Diagnostic and Prognostic Value of Very High Serum Lactate Dehydrogenase in Admitted Medical Patients

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ABSTRACT: **Background:** Serum lactate dehydrogenase (LDH) is elevated in various diseases.

Objectives: To analyze serum LDH as a distinguishing clinical biomarker and as a predictor of in-hospital outcome in admitted medical patients.

Methods: We analyzed a cohort of all 158 patients with very high isolated LDH (LDH ≥ 800 IU/ml without concomitant elevations of alanine aminotransferase and aspartate aminotransferase) admitted to our internal medicine department during a 3 year period. Epidemiologic and clinical data, as well as the final diagnosis and outcome were recorded and compared with those of a cohort of all 188 consecutive control patients.

Results: Very high isolated LDH was a distinguishing biomarker for the presence of cancer (27% vs. 4% in the LDH group and controls respectively, $P < 0.0001$), liver metastases (14% vs. 3%, $P < 0.0001$), hematologic malignancies (5% vs. 0%, $P = 0.00019$), and infection (57% vs. 28%, $P < 0.0001$). Very high isolated LDH was a marker for severe prognosis, associated with more admission days (9.3 vs. 4.1, $P < 0.0001$), significantly more in-hospital major complications, and high mortality rate (26.6% vs. 4.3%, $P < 0.0001$). Finally, very high isolated LDH was found in a multivariate regression analysis to be an independent predictor of mortality.

Conclusions: The presence of very high isolated LDH warrants thorough investigation for the presence of severe underlying disease, mostly metastatic cancer, hematologic malignancies, and infection. Moreover, it is a marker for major in-hospital complications and is an independent predictor of mortality in admitted medical patients.

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Serum lactate dehydrogenase, a ubiquitous cellular enzyme, is increased following tissue breakdown. Consequently, elevated serum LDH is present in numerous clinical conditions, such as hemolysis, cancer, severe infections and sepsis, brain infarcts, meningitis, encephalitis, pulmonary infections and infarcts, liver diseases, pancreatitis, muscle injury and myositis, hematologic malignancies, human immunodeficiency virus infections, and many others [1].

As a diagnostic and prognostic marker, serum LDH has previously been reported mainly as a marker of ominous outcome in cancer patients, including a variety of solid tumors [2-7] and hematologic malignancies [8,9]. In addition, the prognostic value of serum LDH was shown in patients with sepsis [10]. However, despite the ubiquitous presence of elevated serum LDH in numerous disease states, it is not known whether high LDH would be a useful diagnostic and/or prognostic marker in patients admitted to the internal medicine ward. We previously showed that simple clinical biomarkers, such as serum C-reactive protein [11], serum uric acid [12] and high platelets count [13], could be valuable in distinguishing diagnoses of admitted general internal medicine patients and could have an important prognostic significance. Likewise, Farah and Makhoul [14] found that CRP level was a reliable marker in the diagnosis and follow-up of pneumonia patients.

Our preliminary observations suggested that a slight to moderate increase in serum LDH in admitted medical patients is very common, but not specific, probably reflecting the ubiquitous distribution of LDH in tissues. In contrast, a very high and isolated serum LDH might be a marker of specific diagnostic groups. Furthermore, whether isolated very high serum LDH would be an independent predictor of in-hospital outcome of admitted medical patients is largely unknown and should be addressed further. To that end, we analyzed a cohort of all consecutive patients with very high isolated serum LDH (defined as serum LDH ≥ 800 IU/ml without elevations of alanine aminotransferase and aspartate aminotransferase > 60 IU/ml) admitted to our department of medicine during a 3 year period. Epidemiologic and clinical data as well as the final diagnosis and outcome were recorded and compared with corresponding data of a cohort of all patients admitted consecutively during a 16 week period.

***The first three authors contributed equally to the study and the manuscript**

LDH = lactate dehydrogenase

CRP = C-reactive protein

PATIENTS AND METHODS

This study was conducted at Tel Aviv Medical Center, the major community and tertiary care university hospital in Tel Aviv (1150 beds). The study population included 346 adult patients (age ≥ 18 years). Of these, 158 consecutive patients, the LDH group, were admitted to the Department of Internal Medicine B during the 3 year period of the analysis with very high isolated LDH levels, defined as serum LDH ≥ 800 IU/L (normal range 208–378 U/L) at admission, with concomitant ALT and AST ≤ 60 (normal range 5–40 U/L) and serum bilirubin ≤ 1.2 mg/dl. Patients with increased LDH levels caused by overt hepatitis and known liver diseases were excluded. Also excluded were patients with explicit tissue necrosis, such as decubitus ulcers, crush injury, rhabdomyolysis, etc. The very high isolated LDH group was compared to a cohort of all 188 consecutive patients (control group) admitted during a 16 week period who did not fulfill the above-defined criteria for isolated very high serum LDH.

DATA COLLECTION

Epidemiologic, clinical and laboratory data were obtained from medical records. All clinical and laboratory parameters analyzed represent values obtained on the first day of admission. Adverse outcome (complications) were defined as the need for intubation, transfer to the intensive care unit, or need for urgent surgery during hospitalization. Mortality rates refer to in-hospital mortality. The study was approved by Tel Aviv Sourasky Medical Center's Helsinki Committee. The main diagnoses or causes of admission, as well as background co-morbidities, were recorded and defined. Each patient was assigned a single cause of admission.

LDH LEVEL

LDH levels (U/L) were routinely measured within the first 24 hours of admission for every patient admitted to the department.

STATISTICAL ANALYSIS

The analysis compared the two groups, LDH and control, with regard to the reason for admission, background co-morbidities, clinical and laboratory parameters, as well as adverse outcome and mortality. The comparison was carried out using the two-sample *t*-test for continuous variables and chi-square test for categorical variables. A multivariate logistic regression model was applied to the data to assess the independent association between each risk factor and mortality after adjustment for other risk factors. The model building methods that were applied were forward selection and backward elimination. Odds ratio and 95% confidence intervals were calculated and the *C* statistics was used to assess goodness of fit of the model ($C = 0.893$). The SAS for Windows version 9.1.3 was used for all statistical analysis.

ALT = alanine aminotransferase
AST = aspartate aminotransferase

RESULTS

EPIDEMIOLOGIC DATA AND BACKGROUND CO-MORBIDITIES

Of the 346 patients in the study, 158 had very high isolated LDH levels (LDH group), and 188 consecutive patients who did not fulfill the defined criteria for isolated very high serum LDH constituted the control group. As shown in Table 1, while the female-to-male ratio was comparable (51.6% and 48.9% women in the LDH and control groups, respectively), the LDH group was older (72.4 ± 16.7 vs 68 ± 17.8 years respectively, $P = 0.02$). The mean admission and maximal serum LDH in the LDH and control groups were 1025.3 and 1168.9 IU/L compared to 441.1 and 446.9, respectively ($P < 0.0001$). In contrast, serum bilirubin, ALT and gamma-glutaryl transpeptidase were comparable, reflecting and confirming the validity of the predefined groups of patients. Of note, the LDH group had a significantly higher serum alkaline phosphatase, but not GGT (not shown). The LDH group was further characterized by significantly higher

GGT = gamma-glutaryl transpeptidase

Table 1. Epidemiologic, clinical and laboratory data of LDH and control groups

	High LDH group N (% of 158 patients)	Control group N (% of 188 patients)	*P* value
Age (yr), mean ± SD	72.4 ± 16.7	68.0 ± 17.8	0.02
Gender: Female	82 (51.6)	92 (48.9)	0.6
Temperature (°C)	37.2 ± 0.9	36.8 ± 0.5	< 0.0001
CRP (mg/L)	102.6 ± 83.7	41 ± 52.0	< 0.0001
Hb (g/dl)	11.5 ± 2.2	12.3 ± 2.1	0.0003
WBC (cells/µl/% PMN)	14.2 ± 1 0.4/79.9 ± 12.7	10.0 ± 4.7/70.0 ± 13.8	< 0.0001
Platelets (cells/µl)	267.4 ± 11.9	266.2 ± 98.4	0.9
BUN (mg/dl)	34.1 ± 28.2	22.9 ± 15.9	< 0.0001
Creatinine (mg/dl)	1.6 ± 1.4	1.5 ± 3.4	0.8
Uric acid (mg/dl)	6.7 ± 6.3	6.3 ± 3.9	0.5
ALT (IU/L)	30.3 ± 23.8	31.3 ± 32.1	0.7
LDH on admission (IU/L)	1025.3 ± 629.2	441.1 ± 112.7	< 0.0001
LDH max (IU/L)	1168.9 ± 884.9	446.9 ± 115.3	< 0.0001
ALP	139.6 ± 169.0	82.9 ± 59.0	< 0.0001
Bilirubin	0.5 ± 0.3	0.6 ± 0.3	0.3
Albumin	34.5 ± 5.7	38.2 ± 5.1	< 0.0001
Days in hospital	9.3 ± 10.6	4.1 ± 5.0	< 0.0001

$P < 0.05$ was significant

CRP = C-reactive protein, Hb = hemoglobin, WBC = white blood cells, PMN = polymorphonuclear cells, PLT = platelets, BUN = blood urea nitrogen, ALT = alanine aminotransferase, ALP = alkaline phosphatase, LDH = lactic dehydrogenase

serum CRP, leukocyte and neutrophil counts, azotemia, lower hemoglobin values, hypoalbuminemia, as well as positive blood and urine cultures (data not shown). In accordance, the length of hospital stay was more than double in the LDH group (9.3 ± 10.6 vs. 4.1 ± 5 days in hospital respectively, $P < 0.0001$).

Analysis of the frequency of background co-morbidities prior to admission revealed that the LDH group was characterized by significantly higher frequencies of background cancer, both solid and hematologic (42.8% vs. 10.6%, and 8.8% vs. 2.1%, respectively, $P < 0.0001$ and $P = 0.006$, for solid and hematologic cancer, respectively). Moreover, very high isolated LDH was a marker of liver metastasis, present on admission in 15.7% of the group, compared to only 1.6% of the control ($P < 0.0001$). In contrast, very high isolated LDH was not a marker of prior cardiovascular diseases, present in 48.4% compared to 72.3% of the control group ($P < 0.0001$). Other background co-morbidities were comparable between the groups (data not shown), reflecting the rather narrow range of diagnoses represented by very high isolated serum LDH.

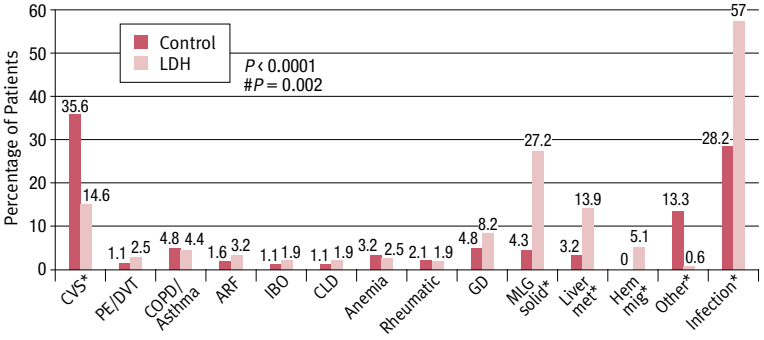
VERY HIGH LDH: A MARKER OF LIMITED GROUPS OF DIAGNOSES

We hypothesized that very high isolated LDH could be a marker of specific groups of diagnoses, in contrast to the rather non-specific slight-to-moderate increase in serum LDH in admitted medical patients, which is very common, probably reflecting the ubiquitous distribution of LDH in tissues. Figure 1 depicts the comparison of frequencies of the main final diagnoses between the LDH and control groups. As shown, very high isolated LDH was a significant marker of infection (57% vs. 28.2% in the LDH and control groups respectively, $P < 0.0001$). Analysis of the frequencies of various infections diagnosed during admissions revealed that although very high isolated LDH was a marker of pneumonia (24.6% vs. 10.1% respectively, $P = 0.0003$), the frequencies of most infections were comparable between the LDH and controls groups (data not shown). Notably, very high isolated LDH was a specific marker for diagnosis of solid tumors (27.2% vs. 4.3%, $P < 0.0001$), liver metastases (13.9% vs. 3.2%, $P < 0.0001$), and hematologic malignancies (5.1% vs. 0%, $P = 0.002$). In accordance, as shown in Figure 1, most of the major diagnostic groups were comparable between the LDH and control groups. Similar to the analysis of background co-morbidities, as described above, cardiovascular causes of admission were significantly less frequent in the LDH group, confirming the notion that very high isolated LDH is a specific marker of limited diagnoses.

VERY HIGH LDH: A MARKER OF SEVERE OUTCOME PARAMETERS

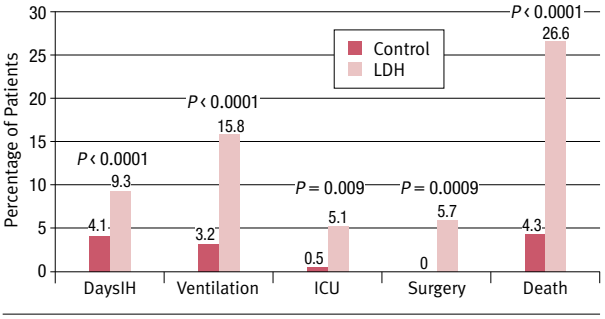
A major aim of the present study was to examine whether very high isolated LDH could be a clinical biomarker for outcome. As shown in Figure 2, the presence of very high isolated LDH indicated a severe and ominous outcome manifested by significantly more admission days (9.3 ± 10.6 vs. 4.1 ± 5.0 days respectively,

Figure 1. Frequencies comparison of main causes for admission. The percentage of patients in the LDH and control groups admitted with each admission cause is shown. The diagnoses were CVS (cardiovascular diseases: coronary artery disease, acute coronary syndrome, chest pain, heart failure, arrhythmia, hypertension, stroke, etc.). Other diagnoses included non-specific chest pain, vertigo, procedures (kidney biopsy, pacemaker implantation), fall, seizure, peptic ulcer disease, hemoptysis



PE/DVT = pulmonary embolism and/or deep vein thrombosis, COPD/Asthma = exacerbation of chronic obstructive lung disease and asthma, ARF = acute renal failure and any worsening of chronic kidney disease, IBD = inflammatory bowel diseases, CLD = chronic liver disease and complications (peritonitis, encephalopathy, ascites, etc.), Anemia (Hb < 10 g/dl), Rheumatic = rheumatologic inflammatory disease (rheumatoid arthritis, lupus, other connective tissue diseases, vasculitis), GD = general deterioration, MLG solid = solid malignancy diagnosed during admission, Liver met = liver metastases, Hem mlg = hematologic malignancies, infection = all infections that were the main cause of admission.

Figure 2. Comparison of main outcome parameters. Shown here is the percentage comparison of several outcome parameters (such as need for intubation and mechanical ventilation), the number of patients transferred to intensive care units or to immediate operation, and the mortality rate. DaysIH means comparison of the number of days of admission between the groups. The *P* values are shown for each comparison. $P < 0.05$ is significant



$P < 0.0001$), a substantial number of patients who required intubation (15.8% vs. 3.2% respectively, $P < 0.0001$), transfer to an ICU (5.1% vs. 0.5% respectively, $P = 0.009$), and in-hospital surgery (5.7% vs. 0% respectively, $P = 0.0009$). Moreover, mortality was very high in the LDH group, with a rate of 26.6% as compared to only 4.3% in the controls ($P < 0.0001$).

Finally, as shown in Table 2, a multivariate regression analysis revealed that very high isolated LDH was an independent

ICU = intensive care unit

Table 2. Isolated very high LDH: an independent risk factor for in-hospital mortality: multivariate regression analysis

Parameters found to be significant by final elimination*	Odds ratio for mortality	95% confidence limits	*P* value
Very high isolated LDH	2.9	1.1–7.9	0.03
Age	1.05	1.01–1.09	0.008
% PMN	1.08	1.01–1.09	0.003
Serum albumin	0.85	0.7–0.9	0.0002

*The multivariate regression analysis was performed with all significant prognostic factors as described in detail in the text. Similar results were found in both forward and backward eliminations

LDH = lactic dehydrogenase, % PMN = percentage of neutrophils

risk factor for in-hospital mortality (odds ratio for mortality 2.95, confidence limit 1.1–7.9, $P = 0.03$). This independent prediction for mortality was found both in forward and backward elimination models (The prognostic parameters were: the presence of positive blood cultures, urine cultures, age and gender, temperature, serum hemoglobin, platelet counts, serum CRP, leukocyte counts, percentage of neutrophils, serum blood urea nitrogen, serum uric acid, serum albumin and serum alkaline phosphatase), with a very high *C* (fitness of the statistical model) of 0.893. Moreover, in this regression analysis, very high isolated LDH was a risk factor for mortality independent of serum CRP and uric acid, previously established clinical prognostic biomarkers [11,12]. Notably, and as expected, high serum albumin was significantly and inversely correlated with mortality.

DISCUSSION

The clinical burden imposed on the departments and wards of general internal medicine nowadays is extremely heavy. Thus, the mission of providing excellent up-to-date diagnosis and care of complex patients with myriad co-morbidities, within a short hospital stay and limited budget, is challenging. Simple clinical biomarkers that are both inexpensive and widely available would be invaluable to the clinician. We have previously shown that simple clinical biomarkers, such as serum CRP [11], serum uric acid [12] and high platelet count [13], could be beneficial for distinguishing between the diagnoses of admitted general internal medicine patients and could have an important prognostic significance. In contrast, high serum LDH is generally considered not helpful diagnostically [15].

In the present study we challenged this notion, as the current data show that very high isolated LDH is a valuable and significant simple clinical biomarker and that its presence should alert the clinician to a thorough investigation of the patient for the presence of severe underlying disease, mainly metastatic cancer, hematologic malignancies, and infection. Moreover, the present data show that very high isolated LDH is a marker for major in-hospital complications and is an independent predictor of mortality in admitted medical patients.

Moreover, the present study is unique, and to the best of our knowledge the first, to assess the diagnostic and prognostic value of very high isolated LDH as a clinical biomarker in a cohort of consecutive in-hospital internal medicine patients, directly comparing them to similar patients without very high isolated LDH. Our major hypothesis was that unlike the common non-specific slight to moderate increase in serum LDH in admitted medical patients, reflecting the ubiquitous distribution of LDH in tissues, a very high and isolated serum LDH might be a marker of specific groups of diagnoses, mostly severe infections and advanced cancer. Accordingly, we assumed that the finding of very high isolated LDH in admitted medical patients is a marker of worse prognosis. As shown, the data of the present study confirm these assumptions.

The exact mechanisms that direct the biochemical phenotype of patients with very high isolated LDH is unknown. Severe infection, liver metastases and/or infiltration with malignant hematologic cells might inflict direct and cytokine-mediated tissue damage, inducing LDH release, frequently together with elevation of serum alkaline phosphatase, a known marker of liver infiltration and metastasis [16]. Indeed, as shown in Table 1, of all the liver enzymes, only alkaline phosphatase was significantly higher in the LDH group. Interestingly, a marked concomitant increase in liver transaminases is not part of this phenotype, in contrast to hepatitis where all liver enzymes are increased [17]. It is also possible that the isolated LDH elevation was due to the breakdown of hematopoietic cells [18] and/or damage to lung tissue [19], as the very high isolated LDH phenotype was a marker of pneumonia but was comparable in other infection types. In the present study we could not address the intriguing question of what fraction(s) of LDH is elevated [20], which might give a pathogenic clue to the presence of the phenotype of very high isolated LDH in the limited clinical conditions shown here.

Whatever the mechanisms that mediate the phenotype of LDH, the present data show that very high isolated LDH is an important distinguishing marker for the presence of a limited list of underlying diseases, mostly infections, particularly pneumonia, cancer (27% vs. 4%, in the LDH group and controls respectively, $P < 0.0001$), liver metastases (14% vs. 3%, $P < 0.0001$), and hematologic malignancies (5% vs. 0%, $P = 0.00019$). In contrast, cardiovascular diagnoses were 2.5 times more common in the control group. Of note, the regression analysis [Table 2] showed that serum albumin was also a significant prognostic factor, though inversely correlated to LDH as higher levels were correlated with lower mortality. Accordingly, as shown in Table 1, the LDH group had a significantly lower serum albumin. Altogether, the data indicate that very high isolated LDH in admitted medical patients is a marker of restricted underlying diseases and co-morbidities.

Another aim of the present study was to examine whether very high isolated LDH is a clinical biomarker for outcome. Previous reports have already shown that serum LDH is a marker of ominous outcome in various types of cancer [2-7], hematologic malignancies [8,9], and sepsis [10]. However, to the best of our knowledge, the present study is the first to show that very high isolated LDH is a marker for major in-hospital complications and is an independent predictor of mortality in admitted medical patients.

In conclusion, the data presented here show that very high isolated LDH is a quite specific phenotype. Its presence warrants thorough investigation for the presence of severe underlying diseases, mostly solid and hematologic malignancies, metastatic liver diseases and severe infections. Moreover, it is an independent predictor of mortality in admitted medical patients.

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