 participants (11.2% of entire cohort) included in the COVID-19 subpopulation analysis.

Baseline characteristics by COVID-19 infection status are presented in Supplementary data, Table S2. There were 52 deaths in the COVID-19 subpopulation (27.0%), 30 of which occurred within 28 days and are therefore considered COVID-19-related deaths (57.7% of those who died; 15.6% of those infected). The median time from NLR at haemodialysis initiation to COVID-19 infection diagnosis was 23 (9–45) months (Fig. 2). The majority (17, 77.2%) of coded deaths were recorded as 'pulmonary infection (viral)'. Cause of death as reported within the electronic patient record for these 30 participants is summarized in Supplementary data, Table S3.

NLR and PLR recorded around the time of dialysis initiation were both significantly higher in those who died within 28 days of COVID-19 infection than survivors. There was cumulatively worse survival across NLR and PLR quartiles [log rank χ^2 for trend 6.34, $P = .012$ (Fig. 3) and 4.13, $P = .042$, respectively].

Participants in NLR quartile 4 (NLR ≥8.23) at the time of haemodialysis initiation, who later developed COVID-19 infection, had a greater than four times increased risk of COVID-19-related death compared with those in quartile 1 (NLR <3.12), after adjustment for age and sex (HR 4.69, 95% CI 1.48–14.92; Table 4). The highest quartile of PLR (PLR ≥281.5) conferred a tripling of risk [HR 3.40, 95% CI 1.02–11.36 vs quartile 1 (PLR ≤132.0), adjusted for age and sex; Table 4].

DISCUSSION

In this cohort of incident haemodialysis patients, NLR—but not PLR—at the time of haemodialysis initiation was independently associated with all-cause mortality. These associations were consistent in analyses by cardiovascular and non-cardiovascular causes of death though NLR was more strongly associated with cardiovascular mortality. In a subpopulation of participants who developed COVID-19 infection following haemodialysis initiation, both baseline NLR and PLR were associated with increased hazards of death; however, COVID-19 infection did not modify the relationship between NLR, PLR and mortality observed in the entire study cohort.

Lymphocyte ratios reflect systemic inflammation and endothelial dysfunction, key pathophysiological processes in CKD, and NLR is well-established as an adverse prognostic factor in cancer and cardiovascular disease [1]. In keeping with previous studies, we demonstrate strong evidence in support of an association between NLR and mortality and cardiovascular disease outcomes in the haemodialysis population [6, 20–30]. We believe our study is the largest European cohort studied and the only reported study within the UK [29, 30]. The association between NLR and clinical outcomes is less well studied in patients with non-dialysis CKD; however, evidence is emerging supporting the association of higher NLR with progression to kidney failure [31, 32] as well as adverse cardiovascular outcomes in patients receiving peritoneal dialysis [33, 34]. In keeping with our own study, PLR has shown an inconsistent relationship with mortality outcomes in CKD populations [6, 27, 28].

NLR and PLR are convenient markers of inflammation and prognosis as they are inexpensive and readily available. The clinical utility of NLR and PLR is currently limited by the absence of validated thresholds of clinical significance; however, NLR thresholds of ≥3.0 and ≥3.5 [1, 30], and a PLR threshold of

Table 3: Cox proportional hazard model estimates for all-cause, cardiovascular and non-cardiovascular mortality.

	All-cause mortality ($n = 840$)				Cardiovascular mortality ($n = 213$)				Non-cardiovascular mortality ($n = 362$)			
	Univariable		Multivariable[a]		Univariable		Multivariable[b]		Univariable		Multivariable[c]	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
NLR												
Log NLR[d]	1.42 (1.30–1.55)	<.001	1.22 (1.11–1.34)	<.001	1.35 (1.13–1.60)	.001	1.59 (1.19–2.11)	.001	1.50 (1.31–1.71)	<.001	1.24 (1.08–1.43)	.002
NLR quartiles												
Q1 <3.12	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2 ≥3.12 to <4.85	1.34 (1.08–1.65)	.007	1.24 (<1.00–1.53)	.052	0.98 (0.64–1.50)	.923	1.68 (0.82–3.43)	.156	1.62 (1.16–2.26)	.004	1.45 (1.04–2.03)	.030
Q3 ≥4.85 to <8.23	1.72 (1.41–2.11)	<.001	1.35 (1.09–1.65)	.005	1.73 (1.18–2.53)	.005	1.83 (0.95–3.53)	.073	1.86 (1.34–2.58)	<.001	1.38 (0.99–1.92)	.059
Q4 ≥8.23	2.18 (1.78–2.67)	<.001	1.63 (1.32–2.00)	<.001	1.82 (1.23–2.71)	.003	3.06 (1.53–6.09)	.001	2.72 (1.98–3.74)	<.001	1.85 (1.34–2.56)	<.001
PLR												
Log PLRd	1.23 (1.10–1.37)	<.001	1.09 (0.97–1.22)	.140	1.23 (0.99–1.52)	.064	1.15 (0.91–1.44)	.235	1.20 (1.02–1.41)	.033	1.01 (0.85–1.19)	.924
PLR quartiles												
Q1 ≤132	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2 >132 to <188.5	1.14 (0.94–1.39)	.190	1.14 (0.93–1.40)	.196	1.48 (0.99–2.20)	.055	1.44 (0.97–2.16)	.072	0.86 (0.63–1.16)	.324	0.86 (0.63–1.17)	.340
Q3 ≥188.5 to <281.5	1.14 (0.94–1.39)	.183	1.07 (0.88–1.31)	.513	1.23 (0.81–1.86)	.324	1.14 (0.75–1.73)	.535	1.06 (0.79–1.41)	.703	0.96 (0.72–1.29)	.807
Q4 ≥281.5	1.62 (1.34–1.96)	<.001	1.26 (1.03–1.54)	.022	1.90 (1.28–2.82)	.001	1.62 (1.08–2.44)	.020	1.37 (1.03–1.81)	.031	0.97 (0.72–1.31)	.853

[a] Adjusted for age, sex, diabetes, cardiovascular disease, albumin and initial mode of haemodialysis access.
[b] Adjusted for age, sex, diabetes, cardiovascular disease and albumin.
[c] Adjusted for age, sex, diabetes, cardiovascular disease, total WCC, albumin and initial mode of haemodialysis access.
[d] Per one unit increase.

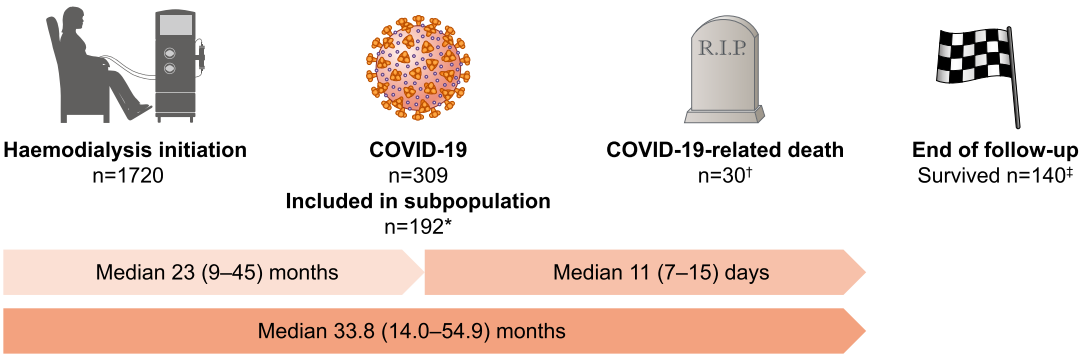


Figure 2: COVID-19 infection timelines.
Reinfection: n=9, median 9 (6-14) months between infections, figure presents time to first infection & time from reinfection to death. *Participants no longer on haemodialysis at first infection were excluded (transplant n=105, peritoneal dialysis n=11, transfer of care n=1). †Death within 28 days of COVID-19 infection. ‡22 patients died more than 28 days after COVID-19 infection.

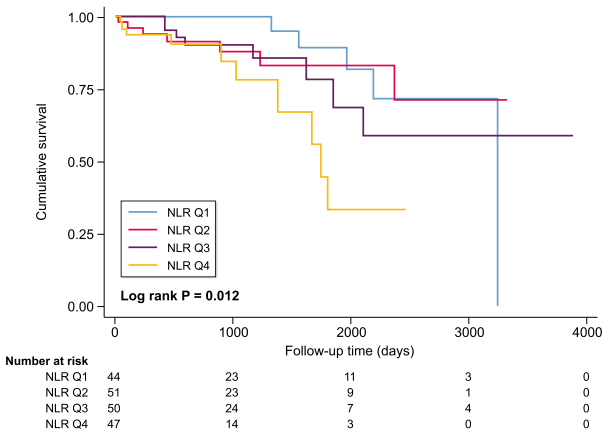


Figure 3: Kaplan–Meier cumulative survival plot in COVID-19 subpopulation by baseline NLR.

132 have been suggested [35], both of which would also be consistent with the 25th percentile in our cohort. Previous studies have evaluated associations between alternative markers of inflammation (such as CRP), NLR and clinical outcomes [23, 24, 27, 36]. We did not explore the potential association between CRP and outcomes because of the risk of bias by indication: in our network, CRP is generally only measured if there is clinical suspicion of infection. As a result, we cannot compare lymphocyte ratios with CRP and it remains possible these are directly correlated. More sophisticated tests of inflammation—such as interleukin-6 and TNF-α—are not routinely available in our cohort.

Elevated lymphocyte ratios (NLR and PLR) are not specific to chronic inflammation and may also be elevated as an acute-phase response. We observed that haemodialysis initiation with a CVC rather than arteriovenous access was positively associated with NLR and also independently associated with all-cause mortality. Elevated NLR in those with CVCs may reflect inflammation related to recent vascular intervention; however, we did not observe a statistical interaction between NLR and CVC use. The association is likely to be confounded by the reality that patients who are required to start haemodialysis with a CVC are likely to be more unwell than those with planned arteriovenous access and may have infective or inflammatory conditions also associated with elevated NLR which alter prognosis. We could not account for acute illness as a trigger for dialysis initiation in this study.

Table 4: Cox proportional hazard model estimates for COVID-19-related death (COVID-19 subpopulation $n = 192$).

	Univariable		Multivariable[a]	
	HR (95% CI)	*P*	HR (95% CI)	*P*
NLR				
Log NLR[b]	1.82 (1.17–2.83)	.008	1.90 (1.21–2.98)	.005
NLR quartiles				
Q1 <3.12	1.00 (reference)		1.00 (reference)	
Q2 ≥3.12 to <4.85	1.48 (0.47–4.67)	.504	2.59 0.77–8.74)	.126
Q3 ≥4.85 to <8.23	1.75 (0.57–5.41)	.330	2.24 (0.71–7.07)	.167
Q4 ≥8.23	3.98 (1.33–11.92)	.013	4.69 (1.48–14.92)	.009
PLR				
Log PLR[b]	2.55 (1.29–5.03)	.007	2.54 (1.29–5.01)	.007
PLR quartiles				
Q1 ≤132.0	1.00 (reference)		1.00 (reference)	
Q2 >132.0 to <188.5	1.66 (0.53–5.18)	.380	1.90 (0.60–6.01)	.272
Q3 ≥188.5 to <281.5	2.05 (0.77–5.47)	.342	2.19 (0.81–5.87)	.120
Q4 ≥281.5	3.21 (<1.00–10.31)	.050	3.40 (1.02–11.36)	.047

[a]Adjusted for age and sex.
[b]Per one unit increase.

Recently, the COVID-19 pandemic has drawn attention to the deleterious effects of widespread inflammation, including multi-organ damage and death. Studies in general COVID-19 cohorts have demonstrated a clear association between NLR at the time of COVID-19 presentation and worse clinical outcomes [11–17]. In this study, we have demonstrated that NLR (and also PLR) assessed almost 2 years prior to COVID-19 infection is associated with risk of death. This finding supports the hypothesis that NLR identifies haemodialysis patients most at risk of adverse outcomes; these patients were also those with the poorest outcomes from COVID-19.

We acknowledge limitations to this study. First, despite a convincing association of NLR with mortality in our population, the observational design does not allow for conclusions of cause and effect. Furthermore, there is the potential for residual confounding due to unmeasured factors such as body composition, other comorbidities including inflammatory disease, medication use and lifestyle factors such as smoking. Second, mortality data were limited to the electronic patient record and was only 75% complete. This could be improved upon by obtaining death certificates; however, this study was intended to be a pragmatic study using routinely collected data. Third, our methods may underestimate COVID-19 incidence and overestimate reinfection and COVID-19-related death. Furthermore, data were not available on COVID-19 disease severity (including cycle threshold) or vaccination status, although COVID-19 was not a primary focus of the study and the subpopulation analysis was intended only to complement the primary analysis.

Despite the above limitations, we feel our conclusions are relevant as the analysis includes a large kidney failure population from a diverse West of Scotland population over a 10-year period, with access to all laboratory reports and absence of exclusions. NLR is an easily assessed and inexpensive marker of inflammation which is convincingly associated with increased hazards of all-cause and cardiovascular mortality. Further research should establish NLR reference ranges in CKD and non-CKD populations to improve its utility in clinical practice, and explore the potential role for NLR in risk stratification in CKD.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly for the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding and senior authors.

CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part. Outside the submitted work, J.S.L. has received lectureship honoraria from Bristol Myers Squibb, Pfizer and AstraZeneca. The University of Glasgow, which employs N.N.L., has received research grant funding from Roche Diagnostics, AstraZeneca and Boehringer Ingelheim (outside the submitted work) on his behalf. N.N.L. has received speaker's fees/advisory board fees from Roche, Pharmacosmos, AstraZeneca and Novartis. P.B.M. reports research funding from Boehringer Ingelheim, paid advisory boards and lecture fees from AstraZeneca, Boehringer Ingelheim, Astellas, GSK, Napp, Vifor-Fresenius, Novartis and Pharmacosmos, and travel support from Pharmacosmos, Napp and Vifor. E.R., J.P.T., P.C.T. and V.D. have no disclosures. Outside the submitted work, K.J.M. reports institutional grant funding from Boehringer Ingelheim and Eli Lilly, paid to the Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford.

REFERENCES

1. Valga F, Monzón T, Henriquez F *et al.* Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as biological markers of interest in kidney disease. *Nefrologia* 2019;**39**:243–9. http://dx.doi.org/10.1016/j.nefro.2018.11.005
2. Hung SC, Lai YS, Kuo KL *et al.* Volume overload and adverse outcomes in chronic kidney disease: clinical observational and animal studies. *J Am Heart Assoc* 2015;**4**:e001918. http://dx.doi.org/10.1161/JAHA.115.001918
3. Kalantar-Zadeh K, Ikizler TA, Block G *et al.* Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. *Am J Kidney Dis* 2003;**42**:864–81. http://dx.doi.org/10.1016/j.ajkd.2003.07.016
4. Sarnak MJ. Cardiovascular complications in chronic kidney disease. *Am J Kidney Dis* 2003;**41**:11–7. http://dx.doi.org/10.1016/S0272-6386(03)00372-X
5. Obi Y, Qader H, Kovesdy CP *et al.* Latest consensus and update on protein-energy wasting in chronic kidney disease. *Curr Opin Clin Nutr Metab Care* 2015;**18**:254–62. http://dx.doi.org/10.1097/MCO.0000000000000171
6. Catabay C, Obi Y, Streja E *et al.* Lymphocyte cell ratios and mortality among incident hemodialysis patients. *Am J Nephrol* 2017;**46**:408–16. http://dx.doi.org/10.1159/000484177
7. Yeun JY, Levine RA, Mantadilok V *et al.* C-reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 2000;**35**:469–76. http://dx.doi.org/10.1016/S0272-6386(00)70200-9
8. Owen WF, Lowrie EG. C-reactive protein as an outcome predictor for maintenance hemodialysis patients. *Kidney Int* 1998;**54**:627–36. http://dx.doi.org/10.1046/j.1523-1755.1998.00032.x
9. Zimmermann J, Herrlinger S, Pruy A *et al.* Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 1999;**55**:648–58. http://dx.doi.org/10.1046/j.1523-1755.1999.00273.x
10. Iseki K, Tozawa M, Yoshi S. *et al.* Serum C-reactive protein (CRP) and risk of death in chronic dialysis patients. *Nephrol Dial Transplant* 1999;**14**:1956–60. http://dx.doi.org/10.1093/ndt/14.8.1956
11. Ulloque-Badaracco JR, Ivan Salas-Tello W, Al-Kassab-Córdova A *et al.* Prognostic value of neutrophil-to-lymphocyte ratio in COVID-19 patients: a systematic review and meta-analysis. *Int J Clin Pract* 2021;**75**:e14596. http://dx.doi.org/10.1111/ijcp.14596
12. Li X, Liu C, Mao Z *et al.* Predictive values of neutrophil-to-lymphocyte ratio on disease severity and mortality in COVID-19 patients: a systematic review and meta-analysis. *Crit Care* 2020;**24**:647. http://dx.doi.org/10.1186/s13054-020-03374-8

13. Simadibrata DM, Calvin J, Wijaya AD *et al*. Neutrophil-to-lymphocyte ratio on admission to predict the severity and mortality of COVID-19 patients: a meta-analysis. *Am J Emerg Med* 2021;**42**:60–9. http://dx.doi.org/10.1016/j.ajem.2021.01.006
14. Hendra H, Vajgel G, Antonelou M *et al*. Identifying prognostic risk factors for poor outcome following COVID-19 disease among in-centre haemodialysis patients: role of inflammation and frailty. *J Nephrol* 2021;**34**:315–23. http://dx.doi.org/10.1007/s40620-020-00960-5
15. Kular D, Chis Ster I, Sarnowski A *et al*. The characteristics, dynamics, and the risk of death in COVID-19 positive dialysis patients in London, UK. *Kidney360* 2020;**1**:1226–43. http://dx.doi.org/10.34067/KID.0004502020
16. Nithya G, Lamech TM, Arumugam V *et al*. A clinical study on the changing dynamics of disease severity, management strategies and outcomes of COVID-19 in patients requiring haemodialysis. *J Nephrol* 2021;**34**:999–1006. http://dx.doi.org/10.1007/s40620-021-01072-4
17. Mutinelli-Szymanski P, Hude I, Merle E *et al*. Neutrophil:lymphocyte ratio predicts short-term outcome of COVID-19 in haemodialysis patients. *Clin Kidney J* 2021;**14**:124–31. http://dx.doi.org/10.1093/ckj/sfaa194
18. The Scottish Renal Registry: ERA-EDTA Primary Renal Diagnosis Codes, and Groupings used in SRR analyses [online]. The Scottish Renal Registry. (No date.) Available from: https://www.srr.scot.nhs.uk/Projects/Methods.html (18 April 2022, date last accessed).
19. Public Health Scotland: COVID-19 reporting to include further data on reinfections [online]. Public Health Scotland, 2022. (Updated 4 March 2022.) Available from: https://publichealthscotland.scot/news/2022/february/covid-19-reporting-to-include-further-data-on-reinfections/#:~:text=The%20PHS%20COVID%2D19%20Winter,first%20positive%20test%20result%20only (18 April 2022, date last accessed).
20. Zhu X, Li G, Li S *et al*. Neutrophil-to-lymphocyte ratio and red blood cell distribution width-to-platelet ratio predict cardiovascular events in hemodialysis patients. *Exp Ther Med* 2020;**20**:1105–14. http://dx.doi.org/10.3892/etm.2020.8756
21. Abe T, Kato S, Tsuruta Y *et al*. Neutrophil/lymphocyte ratio as a predictor of cardiovascular events in incident dialysis patients: a Japanese prospective cohort study. *Clin Exp Nephrol* 2015;**19**:718–24. http://dx.doi.org/10.1007/s10157-014-1046-2
22. Chandra A, Raj G, Awasthi NP *et al*. Evaluation of the relationship between blood cell parameters and vascular calcification in dialysis-dependent end-stage renal disease patients. *Saudi J Kidney Dis Transpl* 2020;**31**:136–43.
23. Li H, Lu X, Xiong R *et al*. High neutrophil-to-lymphocyte ratio predicts cardiovascular mortality in chronic hemodialysis patients. *Mediators Inflamm* 2017;**2017**:9327136. http://dx.doi.org/10.1155/2017/9327136
24. Neuen BL, Leather N, Greenwood AM *et al*. Neutrophil-lymphocyte ratio predicts cardiovascular and all-cause mortality in hemodialysis patients. *Ren Fail* 2016;**38**:70–6. http://dx.doi.org/10.3109/0886022X.2015.1104990
25. Yaprak M, Turan MN, Dayanan R *et al*. Platelet-to-lymphocyte ratio predicts mortality better than neutrophil-to-lymphocyte ratio in hemodialysis patients. *Int Urol Nephrol* 2016;**48**:1343–8. http://dx.doi.org/10.1007/s11255-016-1301-4
26. Ouellet G, Malhotra R, Penne EL *et al*. Neutrophil-lymphocyte ratio as a novel predictor of survival in chronic hemodialysis patients. *Clin Nephrol* 2016;**85**:191–8. http://dx.doi.org/10.5414/CN108745
27. Kato A, Tsuji T, Sakao Y *et al*. A comparison of systemic inflammation-based prognostic scores in patients on regular hemodialysis. *Nephron Extra* 2013;**3**:91–100. http://dx.doi.org/10.1159/000355148
28. Balboul Y, Gurshumov A, Azar A *et al*. Biological basis of lymphocyte ratios for survival prediction in hemodialysis patients: a longitudinal study. *Int Urol Nephrol* 2020;**52**:1345–56. http://dx.doi.org/10.1007/s11255-020-02471-5
29. Zhao WM, Tao SM, Liu GL. Neutrophil-to-lymphocyte ratio in relation to the risk of all-cause mortality and cardiovascular events in patients with chronic kidney disease: a systematic review and meta-analysis. *Ren Fail* 2020;**42**:1059–66. http://dx.doi.org/10.1080/0886022X.2020.1832521
30. Ao G, Wang Y, Qi X *et al*. Association of neutrophil-to-lymphocyte ratio and risk of cardiovascular or all-cause mortality in chronic kidney disease: a meta-analysis. *Clin Exp Nephrol* 2021;**25**:157–65.
31. Yoshitomi R, Nakayama M, Sakoh T *et al*. High neutrophil/lymphocyte ratio is associated with poor renal outcomes in Japanese patients with chronic kidney disease. *Ren Fail* 2019;**41**:238–43. http://dx.doi.org/10.1080/0886022X.2019.1595645
32. Yuan Q, Wang J, Peng Z *et al*. Neutrophil-to-lymphocyte ratio and incident end-stage renal disease in Chinese patients with chronic kidney disease: results from the Chinese Cohort Study of Chronic Kidney Disease (C-STRIDE). *J Transl Med* 2019;**17**:86. http://dx.doi.org/10.1186/s12967-019-1808-4
33. Lu X, Wang S, Zhang G *et al*. High neutrophil-to-lymphocyte ratio is a significant predictor of cardiovascular and all-cause mortality in patients undergoing peritoneal dialysis. *Kidney Blood Press Res* 2018;**43**:490–9. http://dx.doi.org/10.1159/000488696
34. Zeng Y, Chen Z, Chen Q *et al*. Neutrophil to lymphocyte ratio predicts adverse cardiovascular outcome in peritoneal dialysis patients younger than 60 years old. *Mediators Inflamm* 2020;**2020**:4634736. http://dx.doi.org/10.1155/2020/4634736
35. Lee JS, Kim NY, Na SH *et al*. Reference values of neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, and mean platelet volume in healthy adults in South Korea. *Medicine (Baltimore)* 2018;**97**:e11138. http://dx.doi.org/10.1097/MD.0000000000011138
36. Solak Y, Yilmaz MI, Sonmez A *et al*. Neutrophil to lymphocyte ratio independently predicts cardiovascular events in patients with chronic kidney disease. *Clin Exp Nephrol* 2013;**17**:532–40. http://dx.doi.org/10.1007/s10157-012-0728-x