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Association of aspartate aminotransferase with mortality in hemodialysis patients

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ORIGINAL ARTICLE

ABSTRACT

Background. Liver disease is a common comorbid condition in maintenance hemodialysis (MHD) patients and may be associated with poor survival. The relationship between aspartate aminotransferase (AST) and survival has not yet been addressed in these patients. We hypothesized that higher AST level is associated with higher death risk in MHD patients.
Methods. A 5-year (January 2007–December 2011) cohort of 109 718 MHD patients was studied in the USA in dialysis clinics where AST was measured in at least 50% of all outpatients in the baseline calendar quarter. Survival models were adjusted for demographic variables, and available clinical and laboratory surrogates of malnutrition-inflammation complex, and cubic survival splines were plotted.
Results. A linear association existed between baseline serum AST levels and mortality. Increasing AST of >20 IU/L was incrementally and almost linearly associated with higher death risk at all levels of adjustment. In fully adjusted models, AST levels of ≥40 IU/L were associated with the highest risk of mortality (hazard ratio: 1.46, 95% CI: 1.38–1.54). Low AST levels (<15 IU/L) were associated with increased death risk only in fully adjusted models examining hepatitis C virus-positive patients.
Conclusions. Higher AST level of >20 IU/L is incrementally associated with higher mortality in MHD patients whereas AST in the 15–20 IU/L range is associated with the greatest survival. These findings suggest that the assessment of liver function and improving liver disease may confer survival benefit to MHD patients.

Keywords: all-cause mortality, aspartate aminotransferase, end-stage renal disease, hemodialysis, liver enzymes

INTRODUCTION

End-stage renal disease (ESRD) is frequently accompanied by major chronic diseases such as coronary heart disease (13–24%), chronic heart failure (5–20%), diabetes mellitus (12–28%), hypertension (34–50%) and stroke or transient ischemic attack (6–13%) [1]. While not as common, chronic liver disease can coexist with ESRD and its presence may be associated with poor clinical outcomes. Hepatitis C virus (HCV) infection, which itself can lead to chronic kidney disease [2], is the most common cause of liver damage in maintenance hemodialysis (MHD) patients [3–8].

Some of the most useful laboratory tests to screen for liver disease are serum aspartate aminotransferase (AST) and serum alanine transaminase (ALT). Many studies report that serum AST levels are low in patients undergoing dialysis. This is true even in HCV-positive patients, and some of these studies suggest lowering the upper limits of normal AST and ALT levels in this patient population [9–14]. Previous investigations have identified vitamin B6 deficiency as a potential mechanism responsible for hypoaminotransferasemia in dialysis patients given that vitamin B6 is required as a co-enzyme for aminotransferases to express their activity [15–21]. However, subsequent investigations noted that hemodilution may also be another mechanism underlying the lower aminotransferase level in dialysis patients [22, 23].

While some studies have reported a positive association between elevated liver enzymes and increased risk of mortality in MHD patients, the relationship between AST and all-cause mortality in MHD patients has not been thoroughly examined. The present study was therefore designed to determine the relationship between serum AST level and all-cause mortality in ESRD patients maintained on hemodialysis. To this end, we

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examined a large national database of incident MHD patients of contemporary origin with mostly uniform practice patterns and highly standardized laboratory testing criteria that were all measured in a single laboratory. We hypothesized that higher levels of AST would be associated with increased all-cause mortality in MHD patients.

MATERIALS AND METHODS

Study population and data source

This study included MHD patients initiating treatment between 2007 and 2011, with follow-up through 31 December 2011. All data were obtained from the electronic records of one of the large dialysis organizations (LDO). The study was approved by the Institutional Review Committees of the Los Angeles Biomedical Research Institute at Harbor-UCLA, University of California, Irvine Medical Center and DaVita Clinical Research. Given the large sample size, anonymity of the patients studied and nonintrusive nature of the research, the requirement for written consent was waived.

Patients were considered to be on MHD if they were treated for at least 60 consecutive days ('60-day rule' as used by the United States Renal Data System). The first (baseline) studied quarter for each patient was the first 91-day period starting from the date of first dialysis treatment. Follow-up was available for 20 quarters. Patients aged <18 years at baseline, those who did not receive treatment for at least 60 days or who were missing AST at baseline were excluded from the cohort.

Clinical and demographic measures

The analytic cohort comprised of 109 718 MHD patients. Cohort construction is summarized in Supplementary data, Figure S1. Information on race/ethnicity, primary insurance and the presence of diabetes at baseline was obtained from the LDO's electronic records database. In this database, race/ethnicity is self-categorized in that dialysis patients select the race and/or ethnicity with which they were most closely identified according to US Census Bureau categorizations [24].

To minimize measurement variability, all repeated laboratory and clinical measurements for each patient during the calendar quarter of entry were averaged. Average values were obtained from up to 20 entry calendar quarters (from 1 January 2007 through 31 December 2011) for each patient. Post-hemodialysis dry weight and baseline height were used to calculate body mass index (BMI). Furthermore, the presence or absence of diabetes and pre-existing comorbid conditions were categorized into 11 baseline comorbid conditions: (i) alcohol dependence, (ii) congestive heart failure, (iii) chronic obstructive pulmonary disease, (iv) cerebrovascular disease, (v) HIV, (vi) history of cancer, (vii) history of hypertension, (viii) atherosclerotic heart disease, (ix) liver disease, (x) other cardiac disease and (xi) drug dependence.

Laboratory measures

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 were measured monthly, including urea nitrogen, albumin, creatinine, total iron-binding capacity (TIBC), bicarbonate, phosphorus and calcium. Serum ferritin was measured at least quarterly. Hemoglobin was measured at least monthly in all patients and weekly to biweekly in most patients. Kt/V was used to estimate dialysis dosage, and normalized protein catabolic rate (nPCR) was measured monthly as an indicator of daily protein intake. Most blood samples were collected before dialysis, except for post-dialysis serum urea nitrogen to calculate urea kinetics.

Outcome ascertainment

The outcome of interest was all-cause death, which was ascertained from the LDO database. We evaluated the association between AST levels and all-cause mortality using Cox proportional hazards models in which patients remained at-risk until death or censoring for renal transplantation, transfer to another dialysis clinic or end of the study period (31 December 2011).

Statistical analysis

Data were summarized using proportions, means (±standard deviation, SD) or median [interquartile range (IQR)] as appropriate, and multiple linear regression models were fitted to construct Pearson's and partial correlations. Plots of log [−log (survival rate)] against log (survival time) were performed to test the proportionality assumption. We divided serum AST levels into eight categories (<10, 10–<15, 15–<20, 20–<25, 25–<30, 30–<35, 35–<40 and ≥40 IU/L), and using Cox proportional hazards regression models, we evaluated the association between all-cause mortality and AST within the aforementioned eight AST groups using 15–<20 IU/L as reference.

For each analysis, three models were examined based on the level of multivariate adjustment: (i) a minimally adjusted model that included mortality as the outcome, AST groups (<10, 10–<15, 15–<20, 20–<25, 25–<30, 30–<35, 35–<40 and ≥40 IU/L) and entry calendar quarter (q1 through q20) as covariates; (ii) case-mix-adjusted models that included all of the above plus age, gender, ethnicity (African American and other self-categorized black, non-Hispanic white, Asian, Hispanic and other), diabetes and 11 pre-existing comorbid states, baseline HCV status, primary insurance (Medicare, Medicaid and other), dialysis dosage as indicated by Kt/V and residual renal function during the entry quarter (i.e. urinary urea clearance); and (iii) malnutrition-inflammation complex syndrome (MICS)-adjusted models, which included all of the covariates in the case-mix model as well as 13 surrogates of nutritional status and inflammation including BMI and 12 laboratory variables, together also known as MICS, with known association with clinical outcomes in MHD patients: (a) serum albumin, (b) serum creatinine, (c) serum TIBC, (d) serum ferritin, (e) serum phosphorus, (f) serum calcium, (g) serum bicarbonate, (h) peripheral white blood cell (WBC) count, (i) lymphocyte percentage, (j) hemoglobin, (k) iron saturation and (l) nPCR as an indicator of daily protein intake, also known as the normalized protein nitrogen appearance (nPNA).

Associations between continuous AST and mortality across the three levels of multivariable adjustment were also modeled using

restricted cubic splines with knots at AST of 10, 25 and 40 IU/L. In order to verify the validity of the AST–mortality association, we used Cox models to examine eight-category AST and mortality within strata of baseline HCV status using the above-mentioned three levels of multivariate adjustment. We also performed sensitivity analyses with ALT as the exposure, modeling the ALT-mortality association with Cox regression and splines.

Finally, subgroup analyses were conducted to examine the associations of mortality with higher AST (≥20 IU/L) versus reference lower AST (<20 IU/L) across strata of *a priori* selected subgroups including: gender (male, female), age (<65, ≥65 years), race/ethnicity (Caucasian, African American, Hispanic, Asian), diabetes (diabetic, non-diabetic), albumin (≥3.8, <3.8 g/dL), baseline HCV status and ever HCV status. Missing covariate data (<1% for most laboratory and demographic variables) were imputed by means or medians of recorded values. Data on baseline HCV status and ever HCV status were missing in 31 and 12%, respectively, and were imputed by means when used as a covariate but not imputed when used in the subgroup analyses. Most analyses were carried out with SAS version 9.4, SAS Institute, Inc., Cary, NC. Splines were carried out using Stata version 13.1 (Stata Corporation, College Station, TX).

RESULTS

The original 5-year national database included 112 017 MHD patients. After excluding patients with no information on baseline AST, the final study population consisted of 109 718 patients, of which 5896 (5.4%) were HCV positive at baseline. These patients had a median follow-up time of 493 days (IQR = 230–921) and 29 000 deaths (26%). The patient's average age was 63 ± 15 years old with 44% female, 33% African Americans and 58% diabetics. Table 1 shows baseline demographic, clinical and laboratory characteristics of all patients with baseline AST serum measurements as well as those in each AST subset (<10, 10–<15, 15–<20, 20–<25, 25–<30, 30–<35, 35–<40, ≥40 IU/L). Approximately 2% of patients had plasma AST levels of <10 IU/L and 5% had AST levels of >40 IU/L. Patients with AST of <10 IU/L were younger, included more men and tended to have a lower prevalence of diabetes when compared with patients in the highest AST levels. Mean (±SD) baseline AST concentration was 30.9 ± 19.6 IU/L in HCV-positive patients and 20.6 ± 13.2 IU/L in HCV-negative patients (Figure 1).

Comparisons of the bivariate (unadjusted) and multivariate adjusted correlation coefficients between AST and some clinically relevant variables in the baseline quarter are shown in Supplementary data, Table S1. Serum albumin, ferritin and TIBC concentrations displayed the strongest correlations with AST.

Figure 2 displays 5-year death hazard ratios (HR) for eight categories of AST in all 109 718 MHD patients studied. Using AST 15–<20 IU/L as reference, there was an incremental linear association between AST levels and all-cause mortality in all levels of adjustment. In case-mix and fully adjusted models, the higher survival for patients with AST of <10 was attenuated and no longer significant. In fully adjusted models, AST levels of ≥40 IU/L were associated with the highest risk of mortality (HR: 1.46, 95% CI: 1.38–1.54). Similar results were seen in Figure 3, which displays continuous AST and all-cause mortality using splines. Harrell's *c*-index was 0.74. In sensitivity analyses using ALT, we also found an incremental, almost linear relationship between this liver enzyme and mortality (Supplementary data, Figures S2 and S3).

Figure 4 shows the association between AST and all-cause mortality within strata of HCV status. In the fully adjusted model, the lowest AST is associated with higher death risk only in HCV-positive patients (Figure 4A, HR: 2.13, 95% CI: 1.21–3.74). The incremental, almost linear association between AST and mortality among HCV-negative MHD patients (Figure 4B) is almost identical to that seen in the entire cohort (Figure 2).

In subgroup analyses, the unadjusted all-cause mortality HRs were above unity in almost all examined subgroups, indicating a higher risk of death with higher AST (≥20 IU/L) compared with low AST (<20 IU/L). These associations persisted after full adjustment in all subgroups but Asian (Figure 5).

In logistic regressions adjusted for case-mix and MICS covariates, main predictors of high AST (AST ≥20 IU/L) included Asian race, HIV positivity, baseline HCV-positive status and serum TIBC. After adjustment, we found that the odds of experiencing high AST levels were 59% higher for Asians compared with all other race/ethnicities, 164% higher for HIV-positive patients and 277% higher for HCV-positive patients. In addition, a 100 mg/dL increase in serum TIBC increased the odds of finding an elevated AST level by 171%. Other significant predictors of high AST included central venous catheter access, liver disease, alcohol dependence and iron saturation ratio (Table 2).

DISCUSSION

We examined the association between AST level and all-cause mortality in a nationally representative cohort of 109 718 incident MHD patients. As expected, higher AST levels were associated with increased all-cause mortality. Patients with AST levels of 15–20 IU/L showed the best survival whereas AST levels of >20 IU/L were associated with a significantly higher risk of mortality. This association was consistent across various subgroups of MHD patients. However, when we examined the association within strata of baseline HCV status, lower AST levels were also associated with increased mortality in HCV-positive patients.

There are several mechanisms that can explain the findings from this investigation. One obvious possibility is that higher AST levels are indicative of underlying liver disease, which can be associated with increased morbidity and mortality. The similar results observed from the sensitivity analysis using ALT as an exposure further support this mechanism. Nevertheless, the data from our study clearly indicate a statistically significant trend for increased all-cause mortality for small incremental increases in AST levels even within the 'normal' range in the MHD patient population. Therefore, even patients with presumed normal liver function based on liver enzyme levels can be at risk for increased mortality. Hence, additional underlying mechanisms may be at play that can contribute to

Table 1. Demographic and clinical characteristics of 109 718 MHD patients, including patients in eight groups of AST

Characteristics	All MHD patients	AST (IU/L)								P-value
		AST < 10	10 ≤ AST<15	15 ≤ AST < 20	20 ≤ AST < 25	25 ≤ AST < 30	30 ≤ AST < 35	35 ≤ AST < 40	AST ≥ 40	
	n = 109 718	*n* = 2399	*n* = 22 997	*n* = 36 585	*n* = 22 766	*n* = 11 071	*n* = 5415	*n* = 2965	*n* = 5520	
Age (years)	63 ± 15	56 ± 17	61 ± 15	63 ± 15	65 ± 15	64 ± 15	63 ± 15	62 ± 14	60 ± 14	<0.001
Gender (% women)	44	29	42	45	45	50	43	41	41	0.35
Diabetes mellitus (%)	58	46	54	59	61	49	61	61	58	<0.001
Race (%)										
White	47	42	46	48	48	47	45	41	40	<0.001
African American	31	35	33	30	29	31	33	36	39	0.008
Hispanic	15	18	15	15	15	14	14	15	13	<0.001
Asian	3	2	2	3	4	4	4	4	4	<0.001
Other	4	3	4	4	4	4	4	3	4	<0.001
Primary insurance (%)										
Medicare	54	46	52	54	55	55	55	53	51	<0.001
Medicaid	7	9	7	6	7	7	8	9	9	0.01
Other	39	45	41	40	38	38	37	38	40	0.006
Dialysis access type (%)										
CVC	78	61	72	77	80	81	82	82	83	<0.001
AV fistula	15	30	19	15	13	12	11	11	10	<0.001
AV graft	4	5	5	4	4	4	3	4	3	<0.001
AV other	<1	<1	<1	<1	<1	<1	<1	<1	<1	<0.001
Unknown	3	4	3	3	3	3	3	3	4	<0.001
Kt/V (dialysis dose)	1.47 ± 0.33	1.42 ± 0.31	1.45 ± 0.31	1.47 ± 0.32	1.49 ± 0.34	1.48 ± 0.33	1.46 ± 0.32	1.47 ± 0.34	1.45 ± 0.33	<0.001
KRU (residual renal function) (mL/min)	4.06 ± 3.55	3.63 ± 3.30	3.96 ± 3.28	4.07 ± 3.41	4.13 ± 3.79	3.45 ± 2.72	4.05 ± 3.51	4.44 ± 4.68	4.04 ± 4.14	<0.001
PT/INR	2.00 ± 1.03	1.57 ± 0.70	1.86 ± 1.05	1.99 ± 1.04	2.00 ± 0.94	2.12 ± 1.07	2.16 ± 1.01	2.28 ± 1.24	2.07 ± 1.11	<0.001
Comorbidities (%)										
Alcohol dependence	<1	<1	<1	<1	<1	<1	<1	<1	<1	<0.001
Congestive heart failure	37	33	34	37	38	39	40	38	38	<0.001
Chronic obstructive pulmonary disease	5	4	5	5	5	5	5	5	5	<0.001
Cerebrovascular disease	2	1	2	2	2	2	2	2	1	<0.001
HIV-positive status	<1	<1	<1	<1	<1	<1	1	1	2	0.69
History of cancer	2	2	2	2	2	3	2	2	2	0.69
History of hypertension	51	54	51	51	51	52	51	51	49	<0.001
Atherosclerotic heart disease	14	12	13	15	15	16	15	15	14	0.647
Liver disease	1	<1	<1	1	1	2	2	4	5	0.002
Other cardiovascular disease	15	12	15	15	16	17	16	16	15	<0.001
Drug dependence	<1	<1	<1	<1	<1	<1	<1	<1	<1	<0.001
Ever HCV positive	8	3	2	4	7	13	19	24	31	<0.001
Serum levels										
ALT (IU/L)	16.1 ± 14.2	8.16 ± 3.50	10.2 ± 4.08	13.2 ± 5.34	17.3 ± 7.93	21.7 ± 11.8	26.2 ± 14.7	29.3 ± 15.1	47.9 ± 43.5	<0.001
Albumin (g/dL)	3.51 ± 0.48	3.69 ± 0.48	3.58 ± 0.45	3.54 ± 0.46	3.50 ± 0.46	3.45 ± 0.48	3.39 ± 0.51	3.35 ± 0.52	3.22 ± 0.55	<0.001
Calcium (mg/dL)	8.68 ± 0.63	8.67 ± 0.66	8.65 ± 0.63	8.69 ± 0.62	8.72 ± 0.62	8.70 ± 0.64	8.66 ± 0.65	8.62 ± 0.66	8.54 ± 0.66	<0.001
Bicarbonate (mg/dL)	23.6 ± 2.70	22.7 ± 2.75	23.2 ± 2.69	23.6 ± 266	23.8 ± 2.68	23.9 ± 2.72	23.8 ± 2.73	23.7 ± 2.76	23.6 ± 2.76	<0.001
Creatinine (mg/dL)	5.86 ± 2.36	7.59 ± 3.01	6.39 ± 2.49	5.86 ± 2.28	5.59 ± 2.22	5.48 ± 2.23	5.48 ± 2.33	5.46 ± 2.24	5.44 ± 2.24	0.001
Ferritin (ng/mL)	283 (164, 486)	231 (133, 400)	253 (148, 428)	273 (160, 459)	292 (170, 501)	305 (177, 526)	332 (188, 573)	241 (193, 599)	400 (217, 719)	<0.001
Blood hemoglobin (g/dL)	11.1 ± 1.18	10.9 ± 1.23	11.0 ± 1.15	11.1 ± 1.15	11.2 ± 1.17	11.2 ± 1.22	11.2 ± 1.26	11.1 ± 1.25	11.0 ± 1.30	<0.001
Iron saturation ratio	23.1 ± 9.13	22.7 ± 8.71	22.2 ± 8.11	22.5 ± 1.19	23.0 ± 8.62	23.7 ± 9.37	24.5 ± 10.8	25.4 ± 11.6	27.8 ± 14.3	<0.001

Continued

Table 1. Continued

Characteristics	All MHD patients	AST (IU/L)							P-value
		AST < 10	10 ≤ AST<15	15 ≤ AST < 20	20 ≤ AST < 25	25 ≤ AST < 30	30 ≤ AST < 35	35 ≤ AST < 40	AST ≥ 40	
	n = 109 718	*n* = 2399	*n* = 22 997	*n* = 36 585	*n* = 22 766	*n* = 11 071	*n* = 5415	*n* = 2965	*n* = 5520	
Lymphocyte (% of total WBC)	20.7 ± 7.54	21.1 ± 7.56	20.6 ± 7.17	20.6 ± 7.33	20.6 ± 7.53	20.7 ± 7.91	20.9 ± 8.08	21.3 ± 8.25	21.6 ± 8.53	<0.001
Protein catabolic rate (g/kg/day)	0.79 ± 0.22	0.82 ± 0.22	0.80 ± 0.21	0.79 ± 0.22	0.80 ± 0.22	0.79 ± 0.22	0.77 ± 0.22	0.77 ± 0.23	0.76 ± 0.23	<0.001
Phosphorus (mg/dL)	4.92 ± 1.15	5.38 ± 1.27	5.10 ± 1.18	4.93 ± 1.13	4.83 ± 1.12	4.78 ± 1.13	4.77 ± 1.13	4.79 ± 1.16	4.79 ± 1.16	<0.001
TIBC (mg/dL)	225 ± 49.1	225 ± 44.2	223 ± 45.4	224 ± 46.6	226 ± 50.0	227 ± 51.9	227 ± 54.9	229 ± 57.0	226 ± 61.0	<0.001
White blood cell ($\times 10^3/\mu L$)	7.82 ± 2.68	7.69 ± 2.50	7.86 ± 2.49	7.87 ± 2.58	7.82 ± 2.60	7.78 ± 3.02	7.75 ± 3.03	7.67 ± 3.07	7.62 ± 3.05	<0.001
Body mass index (kg/m^2)	28.1 ± 7.33	28.6 ± 7.57	29.0 ± 7.65	28.3 ± 7.34	27.8 ± 7.19	27.5 ± 7.01	27.2 ± 7.04	27.1 ± 6.81	26.6 ± 6.96	<0.001

Dichotomous/dummy variables are presented as percentage; continuous variables are presented as mean ± SD or median (IQR).
ALT, alanine transaminase; AV, arteriovenous; CVC, central venous catheter; HCV, hepatitis C virus; IQR, interquartile range; KRU, kidney residual time; PR/INR, prothrombin time/international normalized ratio; SD, standard deviation; TIBC, total iron-binding capacity; WBC, white blood cell.

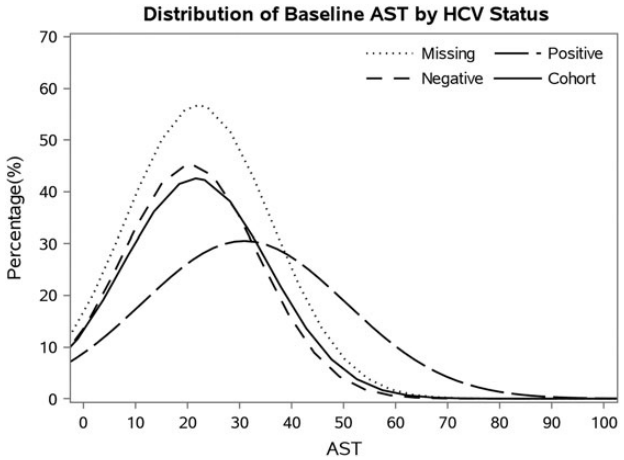

FIGURE 1: Distribution of baseline AST by baseline HCV status.

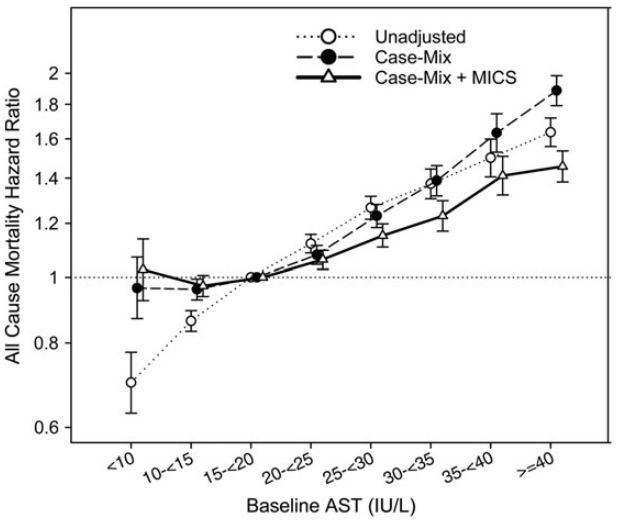

FIGURE 2: Association of AST and all-cause mortality using Cox proportional hazards models in the entire cohort of 109 718 MHD patients.

these observations. This is especially true given the complexity of factors that contribute to all-cause mortality in patients with ESRD. For example, there may be unique underlying biologic factors in MHD patients that impact AST levels and all-cause mortality. This is supported by a study conducted by Skaaby *et al.* that found a statistically significant inverse association between vitamin D level and incident liver disease. These investigators found that the risk of having a higher plasma level of ALT, AST or GGT (gamma-glutamyl transferase) tended to be increased with lower nutritional vitamin D levels [25, 26]. Given the abundance of evidence connecting nutritional vitamin D deficiency to mortality, low vitamin D levels can be a potential mechanism by which elevated AST levels may be linked with increased risk of mortality [27–29].

In addition, a recent report by Van Beek *et al.* found that variations in liver enzyme levels can be explained by genetic variations that are then modified by each patient's environmental factors [30]. In the case of MHD patients, the observed variations in serum AST levels may be partly due to hereditary factors that are impacted by the biological effects of ESRD and the patient's

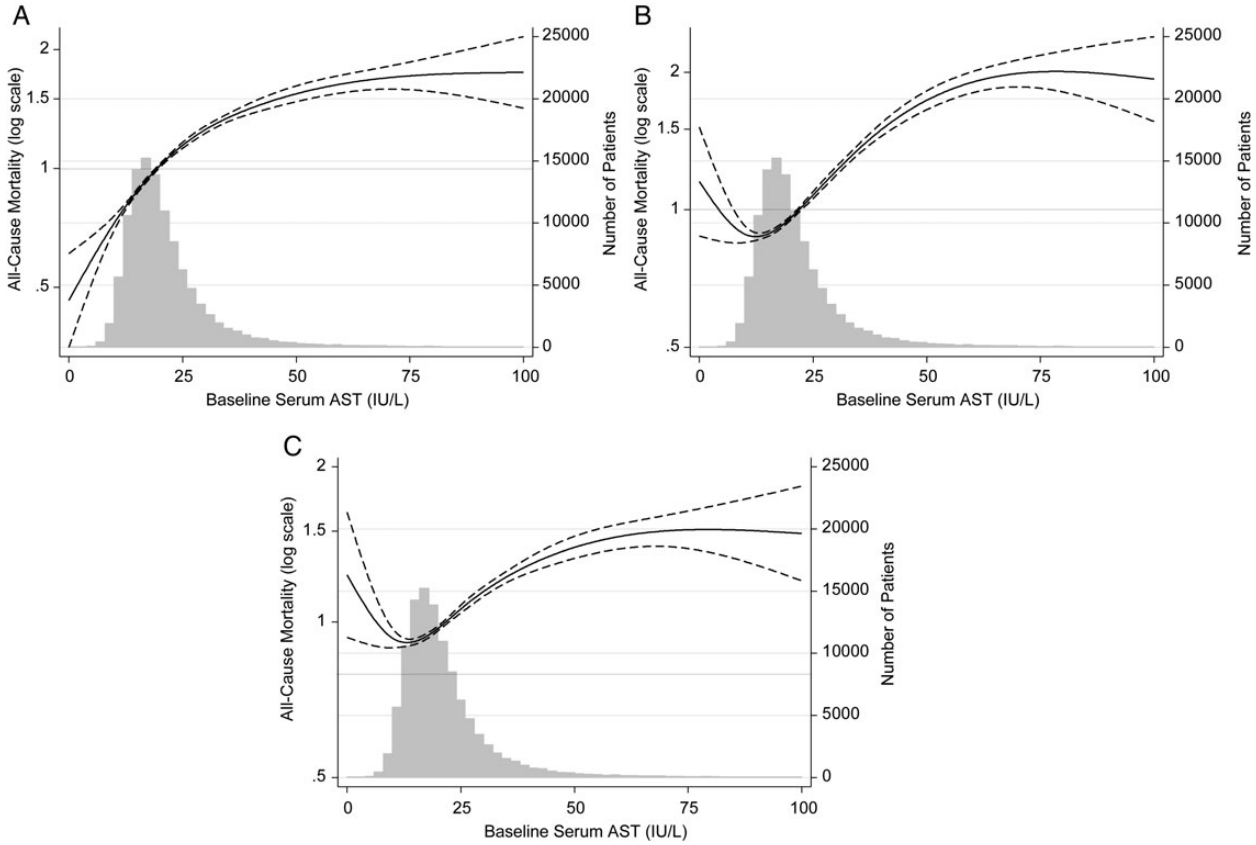

FIGURE 3: Cubic spline models of Cox proportional regression analyses reflecting adjusted mortality predictability (with 95% CI) according to increasing serum ALT concentrations in the entire cohort of 109 718 MHD patients (**A:** unadjusted; **B:** case-mix adjusted; **C:** case-mix and MICS adjusted).

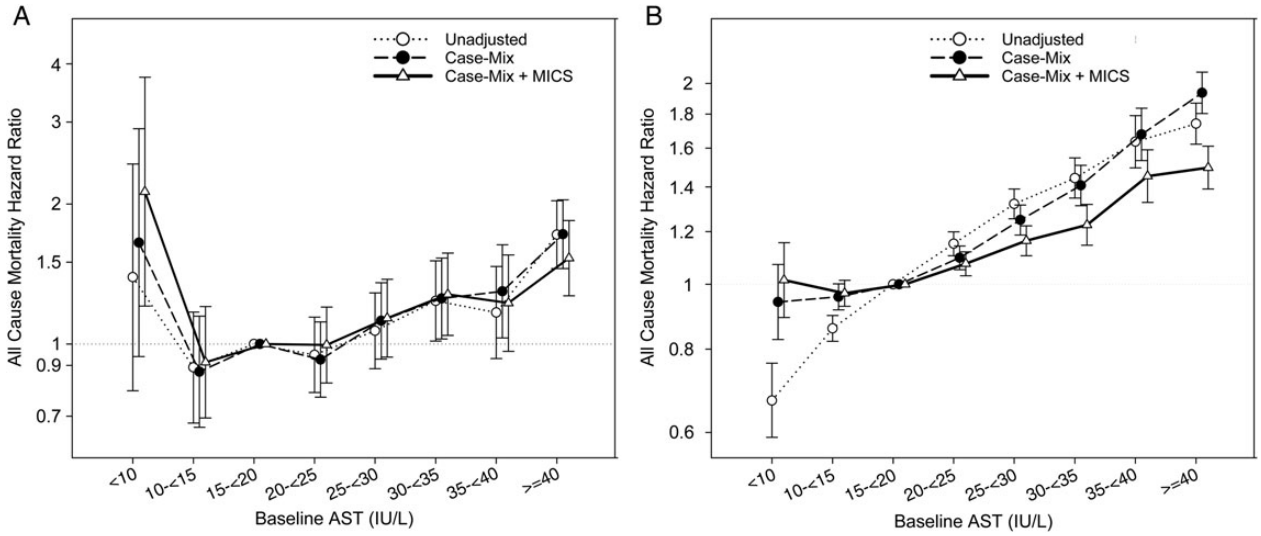

FIGURE 4: (**A**) Association of AST and all-cause mortality using Cox proportional hazards models in 5896 HCV-positive MHD patients. (**B**) Association of AST and all-cause mortality using Cox proportional hazards models in 69 849 HCV-negative MHD patients.

environment. The latter would include metabolic risk factors such as dyslipidemia, inflammation, alcohol use, smoking, vitamin D levels and coffee consumption [30]. Hence, future studies will need to assess the potential genetic, biologic and environmental factors that may be responsible for the association of plasma AST levels with all-cause mortality in MHD patients.

Contrary to HCV-negative patients, low AST level was associated with higher risk of mortality in patients with chronic HCV infection. The most reasonable explanation for this is that HCV patients with low AST levels may have minimal parenchymal reserve and low AST level is just a surrogate marker indicating the severity of their end-stage liver disease. Unfortunately, we could

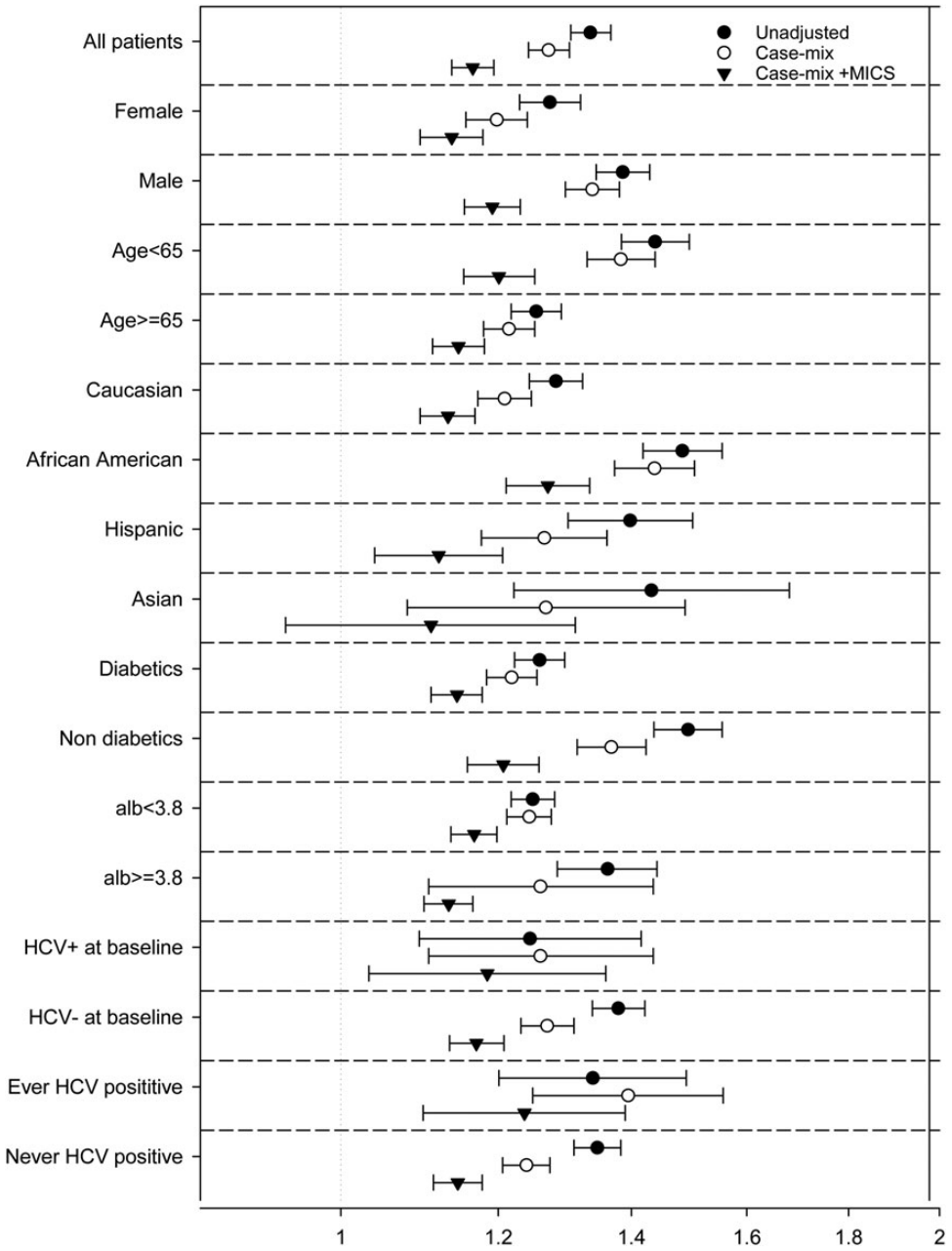

FIGURE 5: Association of AST and all-cause mortality in patients with AST of ≥20 IU/L in selected subgroups of MHD patients.

not test this hypothesis as we did not have reliable markers of liver parenchymal function in our database such as spontaneous prothrombin level or serum cholinesterase. Further studies are needed to explore this potential explanation.

Several limitations of this study should be mentioned. First, the current findings should be qualified given the observational nature of our study design. Another limitation is the potential confounding of therapy with pharmacologic agents, which may have led to increased AST levels. This was not examined because home medication data were not available systematically in this national cohort. It should be mentioned that some patients needed to be excluded given the fact that baseline AST measurements were not available for them. However, we do not believe confounding by indication was present given that the decision to measure AST levels was made uniformly at the clinic level and was not individualized. In addition, we believe the risk of selection 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.

In summary, little is known about the association between AST and mortality in dialysis patients, and in this study, we sought to clarify this relationship. Higher AST levels were incrementally associated with increased all-cause mortality even in fully adjusted models. Moreover, we found an association between low levels of AST and increased mortality in HCV-positive patients. While significantly elevated levels of AST are noted and addressed by most clinicians, moderate increases within the normal range and lower than expected levels may also have clinical relevance and significance.

Table 2. Multivariate logistic regression model predicting AST ≥20 IU/L in 109 718 MHD patients

Variable	Unadjusted		Case-mix		Case-mix + MICS	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age (Δ10 years)	1.07 (1.06, 1.08)	<0.001	1.12 (1.11, 1.13)	<0.001	1.03 (1.01, 1.04)	<0.001
Female	1.01 (0.99, 1.04)	0.28	1.04 (1.00, 1.07)	0.03	0.96 (0.93, 0.99)	0.03
Diabetes mellitus	1.06 (1.03, 1.09)	<0.001	1.04 (1.01, 1.08)	0.02	0.97 (0.94, 1.01)	0.14
Race						
White	0.96 (0.94, 0.98)	0.001	0.86 (0.79, 0.93)	<0.001	0.84 (0.77, 0.91)	<0.001
Black	0.99 (0.97, 1.02)	0.67	0.98 (0.94, 1.01)	0.20	1.09 (1.04, 1.13)	<0.001
Asian	1.51 (1.41, 1.61)	<0.001	1.63 (1.50, 1.77)	<0.001	1.59 (1.46, 1.73)	<0.001
Hispanic	0.96 (0.93, 1.00)	0.03	1.03 (0.98, 1.08)	0.27	1.07 (1.02, 1.13)	0.005
Other	1.11 (1.04, 1.18)	0.002	1.17 (1.07, 1.27)	<0.001	1.20 (1.10, 1.31)	<0.001
Primary insurance						
Medicare	1.05 (1.02, 1.07)	<0.001	1.01 (0.98, 1.04)	0.65	0.98 (0.94, 1.01)	0.15
Medicaid	1.06 (1.01, 1.11)	0.02	0.97 (0.91, 1.04)	0.38	0.98 (0.92, 1.05)	0.64
Other	0.94 (0.92, 0.96)	<0.001	0.99 (0.96, 1.03)	0.65	1.03 (0.99, 1.06)	0.15
Access type						
CVC	1.44 (1.40, 1.49)	<0.001	1.13 (1.03, 1.23)	0.01	1.15 (1.05, 1.26)	0.003
AV fistula	0.65 (0.63, 0.68)	<0.001	0.65 (0.62, 0.68)	<0.001	0.66 (0.63, 0.70)	<0.001
AV graft	0.80 (0.75, 0.85)	<0.001	0.71 (0.66, 0.77)	<0.001	0.72 (0.66, 0.78)	<0.001
AV other	0.74 (0.50, 1.11)	0.15	0.68 (0.42, 1.11)	0.12	0.70 (0.43, 1.15)	0.16
Unknown	0.97 (0.90, 1.03)	0.31	0.89 (0.81, 0.97)	0.01	0.87 (0.79, 0.95)	0.003
Kt/V (dialysis dose) (Δ1)	1.18 (1.13, 1.22)	<0.001	1.11 (1.05, 1.16)	<0.001	0.90 (0.85, 0.96)	<0.001
Residual renal function	1.02 (1.01, 1.03)	<0.001	1.02 (1.01, 1.03)	<0.001	1.00 (0.99, 1.01)	0.90
Comorbid States						
Alcohol	1.87 (1.45, 2.39)	<0.001	1.55 (1.12, 2.15)	0.009	1.47 (1.05, 2.08)	0.03
Congestive heart failure	1.05 (1.02, 1.08)	<0.001	1.07 (1.03, 1.10)	<0.001	1.07 (1.04, 1.11)	<0.001
COPD	0.99 (0.93, 1.04)	0.61	0.81 (0.75, 0.87)	<0.001	0.95 (0.84, 1.07)	0.41
Cerebrovascular disease	1.03 (0.94, 1.13)	0.52	0.95 (0.85, 1.07)	0.43	0.81 (0.75, 0.87)	<0.001
HIV	3.48 (2.88, 4.22)	<0.001	3.24 (2.55, 4.11)	<0.001	2.64 (2.05, 3.39)	<0.001
History of cancer	0.99 (0.91, 1.07)	0.77	0.96 (0.87, 1.07)	0.47	0.89 (0.80, 0.99)	0.03
History of hypertension	0.95 (0.93, 0.98)	<0.001	0.92 (0.89, 0.95)	<0.001	1.01 (0.98, 1.04)	0.64
Atherosclerotic heart disease	0.99 (0.96, 1.03)	0.82	0.97 (0.93, 1.02)	0.29	0.97 (0.92, 1.02)	0.19
Liver disease	2.20 (1.99, 2.44)	<0.001	2.14 (1.87, 2.45)	<0.001	1.91 (1.66, 2.20)	<0.001
Other cardiovascular disease	1.06 (1.03, 1.10)	<0.001	1.08 (1.03, 1.13)	0.004	1.04 (0.99, 1.10)	0.11
Drug dependence	1.76 (1.39, 2.27)	<0.001	0.98 (0.71, 1.37)	0.91	0.93 (0.66, 1.32)	0.70
HCV-positive status	4.78 (4.31, 4.87)	<0.001	4.95 (4.65, 5.27)	<0.001	3.77 (3.53, 4.03)	<0.001
Serum levels						
Albumin (g/dL) (Δ0.5 g/dL)	0.76 (0.75, 1.77)	<0.001	0.81 (0.80, 0.82)	<0.001	0.65 (0.64, 0.67)	<0.001
Calcium (mg/dL)	0.90 (0.88, 0.92)	<0.001	0.96 (0.94, 0.99)	0.003	1.07 (1.04, 1.10)	<0.001
Bicarbonate (mg/dL)	1.05 (1.04, 1.06)	<0.001	1.04 (1.04, 1.05)	<0.001	1.02 (1.02, 1.03)	<0.001
Creatinine (mg/dL)	0.88 (0.88, 0.89)	<0.001	0.87 (0.86, 0.87)	<0.001	0.92 (0.91, 0.92)	<0.001
Ferritin (Δ100 ng/mL)	1.08 (1.07, 1.08)	<0.001	1.07 (1.07, 1.08)	<0.001	1.09 (1.08, 1.10)	<0.001
Blood hemoglobin (g/dL)	1.03 (1.02, 1.04)	<0.001	1.04 (1.02, 1.05)	<0.001	1.08 (1.06, 1.10)	<0.001
Iron saturation ratio (Δ10%)	1.23 (1.21, 1.24)	<0.001	1.22 (1.20, 1.24)	<0.001	1.20 (1.17, 1.22)	<0.001
Lymphocyte (% of total WBC) (Δ10%)	1.04 (1.03, 1.06)	<0.001	1.03 (1.01, 1.05)	0.01	1.03 (1.00, 1.05)	0.02
Protein catabolic rate (g/kg/day)	0.74 (0.70, 0.78)	<0.001	0.75 (0.70, 0.81)	<0.001	1.25 (1.14, 1.36)	<0.001
Phosphorus (mg/dL)	0.82 (0.81, 0.83)	<0.001	0.82 (0.81, 0.84)	<0.001	0.89 (0.88, 0.91)	<0.001
TIBC (Δ100 mg/dL)	1.20 (1.18, 1.24)	<0.001	1.26 (1.22, 1.30)	<0.001	2.71 (2.60, 2.84)	<0.001
White blood cell ($\times 10^3/\mu L$)	0.99 (0.98, 0.99)	<0.001	0.99 (0.98, 0.99)	<0.001	0.99 (0.98, 1.00)	<0.001
BMI (kg/m^2)	0.91 (0.90, 0.92)	<0.001	0.93 (0.92, 0.94)	<0.001	0.93 (0.92, 0.94)	<0.001

AV, arteriovenous; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; HCV, hepatitis C virus; TIBC, total iron-binding capacity; WBC, white blood cell.

Therefore, future studies are needed to further delineate the link between alterations in serum AST levels and outcomes and describe the mechanisms that can explain these associations.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

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