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ORIGINAL ARTICLE

Association of lactate dehydrogenase with mortality in incident hemodialysis patients

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ABSTRACT

Background. Lactate dehydrogenase (LDH) plays a role in the glucose metabolism of the human body. Higher LDH levels have been linked to mortality in various cancer types; however, the relationship between LDH and survival in incident hemodialysis (HD) patients has not yet been examined. We hypothesized that higher LDH level is associated with higher death risk in these patients.

Methods. We examined the association of baseline and time-varying serum LDH with all-cause, cardiovascular and infection-related mortality among 109 632 adult incident HD patients receiving care from a large dialysis organization in the USA during January 2007 to December 2011. Baseline and time-varying survival models were adjusted for demographic variables and available clinical and laboratory surrogates of malnutrition–inflammation complex syndrome.

Results. There was a linear association between baseline serum LDH levels and all-cause, cardiovascular and infection-related mortality in both baseline and time-varying models, except for time-varying infection-related mortality. Adjustment for markers of inflammation and malnutrition attenuated the association in all models. In fully adjusted models, baseline LDH levels ≥360 U/L were associated with the highest risk of all-cause mortality (hazard ratios = 1.19, 95% confidence interval 1.14–1.25). In time-varying models, LDH >280 U/L was associated with higher death risk in all three hierarchical models for all-cause and cardiovascular mortality.

Conclusions. Higher LDH level >280 U/L was incrementally associated with higher all-cause and cardiovascular mortality in incident dialysis patients, whereas LDH <240 U/L was associated with better survival. These findings suggest that the assessment of metabolic functions and monitoring for comorbidities may confer survival benefit to dialysis patients.

Keywords: all-cause mortality, end-stage renal disease, hemodialysis, lactate dehydrogenase

INTRODUCTION

The metabolism of glucose allows the human body to generate energy in the form of adenosine triphosphate, which is essential to sustain life. In the absence of oxygen or healthy mitochondria, energy is generated by a less efficient pathway, involving the enzyme lactate dehydrogenase (LDH), which converts pyruvate to lactate. LDH is an intracellular and ubiquitous enzyme [1]; thereby, elevated serum LDH levels in the extracellular space are a marker of tissue breakdown [1, 2].

Serum LDH is a sensitive but not a specific laboratory test that is routinely available. Elevated levels of serum LDH can be found in numerous clinical conditions including inflammation, infection and sepsis [3–8], hemolytic [9–14] or hepatic disorders [15–17], and in various oncologic conditions [18–24]. Erez *et al.* [3] reported that in admitted medical patients higher LDH values were associated with adverse outcomes such as more admission days, admission to intensive care units and number of intubations. Moreover, LDH has been associated with mortality, e.g. in patients with sepsis [25], severe acute pancreatitis [26], acute mesenteric ischemia [27], hypoxic hepatitis [28], idiopathic pulmonary hypertension [29] and patients with cancer [23, 30].

LDH levels are associated with concomitant kidney damage as seen in elevated LDH levels with the advancement of diabetic kidney disease [31] and elevated levels of serum LDH have been observed in end-stage renal disease patients, and were attributed to the process of hemodialysis (HD) itself [32]. However, the relationship of LDH with mortality risk has not yet been studied in incident HD patients. In a large contemporary cohort of incident HD patients, we examined the association of serum LDH levels with mortality. The article aimed to study the impact of LDH from the time of transitioning to HD to remove potential confounding due to time on dialysis. We believe that our time-varying analysis can partly answer the important question of long-term versus short-term impact of increased LDH on mortality.

KEY LEARNING POINTS

What is already known about this subject?

- in previous studies, higher lactate dehydrogenase (LDH) levels have been found to be associated with cancer.

What this study adds?

- this study adds insight on the relationship between LDH levels and survival among hemodialysis patients.

What impact this may have on practice or policy?

- this study will impact practice and improve quality of care by prompting physicians to be more attentive to LDH and its potential impact on patient outcomes and survival.

MATERIALS AND METHODS

Study population and data source

This observational cohort study used data from a large dialysis organization (LDO) in the USA with detailed patient-level sociodemographic, comorbidity, laboratory, dialysis treatment and vital status parameters. The original source population included 208 820 adult (≥18 years old) incident HD patients initiating treatment between 2007 and 2011, with follow-up through 31 December 2011. Patients were included in the study if they had at least 60 days of total treatment during their total follow-up time, were undergoing thrice-weekly in-center HD throughout the entire study period, and had treatment data and at least one LDH measurement during their baseline quarter (the first 91 days) of dialysis. The final study population comprised 109 632 incident HD patients (Supplementary data, Figure S1). All data were obtained from the electronic records of the LDO. The study was approved by the Institutional Review Committee of the University of California, Irvine Medical Center. Given the large sample size, anonymity of the patients studied and non-intrusive nature of the research, the requirement for written consent was waived.

Clinical and demographic measures

In this database, race/ethnicity is self-categorized; dialysis patients select the race and/or ethnicity with which they most closely identify [non-Hispanic White (White), African-American, Hispanic, Asian, others]. Blood samples were drawn using uniform techniques in all dialysis clinics and were transported to a single, central laboratory typically within 24 h. All laboratory values were measured using automated and standardized methods in the central laboratory. Most laboratory parameters, including LDH, albumin, creatinine, bicarbonate, phosphorus and calcium, were measured monthly. Serum ferritin was measured at least quarterly. Hemoglobin was measured at least monthly in all patients and weekly to biweekly in most patients. Single-pool K_t/V was used to estimate dialysis dosage, and normalized protein catabolic rate (nPCR) was measured monthly as an indicator of daily protein intake.

To minimize measurement variability, all repeated laboratory and clinical measurements for each patient during the 91-day patient quarter were averaged. Average values were obtained for up to 20 patient quarters for each patient. Measurements in the first 91-day patient quarter were considered as baseline. Post-HD dry weight and baseline height were used to calculate body mass index (BMI). Furthermore, the presence or absence of comorbid conditions were identified based on International Classification of Diseases-9 codes for the following 13 comorbid conditions (Supplementary data, Table S1): (i) alcohol dependence; (ii) atherosclerotic heart disease (ASHD); (iii) congestive heart failure (CHF); (iv) other cardiovascular disease; (v) cerebrovascular disease; (vi) chronic obstructive pulmonary disease; (vii) diabetes mellitus; (viii) dyslipidemia; (ix) human immunodeficiency virus; (x) malignancy; (xi) hypertension; (xii) sickle cell disease; and (xiii) lupus erythematosus.

Exposure and outcome ascertainment

LDH was the main exposure of interest. Patients were categorized according to the following seven categories of LDH spaced into 40 U/L intervals and according to the distribution of LDH in the population: <160, 160 to <200, 200 to <240, 240 to <280, 280 to <320, 320 to <360 and ≥360 U/L. Both baseline and time-varying LDH models were examined. The main outcome of interest was all-cause mortality, which was ascertained from the LDO database. Cardiovascular and infection-related mortality were also examined.

Cardiovascular mortality was categorized as having one of the following causes of death: acute myocardial infarction; pericarditis, including cardiac tamponade; ASHD; cardiomyopathy; cardiac arrhythmia; cardiac arrest, cause unknown; valvular heart disease; pulmonary edema due to exogenous fluid; CHF; pulmonary embolus; cerebrovascular accident including intracranial hemorrhage; and ischemic brain damage or anoxic encephalopathy. Infection-related mortality was categorized as having one of the following causes of death: septicemia due to internal vascular access; septicemia due to vascular access catheter; bacterial peritoneal access infectious complication; fungal peritoneal access infectious complication; peritonitis (complication of peritoneal dialysis); gangrene septicemia due to peripheral vascular disease; other septicemia; cardiac infection (endocarditis); pulmonary infection (pneumonia, influenza); and abdominal infection [peritonitis (not component of peritoneal dialysis, perforated bowel, diverticular disease, gallbladder)].

Patients were followed from their first dialysis date until they were censored for one of the following reasons: death, renal transplantation, discontinuation of dialysis, transfer to another dialysis clinic or end of the study period (31 December 2011).

Statistical analysis

Baseline patient characteristics were summarized using proportions, means [standard deviation (SD)] or median [interquartile range (IQR)] and were compared across strata of LDH

using tests for trend. We used Cox proportional hazard regressions for both baseline and time-varying measures to examine the association of LDH (reference: 240 to <280 U/L) with 5-year all-cause, cardiovascular and infection-related mortality. The proportionality assumption was checked using plots of log [−log(survival rate) against log(survival time)]. We additionally explored potentially nonlinear relationships between LDH and mortality outcomes using restricted cubic spline models using median LDH values of 235.2 and 191.25 U/L as references for baseline and time-varying models, respectively, and with four knots placed at the 5th, 35th, 65th and 95th percentile values of LDH.

All models were examined across three levels of hierarchical multivariate adjustment as follows: (i) unadjusted: including LDH as primary exposure of interest; (ii) casemix: adjusted for demographic data (age, gender, race/ethnicity), the first 11 of the 13 above-listed comorbid conditions, post-dialysis systolic and diastolic blood pressure (BP), primary insurance (Medicare, Medicaid and other), vascular access type [central venous catheter (CVC), arteriovenous (AV) graft, AV fistula, other AV access and unknown) and dialysis dosage as indicated by single-pool K_t/V; and (iii) casemix + malnutrition inflammation complex (MICS) (fully adjusted): adjusted for covariates of the casemix model plus markers of the MICS including serum albumin, serum creatinine, calcium, phosphorus, ferritin, hemoglobin, alkaline phosphatase, parathyroid hormone, iron saturation, white blood cell (WBC) count, BMI, aspartate aminotransferase, lymphocyte percentage, total iron binding capacity, iron concentration and nPCR. In additional analysis, we also examined a fourth level of adjustment (iv) casemix + MICS + sickle cell + lupus: adjusted for sickle cell disease and lupus erythematosus. In order to investigate possible effect modification of the LDH–mortality association, we additionally examined associations of higher LDH (≥250 U/L) versus lower LDH (<250 U/L) across strata of *a priori* selected demographic, comorbid and laboratory subgroups in fully adjusted models. LDH was dichotomized at 250 U/L (≥250 U/L versus <250 U/L) for subgroup analyses because this was the cohort median. Interactions between LDH and the modifier of interest were tested using the Wald's test.

Missing covariate data (under 1% for most laboratory and demographic variables) were imputed using imputation by means or missing category. Analysis were implemented using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA), Stata version 13 (Stata Corp., College Station, TX, USA) and SigmaPlot version 12.5 (Systat Software, San Jose, CA, USA).

RESULTS

Baseline demographics and clinical characteristics according to LDH

Among the 109 632 incident HD patients, the average age (±SD) was 63 ± 15 years old, and there were 44% females, 31% African-Americans and 58% diabetic patients. Table 1 shows baseline demographic, clinical and laboratory characteristics in the total cohort and across LDH strata. Patients with higher LDH were younger, included more women and had a higher prevalence of diabetes, CHF, Medicaid patients and CVC access type when compared with patients with the lowest LDH levels. In particular, among patients with the highest LDH level ≥360 U/L, 92% had a CVC access type. Patients with higher LDH also had lower albumin levels, higher creatinine, higher iron and higher ferritin levels, as well as higher WBC count.

Association of LDH with mortality

Over a median (IQR) follow-up time of 493 days (230–921), there were 28 972 deaths (26%) and crude death rate of 15.6 death per 100 person-years [95% confidence interval (CI) 15.5–15.8]. Figure 1 displays 5-year all-cause, cardiovascular and infection-related death hazard ratios (HRs) across categories of baseline and time-varying LDH in all 109 632 patients. Using LDH 240 to <280 U/L as the reference, there was a linear relationship between LDH and mortality outcomes. In the baseline model, the highest risk LDH (≥360 U/L) was associated with a 37% higher risk of all-cause mortality in the unadjusted model (HR = 1.37, 95% CI 1.30–1.43; Figure 1A and Supplementary data, Table S2). The association was greater after adjustment for demographics and comorbidities, but attenuated to a 19% higher mortality risk in the fully adjusted model (HR = 1.19, 95% CI 1.14–1.25; Figure 1A and Supplementary data, Table S2). In an additional model, adjusting for sickle cell disease and lupus erythematosus showed comparable mortality risk (Supplementary data, Figure S2). Similar associations were observed for cardiovascular and infection-related mortality, even though less consistent for the infection-related mortality (Figure 1B and C; Supplementary data, Tables S3 and S4). Sensitivity analyses using restricted cubic spline models also showed a linear association between baseline LDH and all-cause mortality across all models of adjustments (Supplementary data, Figure S3A–C).

To ascertain short-term LDH–mortality associations and to account for changes in serum LDH levels over time, we also examined associations of time-varying associations of LDH with mortality outcomes, where direct linear relationships were also observed. Time-varying LDH ≥360 U/L was associated with 48% higher risk of all-cause mortality in the fully adjusted model (HR = 1.48, 95% CI 1.40–1.56; Figure 1D and Supplementary data, Table S5). Restricted cubic spline models for time-varying LDH and all-cause mortality showed J-shaped associations across all models of adjustments; however, LDH levels lower than the reference point of 191.25 U/L had lower mortality risk (Supplementary data, Figure S3D–F). Similar associations were observed for cardiovascular and less consistently for infection-related mortality (Figure 1E and F; Supplementary data, Tables S6 and S7).

Subgroup analyses examining the association between LDH level dichotomized as <250 U/L (reference) and ≥250 U/L with all-cause mortality were examined across strata of clinically relevant subgroups. All-cause mortality effect estimates in fully adjusted models were above unity in all examined subgroups, indicating higher risk of death with higher LDH (≥250 U/L) across all strata (Figure 2). However, significant interactions were noted for the following subgroups: gender, AV fistula, BMI, diabetes, CHF, liver disease, albumin and WBC

Table 1. Baseline characteristics of 109 632 incident HD patients by baseline LDH level

Characteristics	All HD patients $n = 109\,632$	LDH (U/L)							P-value
		<160 $n = 5968$	160 to <200 $n = 21\,826$	200 to <240 $n = 30\,507$	240 to <280 $n = 24\,552$	280 to <320 $n = 14\,062$	320 to <360 $n = 6879$	≥360 $n = 5884$	
Age, years	63 ± 15	64 ± 15	64 ± 15	64 ± 15	63 ± 15	61 ± 15	60 ± 15	59 ± 16	<0.0001
Gender (% female)	44	32	37	42	46	50	53	57	<0.0001
BMI, kg/m^2	28.2 ± 7.38	27.7 ± 6.77	28.0 ± 7.06	28.2 ± 7.23	28.3 ± 7.53	28.5 ± 7.71	28.5 ± 7.88	28.2 ± 7.88	<0.0001
spK_t/V	1.47 ± 0.32	1.47 ± 0.32	1.47 ± 0.31	1.47 ± 0.32	1.46 ± 0.31	1.46 ± 0.31	1.46 ± 0.32	1.46 ± 0.33	<0.0001
Race, %									
White	47	59	52	48	44	42	40	40	<0.0001
African-American	31	24	28	30	33	35	37	39	<0.0001
Hispanic	15	12	14	15	16	16	16	14	<0.0001
Asian	3	2	3	3	4	4	4	3	<0.0001
Other	4	3	3	4	4	4	4	4	<0.0001
Primary insurance, %									
Medicare	54	53	55	54	54	52	53	51	<0.0001
Medicaid	7	6	6	7	7	8	8	8	<0.0001
Other	39	41	39	40	39	40	39	41	<0.0001
Dialysis access type, %									
CVC	78	44	61	77	86	90	92	92	<0.0001
AV fistula	15	43	28	15	8	6	4	3	<0.0001
AV graft	4	8	7	5	3	2	1	1	<0.0001
AV other	<1	<1	<1	<1	<1	<1	<1	0	<0.0001
Unknown	3	5	4	3	3	2	3	3	<0.0001
Comorbidities, %									
Diabetes mellitus	58	45	52	58	63	65	64	59	<0.0001
Malignancy hypertension	51	52	52	51	51	51	50	49	<0.0001
Dyslipidemia	25	23	24	25	26	27	27	27	<0.0001
ASHD	14	12	13	14	15	15	15	14	<0.0001
CHF	37	29	32	36	38	41	42	40	<0.0001
Other cardiovascular disease	15	14	14	15	15	16	17	16	<0.0001
CBVD	2	2	2	2	2	2	2	2	0.5483
COPD	5	5	5	5	5	5	6	5	0.1075
Alcohol dependence	<1	<1	<1	<1	<1	<1	<1	<1	0.0242
HIV (+) status	<1	<1	<1	<1	<1	<1	1	1	<0.0001
History of cancer	2	3	2	2	2	2	2	3	0.3748
Liver disease	1.49	1.36	1.47	1.5	1.43	1.4	1.69	1.84	0.0851
Sickle cell disease	0.15	0.10	0.11	0.10	0.13	0.18	0.26	0.59	<0.0001
Lupus erythematosus	0.48	0.22	0.22	0.29	0.42	0.66	0.96	2.01	<0.0001
Serum levels									
Creatinine, mg/dL	5.87 ± 2.36	5.85 ± 2.22	5.82 ± 2.27	5.83 ± 2.33	5.88 ± 2.40	5.93 ± 2.44	5.94 ± 2.48	5.94 ± 2.48	<0.0001
KRU, mL/min	3.27 (1.69–5.49)	3.69 (2.04–5.91)	3.52 (1.95–5.70)	3.29 (1.72–5.57)	3.18 (1.62–5.41)	3.08 (1.58–5.19)	3.00 (1.51–5.07)	2.60 (1.14–4.78)	<0.0001
Sodium, mmol/L	138 ± 3.04	138 ± 3.05	138 ± 2.91	138 ± 3.00	138 ± 3.04	138 ± 3.14	138 ± 3.09	138 ± 3.30	0.1546
Potassium, mmol/L	4.42 ± 0.52	4.39 ± 0.48	4.41 ± 0.49	4.43 ± 0.51	4.43 ± 0.52	4.43 ± 0.54	4.41 ± 0.55	4.38 ± 0.57	0.6226
Calcium, mg/dL	9.10 ± 0.56	9.18 ± 0.55	9.11 ± 0.53	9.08 ± 0.54	9.08 ± 0.56	9.10 ± 0.57	9.12 ± 0.60	9.12 ± 0.63	0.0224
Phosphorus, mg/dL	4.92 ± 1.15	4.79 ± 1.07	4.85 ± 1.08	4.91 ± 1.12	4.97 ± 1.17	5.01 ± 1.21	4.99 ± 1.22	4.90 ± 1.28	<0.0001
BUN, mg/dL	48.4 ± 14.5	49.3 ± 13.9	49.1 ± 14.0	48.7 ± 14.3	48.2 ± 14.5	47.7 ± 14.9	47.2 ± 15.1	47.4 ± 16.3	<0.0001
CO_2, mEq/L	23.6 ± 2.70	23.1 ± 2.83	23.5 ± 2.71	23.6 ± 2.67	23.7 ± 2.67	23.7 ± 2.70	23.7 ± 2.73	23.6 ± 2.77	<0.0001
PTH, pg/mL	313 (197–486)	279 (162–455)	300 (186–470)	315 (200–487)	323 (204–499)	324 (208–495)	316 (202–489)	314 (199–485)	<0.0001
Albumin, g/dL	3.51 ± 0.48	3.69 ± 0.45	3.64 ± 0.44	3.55 ± 0.44	3.47 ± 0.46	3.39 ± 0.49	3.31 ± 0.51	3.22 ± 0.55	<0.0001
nPCR, g/kg/day	0.79 ± 0.22	0.80 ± 0.22	0.80 ± 0.22	0.80 ± 0.21	0.79 ± 0.22	0.78 ± 0.22	0.77 ± 0.22	0.77 ± 0.24	<0.0001
Hgb, g/dL	11.1 ± 1.18	11.01 ± 1.14	11.1 ± 1.13	11.14 ± 1.16	11.2 ± 1.18	11.2 ± 1.20	11.1 ± 1.24	10.9 ± 1.32	0.0005
Platelet, $\times 10^3/\mu L$	251 ± 88	246 ± 84	247 ± 83	250 ± 86	255 ± 89	260 ± 97	251 ± 100	251 ± 116	<0.0001

Continued

Table 1. Continued

Characteristics	All HD patients $n = 109\,632$	LDH (U/L) <160 $n = 5968$	160 to <200 $n = 21\,826$	200 to <240 $n = 30\,507$	240 to <280 $n = 24\,552$	280 to <320 $n = 14\,062$	320 to <360 $n = 6879$	≥360 $n = 5884$	P-value
WBC, $\times 10^3/\mu L$	7.82 ± 2.67	7.23 ± 2.50	7.38 ± 2.25	7.63 ± 2.41	7.91 ± 2.50	8.18 ± 2.76	8.48 ± 3.16	8.99 ± 4.28	<0.0001
Lymphocyte (% of total WBC)	20.7 ± 7.53	22.0 ± 7.78	21.6 ± 7.54	20.9 ± 7.39	20.5 ± 7.30	20.1 ± 7.38	19.6 ± 7.72	18.5 ± 8.28	<0.0001
Bilirubin, mg/dL	0.40 (0.30–0.50)	0.40 (0.33–0.57)	0.40 (0.30–0.50)	0.40 (0.30–0.50)	0.40 (0.30–0.53)	0.40 (0.30–0.58)	0.40 (0.30–0.60)	0.40 (0.30–0.55)	0.0336
ALP, U/L	87 (69–115)	78 (63–102)	82 (65–106)	86 (68–112)	90 (71–118)	92 (72–121)	94 (74–127)	98 (75–135)	<0.0001
AST, U/L	21.6 ± 14.0	15.8 ± 6.73	17.9 ± 8.07	20.1 ± 11.1	22.2 ± 11.00	24.6 ± 17.7	27.0 ± 18.4	32.6 ± 28.5	<0.0001
Uric acid, mg/dL	6.93 ± 1.85	6.91 ± 1.72	6.92 ± 1.84	6.97 ± 1.88	6.98 ± 1.93	6.91 ± 1.70	6.72 ± 1.79	6.85 ± 1.90	0.5231
Iron, μg/dL	50.5 ± 20.1	52.6 ± 21.1	51.8 ± 20.2	50.4 ± 19.6	49.7 ± 19.3	49.5 ± 19.9	49.2 ± 19.9	51.6 ± 24.3	<0.0001
Ferritin, ng/mL	283 (164–485)	255 (152–424)	261 (154–441)	273 (161–459)	286 (166–484)	300 (171–521)	321 (176–570)	414 (216–766)	<0.0001
TIBC, mg/dL	225 ± 49.0	232 ± 48.5	231 ± 47.7	227 ± 48.3	224 ± 48.4	220 ± 49.3	217 ± 50.0	209 ± 52.9	<0.0001
ISAT, %	23.1 ± 9.12	23.2 ± 9.00	23.0 ± 8.66	22.7 ± 8.61	22.8 ± 8.87	23.2 ± 9.33	23.6 ± 9.86	25.8 ± 12.2	<0.0001
Pre-SBP, mmHg	144 ± 18.3	137 ± 16.3	141 ± 17.1	144 ± 17.9	146 ± 18.4	147 ± 18.8	147 ± 19.4	146 ± 19.8	<0.0001
Pre-DBP, mmHg	75.7 ± 11.0	72.0 ± 9.85	73.7 ± 10.2	75.2 ± 10.6	76.4 ± 11.0	77.7 ± 11.3	78.3 ± 11.8	78.6 ± 12.5	<0.0001
Post-SBP (mmHg)	144 ± 18.3	137 ± 16.3	141 ± 17.1	144 ± 17.9	145 ± 18.4	147 ± 18.8	147 ± 19.4	146 ± 19.8	0.0001
$\Delta BP_{intradialytic}$, mmHg	29.8 ± 11.9	28.5 ± 10.9	29.4 ± 11.6	30.0 ± 11.9	30.2 ± 12.2	30.3 ± 12.2	30.0 ± 12.3	28.6 ± 11.7	<0.0001
UFR, L/h	0.58 ± 0.24	0.55 ± 0.24	0.56 ± 0.24	0.57 ± 0.24	0.58 ± 0.24	0.59 ± 0.24	0.60 ± 0.24	0.59 ± 0.24	<0.0001

Categorical variables are presented as percentage; continuous variables are presented as mean ± SD or median (IQR).
Percentage may not add up to 100% due to rounding.
ALP, alkaline phosphate; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; CBVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; Δ, change; DBP, diastolic blood pressure; Hgb, hemoglobin; HIV, human immunodeficiency virus; ISAT, iron saturation; KRU, residual renal function; nPCR, normalized protein catabolic rate; pre, predialysis treatment; post, postdialysis treatment; PTH, parathyroid hormone; SBP, systolic blood pressure; TIBC, total iron binding capacity; UFR, ultrafiltration rate.

(Supplementary data, Table S8). Stronger associations were observed for those with AV fistula access type, higher albumin, no diabetes and higher BMI.

DISCUSSION

In this study including a large cohort of incident HD patients, both baseline and time-varying models showed higher serum LDH levels had positive associations with higher risk of all-cause and cardiovascular mortality. However, the association with infection-related mortality was less robust. Higher LDH level >280 U/L was incrementally associated with higher all-cause and cardiovascular mortality in incident dialysis patients. Non-diabetic, African-American, younger female patients with Medicaid insurance, CVC or those with CHF also tended to have higher LDH levels. Higher LDH also correlated with elevated aspartate aminotransferase and alkaline phosphatase. Although associations were consistent in showing positive HRs across subgroup analyses, effect estimates were particularly higher in patients with higher albumin, AV fistula, higher BMI and non-diabetics.

Not much is known about LDH, in particular for incident HD patients with past studies focusing on its role in cancer. We speculate that non-diabetic, African-American and younger female HD patients with Medicaid insurance may be getting medical treatment later than their counterparts and receive less predialysis care, resulting in emergent dialysis initiation with a CVC access type. These patients may represent those who are sicker at the time of dialysis initiation. In addition, sickle cell anemia is also commonly found in African-American patients and lupus erythematosus in females, and both conditions have been associated with higher LDH levels [33–35]. Some studies have demonstrated that dialysis patients with lupus erythematosus and sickle cell disease have a higher mortality risk than patients with other causes of end-stage renal disease [36–39]. Of note, McClellan *et al.* [39] highlighted the importance of pre-dialysis nephrology care in attenuating the increased mortality risk in patients with sickle cell disease. However, in our study adjustment for lupus erythematous and sickle cell disease did not reverse the LDH–all-cause mortality association; thereby, the contribution of these comorbidities does not fully explain the relationship between higher LDH and mortality observed in HD patients.

Furthermore, the dialysis procedure itself may cause an increase in LDH levels, since mechanical hemolysis can occur in extracorporeal blood systems such as dialysis and subsequently a raise in LDH can be measured [40, 41]. In this regard, Vaziri *et al.* [32] reported an increase in total serum LDH level after a single passage through the extracorporeal system, which could originate from platelets. In addition, Cheng *et al.* [42] reported that HD patients had higher LDH level in comparison with ischemic heart disease patients and a healthy control group, claiming a higher anaerobic metabolism/activity in HD patients. We therefore speculate that frail dialysis patients might be less likely to compensate an injury caused by the dialysis procedure, which would be represented by higher LDH levels. Conversely, we found that patients with higher baseline LDH tended to have higher pre-dialysis systolic and diastolic

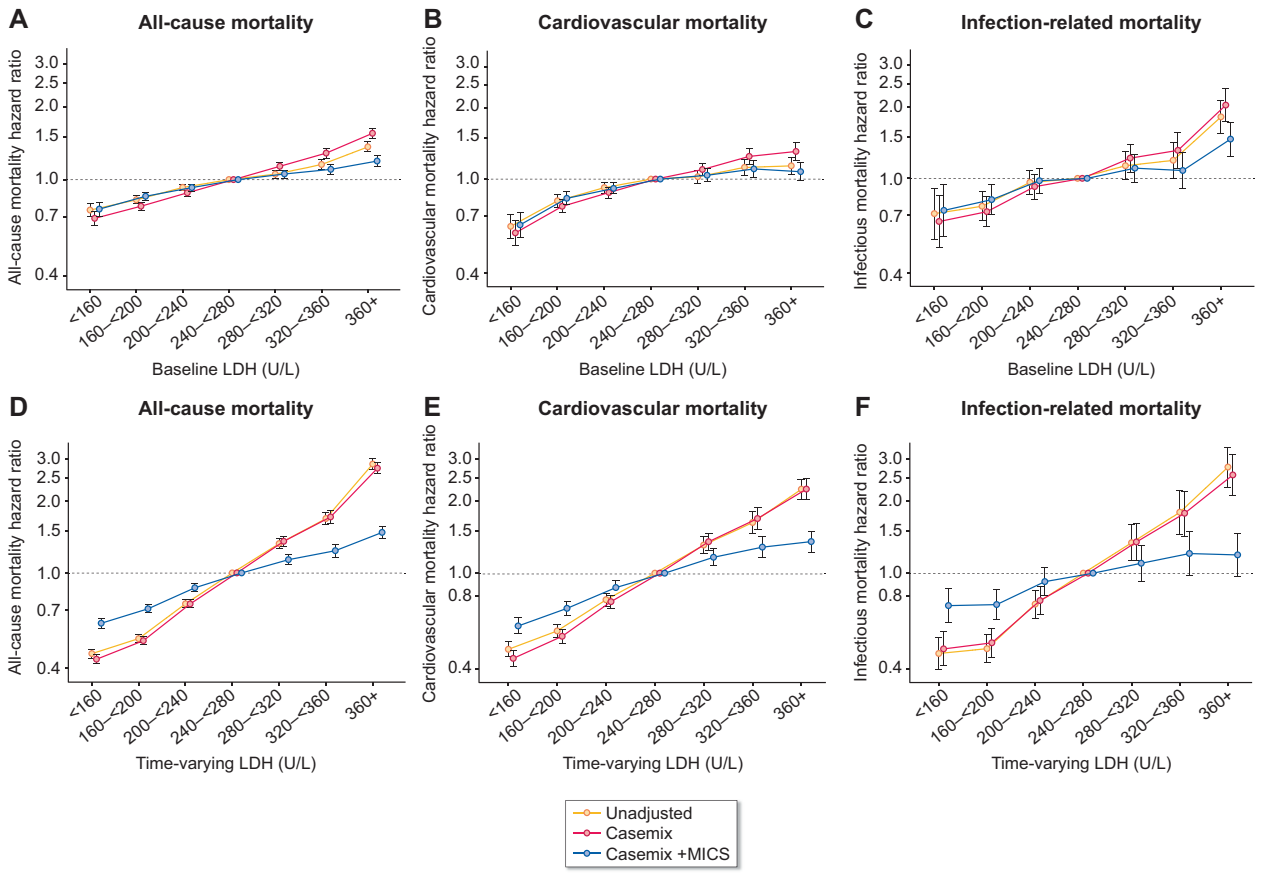

FIGURE 1: Baseline all-cause (**A**), cardiovascular (**B**) and infection-related (**C**) mortality, and time-varying all-cause (**D**), cardiovascular (**E**) and infection-related (**F**) mortality HRs (and 95% CI error bars) by LDH levels across three levels of multivariable adjustment in 109 632 incident HD patients.

BP, as well as higher post-dialysis systolic BP, which may not fit the pattern of a 'typical' frail patient [43, 44].

Moreover, results of our subgroup analysis showed higher risk estimates of mortality for patient subgroups that are seemingly healthier and that prior studies have shown to have better survival on HD, including those with higher BMI [45–48], non-diabetics [45], higher albumin [46, 49, 50] and lower WBC [51, 52]. We cannot explain these counterintuitive findings; however, it may be that LDH might be a useful prognostic marker in the dialysis population that is considered to be at less risk.

Previous published data suggested that inflammatory cells may release LDH to such a degree that higher concentrations may be measured in the serum [5], and LDH has been associated with other inflammatory markers [53–56]. In our study, higher LDH was also associated with higher levels of inflammation as indicated by its relationship with lower levels of albumin, higher levels of WBC and higher ferritin levels at baseline (Table 1). The relationship between inflammation and mortality in end-stage renal disease has been well established [57]; however, the LDH–mortality associated in our study was attenuated but not mitigated after adjustment for surrogates of inflammation and malnutrition. We therefore believe that inflammation may not fully account for the observed LDH–mortality association. In addition, we could not demonstrate a robust association in our baseline and time-varying model of high LDH and increased infection-related mortality risk in incident HD patients, while this association was stronger for CV mortality. However, LDH has been described as a prognostic marker in infectious disease states [58–63]. We can only speculate about reasons for this discrepancy to our findings. For instance, chronic kidney disease patients are more susceptible to infections due to an impaired immune defense [64–68], which might hinder the immune cells to shift their energy production from oxidative phosphorylation to aerobic glycolysis. This step allows immune cells to rapidly generate energy for effector functions in the presence of oxygen [69, 70]. LDH may catalyze the final step of aerobic glycolysis, resulting in the production of lactate. However, a study in renal transplant patients, whose immune response is impaired by immunosuppressive agents, showed an association between higher LDH concentrations and 90-day mortality in patients suffering from severe community-acquired pneumonia [59]. Therefore, we also have to consider that ascertainment of infection-related mortality in our cohort might have occurred less frequent. Further research is warranted to clarify the association between LDH and infection-related mortality in HD patients.

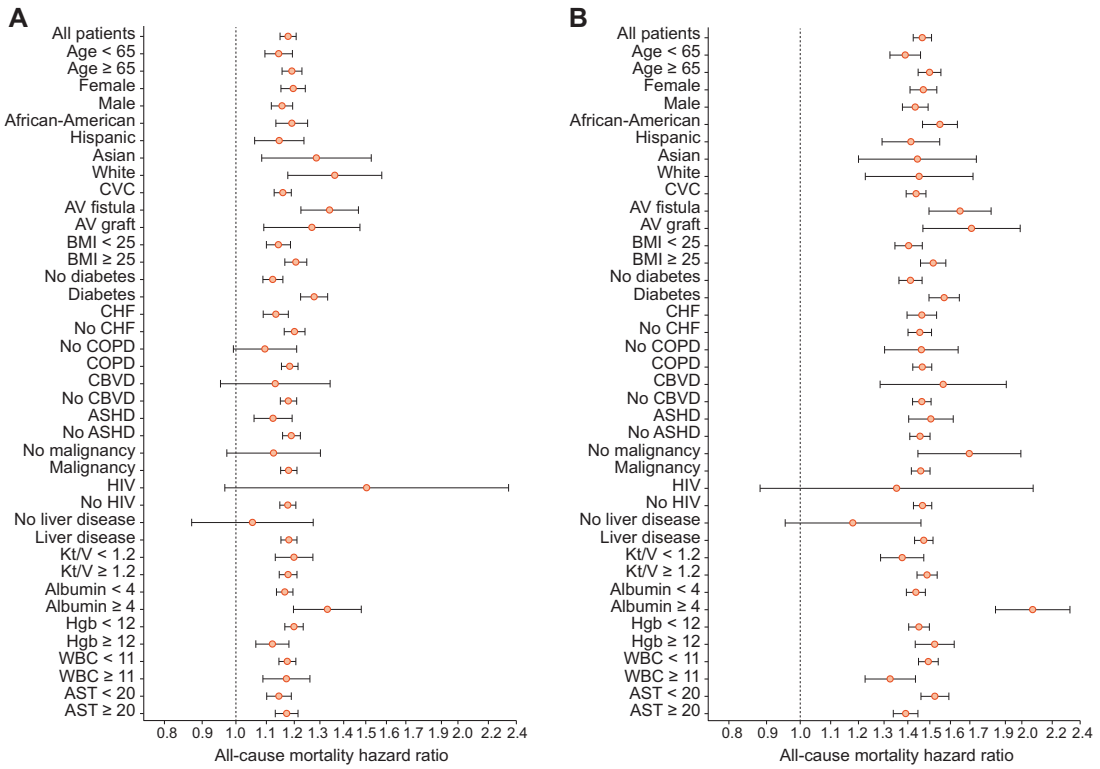

FIGURE 2: Subgroup analysis of all-cause mortality hazard ratios (and 95% CI error bars) of baseline (**A**) and time-varying (**B**) high LDH (LDH ≥250 U/L) versus low LDH (LDH <250 U/L) after adjustment for casemix + MICS variables. AST, aspartate aminotransferase; CBVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; Hgb, hemoglobin; HIV, human immunodeficiency virus.

The above-mentioned shift in energy production from mitochondrial oxidative phosphorylation to aerobic glycolysis may also contribute to the process of diseases such as pulmonary hypertension, heart failure, atherosclerosis or polycystic kidney disease [71]. This shift, also called the 'Warburg effect', results in the production of lactate in the presence of oxygen [71–73]. Thus, higher LDH levels might be a proxy of undiagnosed advancing disease. In our cohort, there was a higher prevalence of CHF and ASHD comorbidity among patients with higher LDH. We suggest that monitoring of LDH levels in HD patients might screen/identify 'seemingly healthy' patients with undiagnosed (advancing) disease. Identifying and cause-specific treatment of the underlying condition might improve outcomes in HD patients. Also, LDH itself might be a promising therapeutic target [74–76].

Our study has some limitations, not merely due to the observational nature of the study design. Furthermore, potential confounding cannot be ruled out. For instance, therapy with pharmacologic agents may result in increased LDH levels. This was not examined because home medication data were not available systematically in this cohort. In addition, we could not account for other comorbidities associated with higher LDH including other benign hemolytic disorders such as post-partum thrombotic microangiopathy/atypical hemolytic uremic syndrome, autoimmune hemolytic anemia or paroxysmal nocturnal hemoglobinuria. We also have no data on markers of inflammation such as C-reactive protein or markers of oxidative stress. In addition, for the time-varying model in our analysis, we could not account for new-onset diseases. However, we do believe that selection bias may be minimal given that the decision to measure LDH levels was made uniformly at the clinic level and was not individualized. In addition, we believe the risk of information bias was not high given that all of the LDO facilities are under uniform administrative care, and all laboratory tests are performed in one single laboratory with optimal quality-assurance monitoring. Even though the data used in this study are approximately a decade old, we believe that our study should be noted for its inclusion of a large, diverse and representative incident cohort of HD patients, with ability to account for a large number of biomarkers and examine cause-specific mortality outcomes.

CONCLUSION

In conclusion, the results of this study signify that among US incident HD patients, higher serum LDH levels substantially increased the risk of all-cause mortality and CV mortality. Further studies using more recent data are needed to qualify our findings, determine the clinical utility of measuring LDH in predicting mortality outcomes in HD and determine the molecular mechanism involved.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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