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Plasma Lactate Dehydrogenase Levels Predict Mortality in Acute Aortic Syndromes

A Diagnostic Accuracy and Observational Outcome Study

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Abstract: In acute aortic syndromes (AAS), organ malperfusion represents a key event impacting both on diagnosis and outcome. Increased levels of plasma lactate dehydrogenase (LDH), a biomarker of malperfusion, have been reported in AAS, but the performance of LDH for the diagnosis of AAS and the relation of LDH with outcome in AAS have not been evaluated so far.

This was a bi-centric prospective diagnostic accuracy study and a cohort outcome study. From 2008 to 2014, patients from 2 Emergency Departments suspected of having AAS underwent LDH assay at presentation. A final diagnosis was obtained by aortic imaging. Patients diagnosed with AAS were followed-up for in-hospital mortality.

One thousand five hundred seventy-eight consecutive patients were clinically eligible, and 999 patients were included in the study. The final diagnosis was AAS in 201 (20.1%) patients. Median LDH was 424 U/L (interquartile range [IQR] 367–557) in patients with AAS and 383 U/L (IQR 331–460) in patients with alternative diagnoses ($P < 0.001$). Using a cutoff of 450 U/L, the sensitivity of LDH for AAS was 44% (95% confidence interval [CI] 37–51) and the specificity was 73% (95% CI 69–76). Overall in-hospital mortality for AAS was 23.8%. Mortality was 32.6% in patients with LDH $\geq$ 450 U/L and 16.8% in patients with LDH $<$ 450 U/L ($P = 0.006$). Following stratification according to LDH quartiles, in-hospital mortality was 12% in the first (lowest) quartile, 18.4% in the second quartile, 23.5% in the third quartile, and 38% in the fourth (highest) quartile ($P = 0.01$). LDH $\geq$ 450 U/L was further identified as an independent predictor of death in AAS both in univariate and in stepwise logistic regression analyses (odds ratio 2.28, 95% CI 1.11–4.66; $P = 0.025$), in addition to well-established risk markers such as advanced age and hypotension. Subgroup analysis showed excess mortality in association with LDH $\geq$ 450 U/L in elderly, hemodynamically stable and in nonsurgically treated patients.

Plasma LDH constitutes a biomarker of poor outcome in patients with AAS. LDH is a rapid and universally available assay that could be used to improve risk stratification and to individualize treatment in patient groups where options are controversial.

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Abbreviations: AAS = acute aortic syndrome, AD = aortic dissection, AltD = alternative diagnosis, AUC = area under the curve, CI = confidence interval, CRP = C-reactive protein, CTA = computed tomography angiography, ED = Emergency Department, IFCC = International Federation of Clinical Chemistry and Laboratory Medicine, IMH = intramural aortic hematoma, IQR = interquartile range, LDH = lactate dehydrogenase, LR− = negative likelihood ratio, LR+ = positive likelihood ratio, NPV = negative predictive value, OR = odds ratio, PAU = penetrating aortic ulcer, PPV = positive predictive value, ROC = receiver operated characteristic, TEE = transesophageal echocardiography.

INTRODUCTION

Acute aortic syndromes (AAS), which include acute aortic dissection (AD), intramural aortic hematoma (IMH), and penetrating aortic ulcer (PAU), are cardiovascular emergencies affecting ~5/100,000 individuals/y. To minimize the heavy morbidity and mortality associated with AAS, key factors are represented by rapid diagnosis and individualization of therapeutic interventions.[1,2] The diagnosis of AAS is challenging, with a misdiagnosis rate as high as 39%, as the clinical manifestations of AAS are unspecific and most diseases in differential diagnosis are by far more frequent than AAS.[3] Therapeutic individualization also constitutes a challenge, with increasing proportions of patients with AAS presenting with advanced age, comorbidities, and AAS types not requiring immediate surgical treatment. Organ malperfusion has emerged as a key risk factor for adverse outcome, but standardized definition and assessment of organ perfusion in AAS is presently lacking.[4,5] In this scenario, circulating biomarkers are advocated to improve diagnosis, risk stratification, and mortality prediction in AAS, as in other acute cardiovascular emergencies such as acute coronary syndromes and pulmonary embolism.[6–9]

Lactate dehydrogenase (LDH) is a widely expressed intracellular enzyme, which reduces pyruvate to lactate during hypoxia. Measurement of plasma LDH levels is rapidly and almost universally available to Emergency Departments (EDs),

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with increased LDH typically found in hemolysis and in myocardial or skeletal muscle ischemia.[10] A previous study from this group found increased plasma LDH in a cohort of patients with AAS, and expert opinion has indicated LDH assay as a potential biomarker applicable in the workup of AAS.[11–13] Furthermore, increased plasma LDH has been associated with worse outcome and mortality in other conditions such as pneumonia, pancreatitis, hemolysis, thrombosis, and bowel ischemia.[14–19] However, evidence supporting the use of plasma LDH in the diagnosis of AAS, or to predict outcome in patients with documented AAS, is currently lacking. In the present study, we sought to evaluate the diagnostic accuracy of plasma LDH for the diagnosis of AAS and the association of plasma LDH with in-hospital outcome. The working hypothesis was that increased plasma LDH at presentation may identify patients at higher risk of in-hospital death.

METHODS

Study Design, Setting, and Enrolment Criteria

This was a bi-centric prospective diagnostic accuracy and a cohort outcome study performed on patients from 2 clinical centers: Molinette Hospital (Torino, Italy) and Careggi Hospital (Firenze, Italy). Both centers are regional hubs for emergency and cardiovascular medicine and surgery. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the local Ethics Committee. The study is compliant with the STARD and STROBE guidelines.[20,21]

From January 2008 to June 2014, consecutive outpatients who presented to the ED were eligible for the study if they had a clinical suspicion of AAS, defined as an acute onset of chest pain, back pain, abdominal pain, syncope, or signs/symptoms of perfusion deficit (including central/peripheral nervous system, mesenteric, myocardial, or limb ischemia), without another known etiology. The suspicion of AAS needed to be high enough for the attending physician to order an urgent aortic imaging examination, as in previous studies.[22–24] Trauma patients were excluded. Plasma LDH was assayed in a convenience sample of patients meeting inclusion criteria. Informed consent was obtained from each patient or next of kin.

LDH Assay

A plasma LDH assay was performed on blood collected in the ED during medical evaluation. Attending physicians caring for the patients were not blinded to the results of plasma LDH assay. Patients underwent venipuncture in the ED as part of the initial diagnostic workup, and venous blood samples were immediately sent to the local laboratory for plasma LDH assay. Plasma LDH levels were measured with a Roche/Hitachi Cobas automated platform, using a colorimetric pyruvate-lactate enzymatic assay technique (Cobas LDHL, Roche Diagnostics, Basel, Switzerland), where LDH catalyzes the following reaction: pyruvate + NADH + H^+ → L-lactate + NAD^+. The initial oxidation velocity of NADH is directly proportional to the catalytic activity of LDH, which is measured by recording absorbance reduction at 340 nm. This assay is optimized by the manufacturer according to the Deutsche Gesellschaft für Klinische Chemie, and is calibrated on the reference lactate-pyruvate assay standardized by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).[25,26] Intra- and inter-assay coefficient of variations were <2.3%. The reference values of plasma LDH levels with this assay are 250 to 450 U/L, and are calibrated on the normal range obtained with the IFCC method.[27]

Final Diagnosis

Enrolled patients underwent an urgent aortic imaging examination for final AAS diagnosis or rule-out in the ED. The examination used to confirm or to exclude the diagnosis of AAS was chest and abdomen computed tomography angiography (CTA) or transesophageal echocardiography (TEE). CTA was performed with Lightspeed VCT 64 (GE, Piscataway, NJ) or with Somatom Definition As4 and AS128 (Siemens, Erlangen, Germany) and interpreted by specialized radiologists not involved in the present study. TEE was performed with MyLab 30 (Esaote, Genova, Italy) and HD7 (Philips, Amsterdam, Holland) and interpreted by specialized cardiologists not involved in the present study.

The results of aortic imaging were used to categorize patients as affected by AAS or by an alternative diagnosis (AltD). Two senior emergency physicians established the AAS subtype or a specific AltD in each study patient after review of all ED and hospital records, including medical, radiological, and surgical data. The following diagnoses were considered in the definition of AAS, according to guidelines: Stanford type A and type B ''classic'' AD, IMH, and PAU.[1]

Data Collection

Relevant clinical data including presenting signs and symptoms, medical history, vital signs, and presence/absence of risk factors for AAS as defined in guidelines were collected and annotated during patient evaluation in the ED. A team of 4 emergency physicians blinded to LDH levels reviewed ED and hospital charts and records to obtain data on in-hospital treatment (medical, surgical, and endovascular) and outcome (survival, death, and date of death). Patients with missing data on in-hospital treatment or outcome were annotated.

Statistical Analysis

Dichotomous data were expressed as proportions and compared with Fisher exact test. Continuous data were expressed as mean and standard deviation for normal variables, or as median and interquartile range (IQR) for non-normal variables (including plasma LDH). For normal data, group comparison was performed with unpaired Student *t* test. For non-normal data, group comparison was performed with Mann–Whitney *U* test. The diagnostic performance of plasma LDH was assessed by receiver operated characteristic (ROC) analysis, estimating the area under the curve (AUC). Sensitivity, specificity, negative/positive predictive values (NPV, PPV), and negative/positive likelihood ratios (LR−, LR+) were computed with their 95% confidence interval (95% CI).

The following variables were evaluated in univariate analysis for association with mortality: female gender, age ≥ 70 years, female gender, hypertension, diabetes, smoke, chest pain, back pain, abdominal pain, syncope, Marfan syndrome, family history of AAS, aortic valve disease, recent aortic manipulation, known thoracic aortic aneurysm, severe pain, abrupt pain, tearing pain, pulse deficit, neurologic deficit, new diastolic murmur, hypotension, surgical intervention, endovascular intervention, and LDH ≥ 450 U/L. The association of categorical variables with in-hospital mortality was compared using the Pearson χ^2 test. We selected for stepwise multivariable logistic regression the variables showing in univariate analysis at least a trend in association with mortality ($P < 0.20$ by Pearson χ^2 test). The calibration of the multivariable model was evaluated by the Hosmer–Lemeshow goodness-of-fit test.[28] In-hospital mortality

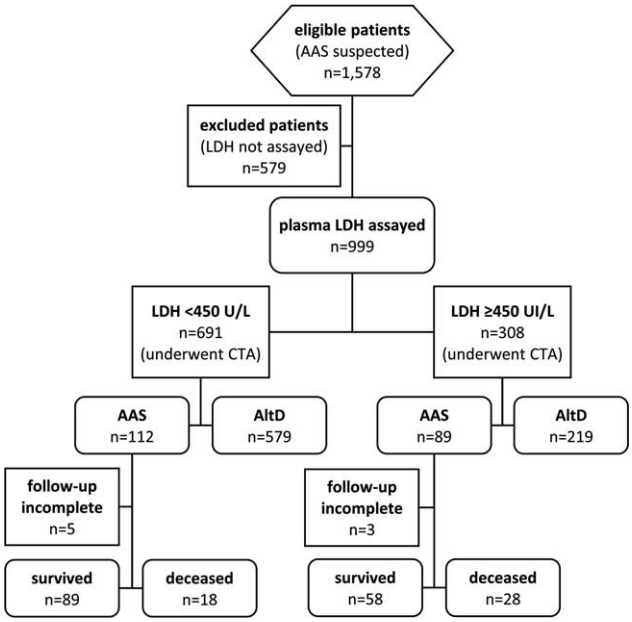

FIGURE 1. Flow diagram of the study. AAS = acute aortic syndrome, AltD = alternative diagnosis, CTA = computed tomography angiography.

in different patient groups was evaluated and compared by standard Kaplan–Meier plots and log-rank test. *P* values were 2-sided, and a *P* value < 0.05 was considered as statistically significant. Analysis was performed with the SPSS statistical package 17.0 (SPSS Inc., Chicago, IL) and Prism 5.0 (GraphPad Software, San Diego, CA).

RESULTS

Study Population

In the study period, 1578 consecutive patients satisfied inclusion criteria defining clinical suspicion of AAS. Plasma LDH was assayed in a convenience sample of 999 patients (Figure 1). The final diagnosis was AAS in 201 (20.1%) patients, while an AltD was made in 798 (79.9%) patients. Table 1 reports the prevalence of AAS subtypes and AltD in the study population. Patients with AAS and patients with AltD were similar in their demographic characteristics, except from a higher prevalence of smokers in patients with AAS (Table 2). Back pain and signs/symptoms of possible perfusion deficit were more prevalent in patients with AAS than in patients with AltD, while blood pressure was significantly lower in patients with AAS.

LDH Levels

Median time from symptom onset to sampling time was 4 h (IQR 2–12) in patients with AAS and 6 h (IQR 2–24) in patients with AltD ($P = 0.043$). Median plasma LDH at presentation was 424 U/L (IQR 367–557) in patients with AAS and 383 U/L (IQR 331–460) in patients with AltD ($P < 0.001$, Figure 2A). Among patients with AAS, median LDH level was 443 U/L (IQR 380–559) in patients with Stanford type A AD, 408 (IQR 336–500) in patients with Stanford type B AD, 424 U/L (IQR 342–561) in patients with IMH, and 341 U/L (IQR 321–375) in patients with PAU ($P < 0.001$, Figure 2B). In patients without AAS, no significant differences were found in LDH levels among different alternative diagnoses (data not shown). Patients with AAS also presented increased levels of white blood cell count, troponin T, creatinine, and D-dimer, and lower levels of hemoglobin and fibrinogen, compared to patients with AltD (Supplementary Table 1, http://links.lww.com/MD/A701).

TABLE 1. Final Diagnosis in Study Patients

Final Diagnosis	n	%
Acute aortic syndrome	201	20.1
Stanford type A aortic dissection	115	11.5
Stanford type B aortic dissection	51	5.1
Intramural aortic hematoma	30	3.0
Penetrating aortic ulcer	5	0.5
Alternative diagnosis	798	79.9
Musculoskeletal chest pain	388	38.8
Acute coronary syndrome*	90	9.0
Gastrointestinal disease	88	8.9
Syncope*	60	6.0
Pericarditis	30	3.0
Pneumonia/pleuritis	14	1.4
Ischemic stroke*	22	2.2
Limb ischemia*	15	1.5
Pulmonary embolism	13	1.3
Other diagnoses	78	7.8

* Not related to acute aortic syndrome.

TABLE 2. Demographic and Clinical Characteristics of Study Patients Classified by Final Diagnosis

	AAS (n = 201)	AltD (n = 798)	*P* Value
Demographics			
Female gender	72 (35.8)	275 (34.5)	0.13
Age, y	69 ± 12	67 ± 15	0.05
Medical history			
Hypertension	130 (64.7)	522 (65.4)	0.85
Smoke	62 (30.8)	185 (23.2)	0.024
Diabetes	17 (8.5)	93 (11.7)	0.20
Clinical presentation			
Chest pain	118 (58.7)	491 (61.5)	0.46
Back pain	80 (39.8)	241 (30.2)	0.009
Abdominal pain	50 (24.9)	167 (20.9)	0.23
Syncope	30 (14.9)	109 (13.7)	0.64
Perfusion deficit	54 (26.9)	58 (7.3)	<0.001
Systolic blood pressure, mm Hg	131 ± 37	143 ± 29	<0.001
Diastolic blood pressure, mm Hg	76 ± 20	82 ± 14	<0.001
Heart rate, bpm	78 ± 20	79 ± 17	0.33

Values are reported as mean ± standard deviation for continuous variables, or as absolute number and percent value (in brackets) for dichotomic variables.

AAS = acute aortic syndrome, AltD = alternative diagnosis, bpm = beats per minute.

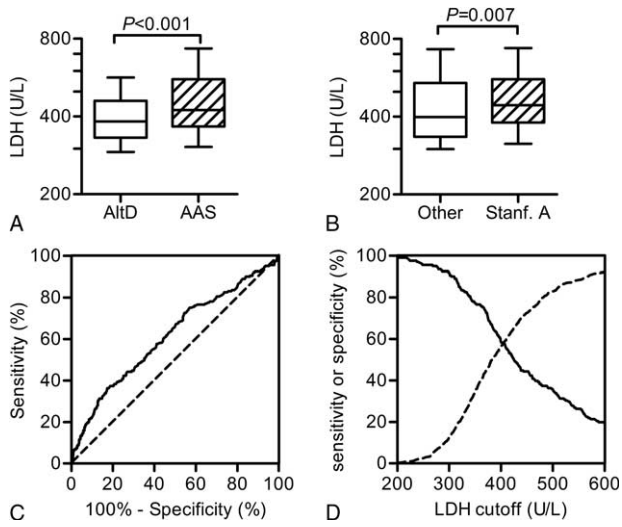

FIGURE 2. Plasma LDH distribution and diagnostic performance in study patients. (A) Box-whisker graph of LDH in patients with final diagnosis of acute aortic syndrome (AAS) or alternative diagnosis (AltD). (B) Box-whisker graph of LDH in patients with final diagnosis of Stanford type A aortic dissection (Stanf. A) or other forms of AAS (Stanford type B aortic dissection, intramural hematoma, and penetrating aortic ulcer). For A and B, central lines represent median value, boxes represent interquartile range, and whiskers the 10th to 90th percentile range. Group comparison was performed with Mann–Whitney nonparametric *U* test. Data are presented in a $\log_2$ scale. (C) Receiver operated characteristic curve of LDH for the diagnosis of AAS. (D) Plots of sensitivity (continuous line) and specificity (dashed line) of LDH for the diagnosis of AAS using different cutoffs. LDH = lactate dehydrogenase.

TABLE 3. Characteristics of Patients With Acute Aortic Syndrome Classified According to Plasma LDH Levels (Cutoff 450 U/L)

Variables	LDH < 450 U/L (n = 112)	LDH ≥ 450 U/L (n = 89)	*P* Value
Demographics and medical history			
Female gender	30 (27)	42 (47)	0.001
Age, y	69 ± 12	70 ± 13	0.76
Hypertension	76 (68)	54 (61)	0.29
Diabetes	11 (10)	6 (7)	0.44
Smoke habit	40 (36)	22 (25)	0.09
Clinical presentation			
Chest pain	72 (64)	46 (52)	0.07
Back pain	53 (47)	27 (30)	0.015
Abdominal pain	25 (22)	25 (28)	0.35
Syncope	14 (13)	16 (18)	0.28
Perfusion deficit	48 (43)	46 (52)	0.21
Systolic blood pressure, mm Hg	136 ± 38	125 ± 35	0.038
Diastolic blood pressure, mm Hg	79 ± 19	73 ± 22	0.043
Heart rate, bpm	77 ± 19	79 ± 20	0.45

Values are reported as mean ± standard deviation for continuous variables, or as absolute number and percent value (in brackets) for dichotomic variables. For continuous variables, *P* value was obtained by Student *t* test. For dichotomic variable, *P* value was obtained by Fisher exact test. Perfusion deficit was defined as presence of ≥1 of the following findings: pulse deficit, systolic blood pressure differential (>20 mm Hg), neurological deficit, hypotension, or shock state.
LDH = lactate dehydrogenase.

Diagnostic Accuracy of LDH

ROC analysis was used to evaluate the diagnostic performance of plasma LDH for AAS (Figure 2C). The AUC of LDH was 0.61 (95% CI 0.57–0.66, $P < 0.001$). Diagnostic sensitivity and specificity values associated with different plasma LDH cutoffs are presented in Figure 2D. Using the higher normality cutoff of 450 U/L (Figure 1), the sensitivity of LDH for the diagnosis of AAS was 44% (95% CI 37–51), the specificity was 73% (95% CI 69–76), the PPV was 29% (95% CI 24–34), the NPV was 84% (95% CI 81–86), the LR+ was 1.61 (95% CI 1.33–1.95), and the LR− was 0.77 (95% CI 0.67–0.87). For the diagnosis of Stanford type A AD, the sensitivity of LDH (cutoff of 450 U/L) was 50% (95% CI 40–59), the specificity was 72% (95% CI 69–75), the PPV was 19% (95% CI 14–23), the NPV was 92% (95% CI 89–94), the LR+ was 1.75 (95% CI 1.42–2.17), and the LR− was 0.70 (95% CI 0.58–0.85).

We next evaluated the demographic and clinical profile of AAS patients presenting with increased plasma LDH to the ED (Table 3). Female gender was more prevalent in AAS patients with LDH ≥ 450 U/L. AAS patients with LDH ≥ 450 U/L were less likely to present with back pain and more likely to present with perfusion deficit. Systolic and diastolic blood pressures were significantly lower in patients with LDH ≥ 450 U/L. Furthermore, AAS patients with LDH ≥ 450 U/L showed significantly higher levels of white blood cell count, liver enzymes, creatine kinase, troponin T, international normalized ratio, and D-dimer levels than AAS patients with LDH <450 U/L (Supplementary Table 2, http://links.lww.com/MD/A701). Stanford type A AD was diagnosed in 33 of 51 (64.7%) patients with LDH ≥ 450 U/L and in 82 of 150 (54.7%) in patients with LDH < 450 U/L ($P = 0.25$).

Association of LDH Levels With In-Hospital Mortality

Follow-up regarding in-hospital outcome was complete for 193 of 201 (96%) patients with AAS (Figure 1). Median follow-up was 11 days (IQR 7–17). Aortic surgery was performed on 113 patients (89 with Stanford type A AD and 24 with other types of AAS) and endovascular intervention was performed on 18 patients (3 with Stanford type A AD and 15 with other types of AAS). Overall in-hospital mortality for AAS was 23.8%; mortality was 29.1% (32 out of 110) in patients with Stanford type A AD and 16.9% (14 out of 83) in patients with other types of AAS ($P = 0.06$). Furthermore, mortality was 24.8% (28 out of 113) in surgically treated patients and 22.5% (18 out of 80) in nonsurgically treated patients ($P = 0.74$).

We next evaluated the association of LDH levels at presentation with in-hospital mortality of AAS. When AAS patients were stratified according to the higher normality cutoff of LDH (450 U/L), in-hospital mortality was 32.6% in patients with LDH ≥ 450 U/L and 16.8% in patients with LDH < 450 U/L (Figure 3A; log-rank 7.6, $P = 0.006$). Furthermore, when AAS patients were stratified according to LDH quartiles, in-hospital mortality was 12% in the first quartile, 18.4% in the second quartile, 23.5% in the third quartile, and 38% in the fourth quartile (Figure 3B; log-rank 11.4, $P = 0.010$).

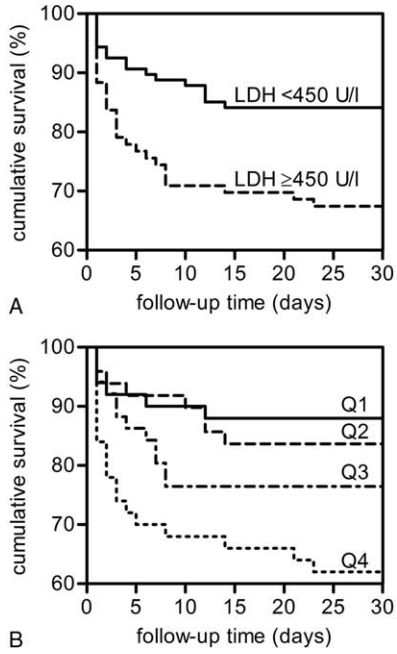

FIGURE 3. In-hospital mortality of study patients (n = 193) with acute aortic syndrome stratified according to plasma LDH at presentation to the Emergency Department. (A) Kaplan–Meier survival curves of patients stratified according to the higher normality cutoff of LDH (450 U/L). (B) Kaplan–Meier survival curves of patients stratified according to quartiles of LDH: Q1 (LDH < 367 U/L), Q2 (LDH 367–424 U/L), Q3 (LDH 425–557 U/L), Q4 (LDH > 557 U/L). LDH = lactate dehydrogenase.

In univariate analysis, LDH $\geq$ 450 U/L was significantly associated with in-hospital death in AAS. Clinical characteristics that also found a significant association with in-hospital death were female gender, age $\geq$ 70 years, back pain, and hypotension (Table 4). Variables showing a trend in association with in-hospital death ($P < 0.20$) were further analyzed in stepwise logistic regression analysis. Only LDH $\geq$ 450 U/L, age $\geq$ 70 years, and hypotension were identified as independent predictors of in-hospital mortality in AAS. The Hosmer–Lemeshow statistic was not statistically significant for departure of observed mortality from predicted mortality ($\chi^2 = 5.78$; df = 8; $P = 0.45$). When data analysis was restricted to 154 of 193 patients with also D-dimer available, also D-dimer > 5.0 μg/mL was found associated with in-hospital death (OR 2.42, 95% CI 1.10–5.38; $P = 0.03$) in univariate analysis. However, D-dimer was not identified as an independent predictor of in-hospital mortality in stepwise logistic regression analysis, while LDH $\geq$ 450 U/L, age $\geq$ 70 years and hypotension remained significant also in this subgroup of patients.

The association of LDH levels with in-hospital mortality was next evaluated in different patient subgroups (Figure 4). Excess mortality was found in association with LDH $\geq$ 450 U/L in elder patients (n = 107, mortality 49.0% with LDH $\geq$ 450 U/L and 20.7% with LDH < 450 U/L; OR 3.68, 95% CI 1.58–8.58; $P = 0.004$), hemodynamically stable patients (n = 146, mortality 28.3% with LDH $\geq$ 450 U/L and 12.8% with LDH < 450 U/L; OR 2.70, 95% CI 1.16–6.28; $P = 0.031$), and in nonsurgically treated patients (n = 80, mortality 36.4% with LDH $\geq$ 450 U/L and 12.8% with LDH < 450 U/L; OR 3.91, 95% CI 1.28–11.88; $P = 0.016$).

DISCUSSION

This is the first study to specifically evaluate the performance of plasma LDH for diagnosis and for prognostic stratification of AAS. Plasma LDH levels were indeed significantly elevated in patients with AAS, but the diagnostic sensitivity of LDH using the standard cutoff of 450 U/L was negligible (44%). The specificity was higher (73%), but also appears hardly suitable for meaningful diagnostic use. A key positive finding of the present study is that LDH levels were positively associated with in-hospital mortality in AAS. Regression analysis identified LDH elevation as an independent predictor of death in addition to well-established variables such as advanced age and hypotension.[28,29] In univariate analysis, also female gender was

TABLE 4. Univariate and Stepwise Logistic Regression Analysis of In-Hospital Death in 193 Patients With Acute Aortic Syndrome

	Univariate			Stepwise Logistic Regression		
Variable	**OR**	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**
Female gender	2.01	1.02–3.96	0.041			
Age $\geq$ 70 y	3.85	1.78–8.34	<0.001	4.05	1.82–8.99	0.001
Smoke	0.56	0.25–1.21	0.136			
Chest pain	0.63	0.33–1.23	0.178			
Back pain	0.37	0.17–0.77	0.007			
Syncope	2.12	0.92–4.86	0.073			
Severe pain	0.63	0.32–1.24	0.178			
Hypotension	2.62	1.28–5.37	0.007	2.52	1.17–5.42	0.018
Endovascular intervention	0.37	0.08–1.68	0.183			
LDH $\geq$ 450 U/L	2.39	1.21–4.70	0.011	2.28	1.11–4.66	0.025

The following variables were evaluated for association with in-hospital mortality: female gender, age $\geq$ 70 y, female gender, hypertension, diabetes, smoke, chest pain, back pain, abdominal pain, syncope, Marfan syndrome, family history of acute aortic syndrome, aortic valve disease, recent aortic manipulation, known thoracic aortic aneurysm, severe pain, abrupt pain, tearing pain, pulse deficit, neurologic deficit, new diastolic murmur, hypotension, surgical intervention, endovascular intervention, and LDH $\geq$ 450 U/L. Only variables showing marginal association ($P < 0.20$) with in-hospital death are shown herein (see the ''Methods'' section).

95% CI = 95% confidence interval of OR, LDH = lactate dehydrogenase, OR = odds ratio.

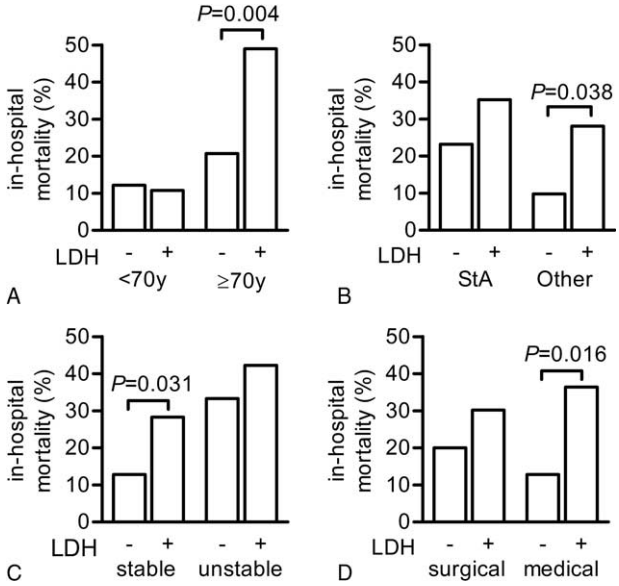

FIGURE 4. Association of plasma LDH levels (cutoff 450 U/L) with in-hospital mortality in patient subgroups. <70y = age < 70 y, ≥70 y = age ≥ 70 y, AAS = acute aortic syndrome, LDH = lactate dehydrogenase, medical = nonsurgical treatment, Other = other types of AAS (Stanford type B aortic dissection, intramural hematoma, and penetrating aortic ulcer), StA = Stanford type A aortic dissection, stable = hemodynamically stable, surgical = surgical treatment, unstable = hemodynamically unstable.

associated with mortality, which was also reported previously and associated with delayed recognition of AD.[29,30] Taken together, our results define LDH as suitable prognostic but not diagnostic biomarker for AAS.

Our finding that increased LDH is associated with poor outcome in AAS is novel, while previous studies have reported an association between LDH and outcome in other acute conditions such as pneumonia, pancreatitis, hemolysis, thrombosis, and bowel ischemia.[14–19] Of note, subgroup analysis indicated that high LDH was associated with increased mortality specifically in patient categories where risk stratification and therapeutic decisions are more controversial, such as patients with AAS other than Stanford type A AD, elderly patients and hemodynamically stable patients. This is relevant, as younger patients with classic type A AD are noncontroversial candidates for urgent surgery. Therefore, our results indicate that LDH as an outcome biomarker would essentially apply to patients without clear-cut surgical indications such as elderly and comorbid patients, which constitute increasingly prevalent challenges for clinicians. In hemodynamically stable and in medically treated patients, for instance, increased LDH could usefully identify individuals with subclinical organ damage at increased risk of complications and death, where advanced treatment options may be beneficial beyond the tube graft.[4]

Previous studies have shown that outcomes for acute AD are highly influenced by presence of organ ischemia and shock.[5,29,31] Other studies have further reported on the correlation between biomarkers and in-hospital mortality in AAS. In particular, increased mortality has been found in patients presenting with high levels of D-dimer and C-reactive protein (CRP), and with low levels of platelets.[6–9] We also found increased D-dimer and lower platelet levels in patients with LDH ≥ 450 U/L, while CRP was not statistically different. Although the present study was not powered to compare the accuracy of different biomarkers for prognostic stratification, in the subgroup of patients with AAS where both D-dimer and LDH were available, LDH ≥ 450 U/L and not D-dimer > 5.0 μg/mL was found as an independent predictor of mortality.

While the present findings identify increased LDH as a potential biomarker of organ malperfusion-related outcome, the actual organ/tissue source of LDH in AAS remains uncertain. The best known tissue sources of LDH are myocardium, skeletal muscle, liver, red blood cells, and bowel. Based on routine biochemical data available only in a minority of study patients, plasma LDH ≥ 450 U/L was indeed associated with significantly higher levels of troponin T, creatine kinase, and liver enzymes, while hemoglobin was unchanged. Therefore, myocardial, skeletal muscle, and liver damage/ischemia all appear as potential sources of plasma LDH rise in AAS, while hemolysis does not appear as quantitatively relevant. Nonetheless, median levels of troponin T, creatine kinase, and liver enzymes fell within normal reference limits in AAS patients with LDH ≥ 450 U/L. The degree of bowel ischemia could not be directly evaluated in our study due to lack of relevant endpoints.

Limitations

A major limitation of study enrolment criteria is that patients where AAS was not suspected by treating physicians were not included, as in previous studies by this and other groups.[22–24] This approach is expected to bias against atypical and mild presentations, at low pretest probability of AAS, where nonetheless rule-in and rule-out biomarkers of AAS may be desirable.[1,2] Second, the present study was performed on a convenience and not on a random sample of 999 patients with suspected AAS, representing 63% of 1578 clinically eligible patients, and attending physicians were not blinded to LDH levels. Although the demographic and clinical characteristics of study patients are in line with the cohorts of previous studies, some degree of selection bias in the present cohort cannot be ruled out.[23,24] Third, the absolute LDH levels found in this study were obtained using a pyruvate-lactate assay, which is different from, albeit calibrated on, the lactate-pyruvate method recommended by the IFCC. Based on available data, in centers using an IFCC method for plasma LDH, 220 U/L may be considered as the high-normality cutoff indicating increased mortality risk in AAS.[27] In addition, plasma LDH kinetics may provide more relevant information rather than a single-point estimate. Indeed, repeated measures of biomarkers appear desirable particularly in patients not undergoing urgent intervention, such as in patients with Stanford type B AD. Finally, as the study was performed in 2 large hospitals functioning as regional hub centers, outcome data might not be generalized to different clinical settings.

CONCLUSIONS

In summary, the results of the present study, performed in a relatively large patient cohort, question the utility of plasma LDH as a diagnostic assay in patients with suspected AAS. Instead, they indicate plasma LDH as a biomarker allowing improved prognostic stratification of patients with AAS, especially if elderly, hemodynamically stable or not surgically treated. In clinical practice, results might implicate that special attention and individualized treatment should be warranted to patients

with AAS presenting with elevated LDH, due to their increased risk of in-hospital death.

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