Incidence, Diagnostic Profiles, and Overall Survival in a Cohort with Severely Elevated Serum Lactate Dehydrogenase at a Tertiary-Care Center in the Autonomous City of Buenos Aires

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ABSTRACT

Introduction: Few studies have focused on patients with severely elevated serum lactate dehydrogenase (LDH), which may serve as an excellent biomarker for a specific group of severe diseases.

Materials and Methods: The aim was to analyze the incidence, associated diagnoses, and overall survival of adult patients with markedly elevated LDH (≥1000 U/L) through a retrospective dynamic cohort study conducted at a university hospital in the Autonomous City of Buenos Aires, between January 1, 2011, and December 31, 2018.

Results: The lowest crude cumulative incidence was recorded in 2011, with 3.31 cases (95% CI: 2.39–4.48) per 10,000 adult patients, and the highest in 2016, with 6.1 (95% CI: 4.85–7.47). Of 522 patients, 433 (83%) presented with LDH ≥ 1000 U/L in the context of oncologic disease or shock/multiorgan failure. Among them, 251 (48.08%) had non-oncologic causes (35.06% non-septic shock or multiorgan failure, 29.48% due to sepsis, and 35.46% other causes), while 271 (51.92%) had malignant causes (58.30% metastatic solid tumors and 41.70% hematologic malignancies). Median survival was 32 days (95% CI: 25–44), and one-year survival was 32.61% (95% CI: 28.59–36.68). Patients with solid tumors showed the highest mortality: median survival of 19 days (95% CI: 13-25) and one-year survival of 6.01% (95% CI: 2.98–10.56). Older age, male sex, diagnosis of solid tumor or hematologic malignancy, presence of shock and/or multiorgan failure, LDH > 2000 U/L, and diagnosis during 2011-2012 were independently associated with increased risk of death during follow-up.

Discussion and Conclusion: The identification of severely elevated serum LDH provides valuable diagnostic and prognostic information. In patients with solid tumors, it may be considered a marker of terminal illness, useful for evaluating the initiation of palliative care and the discontinuation of oncologic-specific treatments.

Keywords: lactate dehydrogenase, incidence, survival analysis, shock, neoplasms.

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Incidencia, diagnósticos y supervivencia global de una población con lactato deshidrogenasa sérica extremadamente elevada de un centro de alta complejidad de la Ciudad Autónoma de Buenos Aires

RESUMEN

Introducción: existen pocas investigaciones que hayan abordado a pacientes con lactato deshidrogenasa (LDH) sérica extremadamente elevada, que podría ser un excelente biomarcador de un grupo muy específico de enfermedades graves.

Materiales y métodos: nos propusimos como objetivo analizar la incidencia, los diagnósticos asociados y la supervivencia global de pacientes adultos con LDH extremadamente elevada (≥ 1000 U/L), a través de una cohorte dinámica retrospectiva de un hospital universitario de la Ciudad Autónoma de Buenos Aires, desde el 1 de enero de 2011 hasta el 31 de diciembre de 2018.

Resultados: la menor incidencia acumulada cruda se registró en el año 2011 con 3,31 (IC 95%: 2,39-4,48) por cada 10 000 pacientes adultos, y la mayor en 2016, con 6,1 (IC 95%: 4,85-7,47). De los 522 pacientes con la condición, 433 pacientes (83%) presentaron una LDH ≥ 1000 U/L interpretada en contexto de enfermedades oncológicas o shock/fallo multiorgánico (FMO) de cualquier etiología. De la totalidad de pacientes, 251 (48,08%) presentaron registros de LDH extremadamente elevada explicados por enfermedades no oncológicas (35,06% shock o fallo multiorgánico diferente de sepsis, 29,48% shock o fallo multiorgánico por sepsis y 35,46% por otras causas) y 271 (51,92%) por enfermedades malignas (58,30% tumores sólidos metastásicos y 41,70% tumores oncohematológicos). La mediana de supervivencia de la muestra fue de 32 días (IC 95%: 25-44) y la supervivencia acumulada al año del 32,61% (IC 95%: 28,59-36,68), destacándose los pacientes con enfermedades oncológicas sólidas como los de mayor mortalidad, con una mediana de supervivencia de 19 días (IC 95%: 13-25) y una supervivencia acumulada al año del 6,01% (IC 95%: 2,98-10,56). La edad, el sexo masculino, el diagnóstico de enfermedad oncológica sólida, el diagnóstico de enfermedad oncohematológica, el diagnóstico de shock y/o fallo multiorgánico de cualquier etiología, un rango de LDH superior a 2000 U/L y el diagnóstico de la LDH extremadamente elevada durante los años 2011-2012 se asociaron independientemente a mayor riesgo de muerte en el período de seguimiento del estudio.

Discusión y conclusión: el solo hecho de que los pacientes presenten un registro de LDH sérica extremadamente elevada aportaría una valiosa información a los médicos tratantes desde el punto de vista diagnóstico y pronóstico. En los pacientes con enfermedades oncológicas sólidas podría tratarse de un biomarcador de terminalidad, considerando el inicio de cuidados paliativos y la suspensión de tratamientos oncoespecíficos.

Palabras clave: lactato deshidrogenasa, incidencia, análisis de supervivencia, shock, neoplasias.

INTRODUCTION

Lactate dehydrogenase or lactic acid dehydrogenase (LDH) is an enzyme present in multiple body tissues that is released into the plasma as a result of cellular destruction (whether physiological or pathological). It is a sensitive marker of tissue damage, although not very specific for identifying the affected organ of origin[1]. Serum LDH levels rise in multiple clinical conditions, including hemolysis, cancer, severe infections and sepsis, stroke, meningitis, encephalitis, pulmonary infections and infarctions, liver diseases, pancreatitis, muscle injury and myositis, malignant hematological disorders, infections associated with the human immunodeficiency virus, among many others[2]. It has even been associated with mortality in hospitalized diabetic patients with COVID-19[3]. This enzyme may also increase due to preanalytical causes, such as in vitro hemolysis, and can lead to falsely elevated results[1].

Although it is possible to distinguish five LDH isoenzymes, which allow for some degree of identification of the organ or organs of origin, the determination of isoenzymes is progressively being abandoned due to their relatively low specificity and the availability of more effective markers nowadays[1].

As a prognostic and diagnostic marker, elevated serum LDH above the upper limit of normal (approximately 100 to 220 U/L, with the lactate-to-pyruvate reaction)[1] has previously been reported as a poor prognostic indicator in cancer patients –including a variety of solid tumors[4,5]–malignant hematological diseases, and in septic patients[2]. Likewise, increased LDH has been associated with the early detection of malignancies and with reduced overall survival; the highest risk was observed in patients diagnosed with prostate, colorectal, gastroesophageal, gynecological, and hematological cancers[6]. In addition, a prospective study in septic patients concluded that

mortality is primarily associated with indicators of organ dysfunction (Sequential Organ Failure Assessment and Glasgow Scores), nutritional status, lactic acid, ferritin, and LDH levels[7].

We found only two studies that specifically examined populations with extremely elevated LDH levels, although using different biomarker cut-off points: one by Erez et al. (Israel), which assessed the associated diagnoses and prognosis of a group of hospitalized patients with LDH > 800 U/L, and another by Liu et al. (China), which analyzed overall survival in 311 cancer patients with LDH levels above 1000 U/L and a median survival of 1.7 months[2,8].

Although a mild or moderate increase in serum LDH is very usual in hospitalized patients, it is not specific. Conversely, the study by Erez et al. suggests that an isolated and extremely elevated serum LDH (> 800 U/L) could serve as an excellent biomarker for the presence of cancer, liver metastases, malignant hematologic diseases, and infections, as well as an independent predictor of mortality[2].

When reviewing the scientific literature in search engines from Latin America and the Caribbean, only articles addressing the prognostic role of LDH in specific diseases were found (Legionella pneumonia[9], opportunistic infections in HIV/AIDS[10,11], cytomegalovirus [CMV] pneumonitis[12], severe disseminated histoplasmosis[13], hantavirus[14], dengue[15,16], preeclampsia[17,18], hemolysis-elevated liver enzymes-low platelet count syndrome [HELLP][19], hemolytic uremic syndrome [HUS][20], and various types of oncologic diseases[21-23]), but no comprehensive studies on a population with elevated LDH levels –and even less so on extremely elevated levels– were found.

In the present study, our objective is to analyze the incidence, associated diagnoses, and overall survival of adult patients with extremely elevated LDH levels (≥ 1000 U/L) at a university hospital in the Autonomous City of Buenos Aires, to identify the subgroups with the highest mortality by etiology and determine the factors independently associated with increased risk of death. Our hypothesis is that subgroups of patients may emerge within the cohort who could be considered palliatives.

MATERIALS AND METHODS

Study design, population, eligibility criteria, setting, and LDH measurement

A retrospective dynamic cohort of all adult patients enrolled in the health plan (HP) of a high-complexity hospital in the Autonomous City of Buenos Aires from January 1, 2011, to December 31, 2018, inclusive. Cases were identified as those with at least one LDH result equal to or greater than 1000 U/L, which allowed for the calculation of the annual cumulative incidence and incidence density of patients with this laboratory finding during the 2011-2018 period. Patients were excluded as cases if they had LDH records equal to or greater than 1000 U/L before the study start date, if they had no prior record in the institution but had a similar history from another center, or if they had an LDH record equal to or greater than 1000 U/L that was ruled out due to a preanalytical situation that could produce erroneous or falsely elevated results (in vitro hemolysis).

The associated diagnoses of the cases were described, and a survival analysis was conducted. For the survival analysis, follow-up began from the first record of extremely elevated LDH and continued until death, disenrollment from the health plan, or last contact –whichever occurred first. The institution is a high-complexity center certified by the Joint Commission International, and its laboratory is accredited by the College of American Pathologists. Until October 2012, LDH measurements were performed using the Beckman Coulter LX20® autoanalyzer in the central laboratory and the CX5® analyzer at the Buenos Aires Province site.

From that date onward, the AU5800® and AU480® analyzers were used, respectively (reference range for LDH across all four devices: 140-280 U/L with the reaction in the lactate → pyruvate direction; linearity range for all four devices: 25-14,000 U/L; acceptable coefficient of variation [CVa] < 5.00%).

Data Collection and Ethical Considerations

We conducted a systematic review of the electronic medical records of patients who met the inclusion criteria in collaboration with the institution's Information Management for Research department, using a structured form specifically designed for this purpose by specialists in Internal Medicine. The research protocol was reviewed and approved by the center's Ethics Committee for Research Protocols before its implementation in compliance with ethical standards established at both national and international levels.

Sample Size and Sampling Procedure

In order to estimate the annual cumulative incidence of extremely elevated LDH in the population, we considered a fixed sample size during the evaluation period of approximately 160,000 adult members of the PS. With this sample size, it is possible to estimate a cumulative incidence of, for example, 1 in 10,000, with a 95% confidence interval ranging from 0.0253 to 5.57 per 10,000 individuals. This level of precision is adequate for calculating cumulative incidence. Given that this is a low-frequency finding, all detected cases were included consecutively and used for the remaining objectives.

Statistical Analysis

We described categorical variables as absolute and relative frequencies (percentages). Quantitative variables were presented as mean and standard deviation (SD) or as median and interquartile range, depending on the observed distribution.

When comparing the characteristics of two or more groups, associations between variables were assessed using the Chi-square test, Fisher's exact test, Student's t-test, Wilcoxon test, or Kruskal-Wallis test, as appropriate according to statistical assumptions.

The crude annual cumulative incidence of adult PS patients with severely elevated LDH was estimated for the years 2011 to 2018, considering the number of new cases of severely elevated LDH per year as the numerator. The denominator was the total number of adult PS patients at risk at the beginning of each year. The denominator is the total number of adult patients enrolled in the PS as of January 1 of each year and subtracting the number of surviving patients who had been diagnosed with extremely elevated LDH in previous years. All cumulative incidence rates are expressed per 10,000 individuals, with 95% confidence intervals (95% CI) calculated using the exact method.

We estimated the crude incidence density of adult PS patients with extremely elevated LDH for the period 2011–2018. In addition, specific incidence rates were presented by sex (male and female) and age group. Rates were standardized using the standard proposed by the World Health Organization (WHO) [24] and the Argentine population based on the 2010 census [25], by sex and age, using the direct method. The numerator was defined as the number of patients with at least one LDH measurement equal to or greater than 1000 U/L. The denominator was the total person-time at risk (person-years) of all adult patients in the affiliate registry. All incidence densities are reported per 10,000 person-years, along with their respective 95% confidence intervals (95% CI). Mortality in patients with LDH ≥ 1000 U/L was estimated over time using the Kaplan-Meier method. Survival curves were presented by etiology, along with estimated survival at 1, 2, 3, 6, and 12 months, including 95% confidence intervals (95% CI) for all patients with the condition and according to etiology. Median survival was calculated for all patients with extremely elevated LDH and by etiology. Survival curves were compared using the Cox-Mantel test according to etiology. For polytomous categorical variables, multiple comparisons were performed, with adjusted p-values obtained by multiplying the p-values by the number of comparisons, following the Bonferroni method.

A Cox proportional hazards regression model was used to estimate both crude and adjusted hazard ratios (HR), including the variables age, sex, LDH range, year of diagnosis, and etiology. The proportional hazards assumption was assessed in each bivariate analysis using Schoenfeld residuals and graphical evaluation. HRs were reported with their corresponding 95% CI [26].

Probabilities below 5% were considered statistically significant. Statistical analysis was performed using STATA software, version 15® (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) [27].

RESULTS

During the period evaluated, 542 patients older than 18 years with at least one LDH value equal to 1000 U/L or higher were registered. Twenty patients (3.69%) were excluded due to a preanalytical condition of the sample so 522 cases (96.31%) were finally included for analysis. Table 1 describes the baseline and clinical characteristics of patients with LDH ≥ 1000 U/L. The mean age was 70.20 years (SD 16.20), with females accounting for 53.10% of the sample. The median LDH level was 1446 U/L (25th percentile: 1103 U/L; 75th percentile: 2131 U/L). The majority of the samples –37.36%– originated from requests made by the adult emergency center.

Annual cumulative incidence of patients with extremely elevated LDH

In the first year of the follow-up period (2011), per 10,000 Health Plan patients, 3.31 patients (95% CI: 2.39-4.48) had at least one record of extremely elevated LDH (42 cases and 126 767 patients at risk); while in the last study year (2018), per 10 000 patients, 4.93 (95% CI: 3.90-6.20) had it (73 cases and 148 001 patients at risk). In the follow-up period, the lowest cumulative incidence was recorded in 2011, while the highest was recorded in 2016, with 6.1 patients (95% CI: 4.85-7.47) per 10,000 (87 cases and 143 631 patients at risk).

Incidence density of patients with extremely high LDH in 2011-2018

The crude incidence density of adult patients with extremely high LDH from the Health Plan in 2011-2018 was 4.63 (95% CI: 4.25-5.04) per 10 000 person-years, while the specific incidence density in men was 5.44 (95% CI: 4.80- 6.17) and in women 4.09 (95% CI: 3.64-4.60). The specific incidence density rose steadily with age, from 0.86 (95% CI: 0.46–1.61) among individuals aged 20–30 years

Table 1. Characteristics of Patients with LDH ≥ 1000 U/L

Charasteristic (n = 522)	
Age in years (mean and SD)	70.20 (16.20)
Male gender (n and %)	245 (46.90%)
LDH in U/L (median and P25–75)	1446 (1103-2131)
LDH Range (n and %)	
1000-1500 U/L	278 (53.26%)
1501-2000 U/L	96 (18.39%)
2001-7999 U/L	144 (27.59%)
≥ 8000 U/L	4 (0.77%)
Year of LDH Diagnosis (n and %)	
2011-2012	93 (17.82%)
2013-2014	123 (23.56%)
2015-2016	157 (30.08%)
2017-2018	149 (28.54%)
Requesting Department (n and %)	
Central Emergency	195 (37.36%)
Critical Care	134 (25.67%)
General Inpatient	108 (20.69%)
Outpatient	82 (15.71%)
Home Hospitalizatio	3 (0.57%)

to 11.51 (95% CI: 9.93-13.33) in those over 80. The rates standardized by age and sex –using WHO standards and the 2010 Argentine census– were 2.25 (95% CI: 1.62–2.88) and 2.39 (95% CI: 1.75-3.02), respectively.

Etiologies

Table 2 describes the etiologies discriminated by group that potentially explained the extremely elevated LDH records of the patients. 96.20% of patients with solid oncological disease had metastases at the time of reporting the first record of LDH ≥ 1000 U/L. The functional status of patients with solid oncologic disease versus those with oncohematologic disease at the time of presenting the first record of extremely elevated LDH was statistically significantly different (p-value < 0.001), with a functional status 3-4 of 44.94% versus 22.12%, respectively.

Survival analysis of patients with LDH ≥ 1000 U/L (overall and by etiology)

Table 3 presents the median survival and cumulative survival at 1, 2, 3, 6, and 12 months for all patients with extremely elevated LDH, discriminated by etiology (univariate analysis). The survival curve of patients with solid oncologic diseases, who presented higher mortality during the first year of follow-up, was highlighted.

Statistically significant differences in survival were observed among patients with solid tumors, hematologic malignancies, non-oncologic conditions with shock/MOCF, and non-oncologic conditions without shock/MOCF (p < 0.001). When we made multiple comparisons between survival curves by etiology, patients with solid oncologic and oncohematologic diseases showed a behavior significantly different, with higher mortality in favor of the former (p < 0.001), as did patients with non-oncologic non-shock/FMO diseases with the rest of the categories (p < 0.001).

Factors associated with mortality

The variables sex, age, LDH range, year of diagnosis (to indirectly analyze progress in health technologies), and etiology were statistically significantly associated with mortality in both the bivariate and multivariate analyses (Table 4). The multiple regression model indicates that etiology is the variable most strongly associated with mortality, with patients diagnosed with solid oncologic diseases showing the highest risk.

Análisis de supervivencia de pacientes con enfermedades oncológicas sólidas tratados vs. no tratados, luego de presentar el primer registro de LDH extremadamente elevada

Of 158 patients with solid oncologic diseases in the sample, after presenting the first record of extremely elevated LDH, 116 patients (73.42%) did not receive oncospecific treatment, while 42 patients (26.58%) did. The median survival and cumulative survival at one year for untreated patients was 12 days (95% CI: 9-16 days) and 2.09% (95% CI: 0.43-6.43), respectively. On the other hand, the same analysis in treated patients was 69 days (95% CI: 47-130 days) and 16.67% (95% CI: 7.33-29.27), respectively. We observed statistically significant differences in the sur-

Table 2. Breakdown of the etiologies of patients with extremely elevated LDH

Etiologyc	n (%)
Solid tumors	**158 (30.27%)**
Breast	27 (17.09%)
Prostate	21 (13.29%)
Lung	20 (12.66%)
Colon and small intestine	19 (12.03%)
Strong suspicion (no biopsy)	16 (10.13%)
Uterus and ovary	11 (6.96%)
Unknown primary tumor	10 (6.33%)
Skin tumors	9 (5.70%)
Esophagus and stomach	8 (5.06%)
Kidney and urinary tract	8 (5.06%)
Pancreas	3 (1.90%)
Testicle	3 (1.90%)
Liver and billiary tract	3 (1.90%)
Hematologic neoplasms	**113 (21.65%)**
Non Hodgkin lymphoma	52 (46.85%)
Acute myeloid leukemia	22 (19.82%)
Chronic leukemias	11 (9.91%)
Acute lymphoblastic leukemia	8 (7.21%)
Primary myelofibrosis	8 (7.21%)
Multiple myeloma and other dyscrasias	6 (5.41%)
Other chronic myeloproliferative disorders	3 (2.70%)
Hodgkin lymphoma	1 (0.90%)
Non oncologic	**251 (48.08%)**
Shock multiorgan failure unrelated to sepsis	88 (35.06%)
Sepsis/septic shock or multiorgan failure due to sepsis	74 (29.48%)
Megaloblastic anemia	
Ischemia of a specific organ	19 (7.57%)
Microangiopathic hemolytic anemia	19 (7.57%)
Autoinmune hemolytic anemia	17 (6.77%)
Rhabdomyolysis	10 (3.98%)
Hepatitis	10 (3.98%)
Other causes	9 (3.59%)
	5 (2.00%)

*1 case of hemolytic anemia due to a prosthetic valve, 1 case of adult-onset Still's disease, 1 case of hemophagocytic syndrome, 1 case of status epilepticus, and 1 case of pancreatitis.
The Kaplan-Meier plot of patients with extremely elevated LDH by etiology is seen in Figure 1.

Table 3. Survival analysis of patients with extremely elevated LDH, overall and by etiology

Survival Analysis	Overall (n=522)	Solid Tumors (n=158)	Tumors Hematologic (n=113)	Shock/MOF (n=162)	Other Causes (n=89)
Median survival in days (CI 95%)	32 (25-44)	19 (13-25)	66 (28-148)	9 (4-22)	P25 1143 días
Cumulative survival in % Cumulative survival in % (CI 95%)					
At one month	51.06 (46.69-55.26)	38.91 (31.29-46.45)	55.61 (45.96-64.22)	38.27 (30.81-45.68)	86.52 (77.48-92.11)
Al two months	43.93 (39.63-48.14)	24.24 (17.86-31.17)	50.23 (40.67-59.04)	36.42 (29.07-43.79)	–
At three months	40.40 (36.17-44.59)	16.59 (11.26-22.81)	44.75 (35.38-53.67)	35.78 (28.47 - 43.14)	84.27 (74.89-90.37)
At six months	35.85 (31.72-39.98)	10.69 (6.45-16.14)	36.53 (27.68-45.41)	34.48 (27.25-41.81)	81.98 (72.27-88.55)
At one year	32.61 (28.59-36.68)	6.01 (2.98-10.56)	31.90 (23.45-40.65)	33.14 (25.99-40.45)	79.65 (69.66-86.66)

MOF: multiple organ failure

P25: 25th percentile

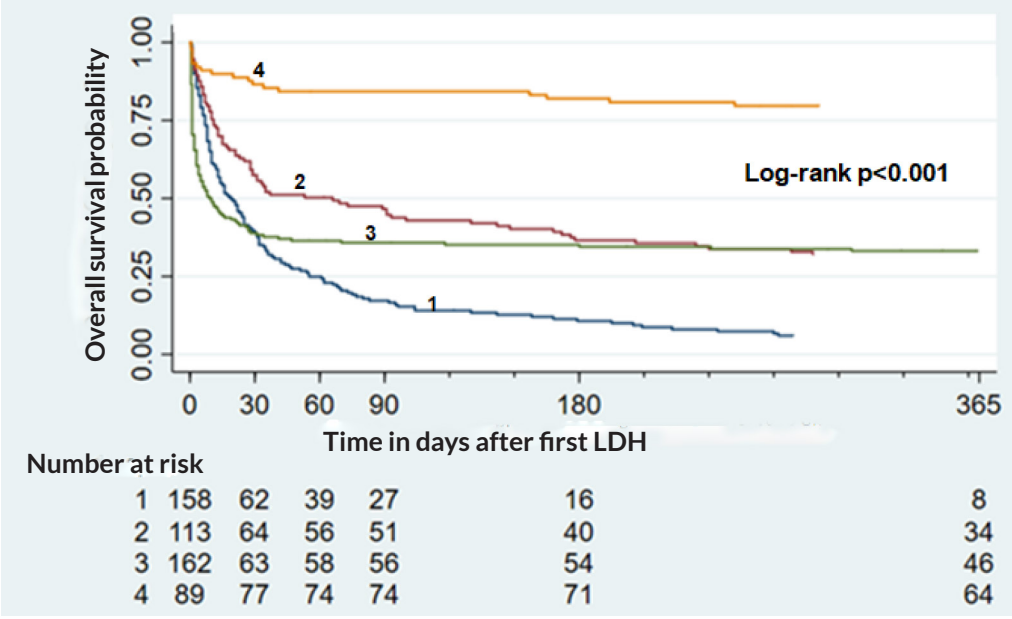

Figure 1. Kaplan-Meier plot of the estimated survival curves of patients with extremely elevated LDH levels by etiology subgroup.1: Patients with solid oncologic diseases; 2: Patients with hematologic malignancies: 3: Patients with shock/multiorgan failure of any origin; 4: Patients with other causes.

vival of both groups (p < 0.001). The only variable that was significantly different between groups was functional status (p < 0.01): untreated patients had a higher percentage of functional status 3-4 (untreated 70% vs. treated 44.4%).

DISCUSSION

To the best of our knowledge, this is the first research study to describe the incidence of patients with extremely elevated LDH, making it a novel contribution. The results support the findings previously reported by Erez et al., who consider isolated and extremely elevated serum LDH levels (>800 U/L) as a marker of a group of very distinct severe diseases, in contrast to mild or moderate elevations, which are common among hospitalized patients but lack specificity [2]. Of the 522 patients with extremely elevated LDH analyzed in our study, 433 (83%) had oncologic diseases or shock/multiorgan failure of any etiology.

Unlike the work mentioned above, which emphasizes that most of the causes were advanced cancer and severe infections2, we would like to highlight that –beyond solid and hematologic malignancies– shock or multiorgan failure from any cause is associated with extremely elevated LDH, not only severe infections.

One strength of the study by Erez et al. is the inclusion of a control group, which revealed an in-hospital mortality rate of 26.6% among patients with the condition, compared to 4.3% in those without it. Our study did not include a control group, but it had the benefit of evaluating long-term outcomes and incorporating a palliative care perspective in a few patient subgroups.

Regarding mortality by etiology in patients with extremely elevated serum LDH, we found statistically significant differences between groups. It is worth emphasizing the importance of separating the analysis of patients with solid tumors from those with hematologic malignancies –an approach not explored in as much depth in other similar studies. We hypothesized that survival in these subgroups would differ which our findings ultimately supported (p < 0.001). Liu et al. estimated a median survival of 1.7 months and a one-year cumulative survival of 15.6% for all cancer patients with LDH > 1000 U/L[8]. In our cohort, patients with solid tumors had a median survival of 0.63 months and a one-year cumulative survival of 6.01%, whereas patients with hematologic malignancies had a median survival of 2.2 months and a cumulative survival of 31.90% over the same period. That indicates a more favorable prognosis both in the short and long term, as well as a slower progression of the event in the latter group.

Among the etiologies, patients with solid oncologic diseases stand out as those with the worst prognosis; they may be candidates for palliative care follow-up and oncologic-specific treatments. We cannot say with certainty whether a small subset of patients might benefit

Table 4. Factors associated with mortality in patients with extremely elevated LDH. Bivariate and multivariate analysis

Variable	Crude HR (IC 95%)	p	HR Adjusted (CI 95%)	p
Sex (male	1.32 (1.08-1.62)	0.006	1.23 (1.004-1.51)	0.046
Age (years	1.02 (1.02-1.03)	< 0.001	1.023 (1.02-1.03)	< 0.001
LDH range				
1000-1500 U/L	ref	ref	ref	ref
1501-2000 U/L	1.10 (0.84-1.45)	0.47	1.15 (0.87-1.52)	0.33
> 2000 U/L	1.34 (1.07-1.7)	0.01	1.51 (1.19-1.92)	0.001
Year of diagnosis				
2017-2018	ref	ref	ref	ref
2015-2016	1.12 (0.86-1.47)	0.4	1.06 (0.80-1.39)	0.69
2013-2014	1.00 (0.75-1.34)	0.97	1.03 (0.77-1.39)	0.84
2011-2012	1.48 (1.10-2.00)	0.01	1.44 (1.07-1.95)	0.02
Etiology				
Non oncologic, non shock/MOF	ref	ref	ref	ref
Oncohematologic	5.00 (3.16-8.00)	< 0.001	4.33 (2.70-6.93)	< 0.001
Shock / MOF	5.70 (3.60-8.90)	< 0.001	4.63 (2.93-7.31)	< 0.001
Solid tumors	8.50 (5.40-13.30)	< 0.001	7.47 (4.73-11.82)	< 0.001

1 The multivariate model includes the variables sex, age, LDH range, year of diagnosis, and etiology.

MOF: multiorgan failure; HR: hazard ratio; 95% CI: 95% confidence interval; ref: reference group.

from treatments. The study by Liu et al. identified a small subset of patients with a performance status of 1-2 and reduced LDH levels after two months of treatment who might benefit; however, it does not distinctly differentiate between patients with oncohematologic and solid tumors. To draw definitive conclusions about the role of such treatment in this population, other confounding variables and a more appropriate study design would need further consideration to explore this hypothesis. There has long been recognition of the prognostic role of serum LDH in oncology. LDH is a key enzyme in the energy production process in cancer cells; it catalyzes the conversion of pyruvate to lactate under hypoxic conditions.[26] Due to its role in anaerobic metabolism, cancer cells continue to grow even after their rapid proliferation leading to low oxygen conditions in the tumor microenvironment.[27] Therefore, LDH plays a key role in tumor progression and maintenance and has been considered a therapeutic target.[28,29] LDH levels increase in response to tissue damage and according to the stage of the disease and could serve as a marker of tumor burden in patients with advanced cancer.[30] Higher LDH levels have been associated with shorter survival in several types of cancer.[26]

Patients with shock or multiorgan failure of any origin had, strikingly, the lowest median survival across all etiologies –9 days– indicating a rapid initial occurrence of the event. These patients appeared to exhibit an "all or nothing" pattern during the first month, followed by stabilization, as evidenced by a 30-day cumulative survival of 38.27% and a one-year survival of 33.14%.

Finally, the non-oncologic patients, apart from shock and multiorgan failure, exhibited statistically differentiated survival behavior from the other etiologies and had the best prognosis with a one-year cumulative survival of 79.65%.

Age, male sex, diagnosis of solid oncologic disease, diagnosis of oncohematologic disease, diagnosis of shock and/or multiorgan failure of any cause, an LDH level above 2000 U/L, and diagnosis of extremely elevated LDH during the years 2011-2012 were independently associated with an increased risk of death during the study follow-up period.

One of the weaknesses of our study is that, first, it was a single-center study and may not be representative of the city's population. The sample size is also relatively limited, making it difficult to assess the impact of multiple clinical characteristics on survival and inadequate for conducting subgroup analyses. Moreover, this was a retrospective cohort study, and some data were more difficult to collect. Finally, we did not identify which patients maintained extremely elevated LDH levels and in whom it decreased or normalized after the initial measurement–an aspect that other studies have associated with mortality.

On the other hand, our study also has strengths. Working with a closed population offers the advantage of low follow-up loss, resulting in a more accurate estimation of mortality. Additionally, the use of electronic medical records ensured proper identification of the patients in question, high-quality clinical documentation, and a well-controlled data entry process.

CONCLUSION

The mere fact that patients present with a record of extremely elevated serum LDH could provide valuable diagnostic and prognostic information to treating physicians.

In patients with solid oncologic diseases, a record of extremely elevated serum LDH could be considered a biomarker of terminal status, prompting the initiation of palliative care and the discontinuation of oncologic-specific treatments.

Further studies with designs that include a control group are needed to confirm these hypotheses.

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