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Research Article

Keywords: LDH, Malignancy, Infection, B symptoms

Posted Date: November 20th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11501795/v1

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Additional Declarations: No competing interests reported.

Clinical Significance of Markedly Elevated Lactate Dehydrogenase in Children

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What's Known: Elevated LDH is associated with numerous pediatric conditions, but its diagnostic significance at markedly elevated levels in pediatric literature is poorly defined.

What's New: In hospitalized children with elevated LDH, malignancy became increasingly common with higher LDH levels and older age.

Key words: LDH, Malignancy, Infection, B symptoms

Abbreviations
ALT - Alanine transaminase , ANC - Absolute neutrophil count, CBC - Complete blood count, CI - Confidence interval, CPK - Creatine phosphor kinase, GGT - Gamma-glutamyl transferase, HLH - Hemophagocytic lymphohistiocytosis, LDH - Lactate dehydrogenase, OR - Odds ratio, ULN - Upper limit of normal.

ABSTRACT

Purpose: Markedly elevated lactate dehydrogenase (LDH) occurs in various pediatric conditions, but its association with malignancy remains poorly characterized. We aimed to characterize associated diagnoses and evaluate the relationship between LDH elevation and malignancy alongside clinical and laboratory findings.

Methods: We retrospectively studied children aged 0–18 years hospitalized through the emergency department at a tertiary pediatric center between 2012 and 2022 with LDH ≥1,500 U/L (≥3 times the upper limit of normal). Associations between malignancy and LDH levels, age, complete blood count (CBC) abnormalities, and clinical features were evaluated using odds ratios across cumulative LDH thresholds. Multinomial logistic regression estimated malignancy probabilities across continuous LDH levels.

Results: Among 1,226 children, infection was the most common diagnosis (48%), followed by malignancy (18%; 13% hematologic, 5% solid). Malignancy accounted for 10% of patients with LDH 1,500–2,500 U/L, 46% with LDH >2,500 U/L, and 53% with LDH >5,000 U/L. Malignancy increased with age, from 6% among infants to 38% among children and 39% among adolescents. Among patients with CBC abnormalities, 28% had malignancy, compared with 2% without abnormalities. Of patients with malignancy, 94% had at least one CBC abnormality.

Conclusion: Higher LDH levels were associated with increased likelihood of malignancy, although infection remained the most common diagnosis. Markedly elevated LDH should prompt clinical reassessment and consideration of malignancy alongside other findings.

Introduction

Lactate dehydrogenase (LDH) is a family of NAD+-dependent isoenzymes involved in the final stage of anaerobic glycolysis. Under conditions of limited oxygen availability, LDH catalyzes the conversion of pyruvate to lactate, allowing cells with high metabolic demands, including cancer cells, to maintain glycolytic metabolism. LDH is used as a diagnostic and prognostic marker in various clinical conditions, including liver disease, hemolytic anemia, myopathies, infections, myocardial injury, and malignancy.[1–8]

Studies in adults have demonstrated an association between elevated LDH levels, malignancy, and adverse clinical outcomes.[9] Elevated LDH has been associated with poor prognosis in several malignancies, including hypopharyngeal cancer, melanoma, duodenal adenocarcinoma, lung cancer, and testicular cancer, potentially reflecting increased tumor burden and metabolic activity.[9–12]

Data regarding markedly elevated LDH levels in children are limited, particularly in large cohorts.

Previous pediatric studies have evaluated LDH as a diagnostic or prognostic marker in specific clinical settings. Some have demonstrated associations between LDH levels and malignancy risk groups in acute lymphoblastic leukemia (ALL) or evaluated its diagnostic utility in hematologic malignancies, generally in symptomatic or preselected populations. Other studies have associated elevated LDH with severe complications of respiratory infections, including *Mycoplasma pneumoniae* and adenovirus infection. One study concluded that LDH alone had limited diagnostic utility unless markedly elevated.[13–16]

The aim of the present study was to characterize the diagnoses associated with markedly elevated LDH levels in hospitalized children presenting through the emergency department (ED) and to evaluate the association between LDH elevation and malignancy, both alone and in conjunction with clinical and laboratory findings

Methods and Materials

We retrospectively reviewed the clinical records of all children aged 0–18 years who were hospitalized through the ED at Schneider Children's Medical Center, a university-affiliated tertiary pediatric medical center, over an 11-year period (2012–2022) and had an LDH level ≥3 times the upper limit of normal (ULN), corresponding to ≥1,500 U/L at our institution. This cutoff was selected to minimize the potential contribution of in vitro hemolysis to lower LDH elevations.[17, 18]

LDH elevations occurring following surgical or other mechanical interventions, such as catheterization biopsy, or trauma were excluded. For each patient, demographic characteristics, presenting symptoms, final diagnosis, and laboratory parameters corresponding to the date of the highest recorded LDH level were retrieved from the electronic medical record. Presenting symptoms were reviewed for B symptoms and other symptoms potentially suggestive of malignancy (including prolonged unexplained fever, weight loss, night sweats, lymphadenopathy, hepatosplenomegaly and bone pain). Fever alone was not classified as a B symptom; only prolonged fever (over 5 days) without an identifiable explanation was included in this category.

Laboratory parameters included LDH, and complete blood count (CBC) parameters, including hemoglobin, platelet count, and absolute neutrophil count (ANC). CBC abnormalities were defined using prespecified clinically relevant cytopenia thresholds: platelet count $<100 \times 10^9$/L, ANC $<1.5 \times 10^9$/L, and hemoglobin below age- and sex-specific thresholds according to World Health Organization (WHO) criteria.[19–21]

Final diagnoses were classified into 10 predefined categories: (1) malignancy, further classified as hematologic or solid; (2) hepatic disease; (3) rhabdomyolysis; (4) hemophagocytic lymphohistiocytosis (HLH); (5) bone disease; (6) infectious disease; (7) cardiac disease; (8) non-malignant hematologic disease; (9) other, including conditions following cardiopulmonary resuscitation (CPR) or mechanical injuries not associated with trauma or crush injury, such as drowning or burns; and (10) unknown.

Diagnostic classification was performed manually by pediatricians who reviewed the electronic medical records, including discharge summaries and final diagnoses corresponding to the date of the highest LDH value. When multiple diagnoses were documented, the pediatrician assigned the single diagnostic category considered most representative of the clinical presentation. Each pediatrician independently reviewed several hundred cases and was

unaware of the classifications assigned by the other reviewers. All cases were assigned by only one pediatrician, and under the supervision of the corresponding author Osnat Tausky (OT).

LDH reference ranges at our institution are determined according to the recommendations of the Biochemistry Committee of Clalit Health Services and vary according to age and gender. For cohort selection, we used the highest institutional ULN and included patients with LDH values ≥3 times this threshold (≥3X500U/L ≥1500U/L).

LDH measurements were performed using the Cobas system with a dedicated assay (Roche Diagnostics, Indianapolis, IN, USA). At our institution, LDH is routinely included in blood chemistry panels.

The study was approved by the local institutional review board.

Statistical Analysis

Categorical variables are presented as counts and percentages.

Patients were categorized into three age groups: infants (0–<2 years), children (2–<12 years), and adolescents (12–18 years). The distribution of diagnostic categories was compared across age groups.

The association between LDH level and malignancy was evaluated using cumulative LDH thresholds of ≥1,500, >2,500, and >5,000 U/L. Patients exceeding a higher threshold were therefore also included in the corresponding lower-threshold group. Odds ratios (ORs) were calculated separately for hematologic and solid malignancies compared with other diagnostic categories. Associations between age group and malignancy were similarly evaluated.

A multinomial logistic regression model was used to estimate the probabilities of hematologic malignancy, solid malignancy, and non-malignant diagnoses as a function of LDH level. LDH was entered into the model as an untransformed continuous variable, and predicted probabilities were estimated across the observed range of LDH values.

Additional clinical and laboratory findings included CBC abnormalities involving platelet count, ANC, and hemoglobin; and B symptoms or other predefined clinical features potentially suggestive of malignancy (as specified under methods). For each patient, the number of abnormal clinical and laboratory findings was calculated. The proportion of patients with malignancy was then evaluated according to the number of abnormal findings at

each cumulative LDH threshold. Symptoms and findings were presumed absent unless documented as positive (due to the thorough manual review of each case chart by a trained pediatrician).

Statistical analyses were performed using MedCalc and the Real Statistics Resource Pack for Microsoft Excel.

Results

The initial cohort included 1,478 children with LDH levels ≥1,500 U/L (≥3 times the ULN). Of these, 252 were excluded because LDH elevation occurred following a mechanical or procedural intervention, including surgery or catheterization, and trauma cases. The final study cohort therefore included 1,226 children. Patient diagnoses according to age group are presented in Table 1.

The cohort included 643 males (52%) and 583 females (48%). Patients were categorized into three age groups: 741 infants (60%), 357 children (29%), and 128 adolescents (11%).

Infectious diseases constituted the largest diagnostic category in the overall cohort, accounting for 588 cases (48%). However, the proportion of patients diagnosed with malignancy increased substantially with age. Malignancy accounted for 6% of diagnoses among infants, 38% among children, and 39% among adolescents.

Malignancy was the second most common diagnostic category overall, accounting for 225 cases (18% of the cohort), including 159 hematologic malignancies (13%) and 66 solid malignancies (5%). Non-malignant hematologic disorders and hepatic disease accounted for smaller proportions of the cohort. The remaining patients were classified as having rhabdomyolysis, cardiac disease, hemophagocytic lymphohistiocytosis (HLH), bone disease, or other diagnoses. Bone disease was the least frequent category, with only two cases.

The relative proportions of diagnoses according to cumulative LDH thresholds are presented in Figures 1a–c. Compared with patients with LDH levels of 1,500–2,500 U/L, the odds of hematologic malignancy were higher among patients with LDH >2,500 U/L (OR, 7.62; 95% CI, 5.31–10.93) and increased further among those with LDH >5,000 U/L (OR, 9.91; 95% CI, 6.06–16.22). Similarly, the odds of solid malignancy were higher among patients with LDH >2,500 U/L (OR, 5.94; 95% CI, 3.55–9.94) and among those with LDH >5,000 U/L (OR, 6.63; 95% CI, 3.22–13.64).

The proportion of patients with malignancy increased with increasing LDH thresholds. Among patients with LDH levels of 1,500–2,500 U/L, 10% had malignancy (7% hematologic and 3% solid), compared with 46% among patients with LDH >2,500 U/L (34% hematologic and 12% solid) and 53% among those with LDH >5,000 U/L (40% hematologic and 13% solid).

Figure 2 presents the distribution of diagnoses according to age group. Increasing age was strongly associated with hematologic malignancy. Compared with infants, children had an OR of 13.55 (95% CI, 8.32–22.07), and adolescents had an OR of 17.13 (95% CI, 9.83–30.19) for hematologic malignancy. For solid malignancy, the corresponding ORs were 6.44 for children (95% CI, 3.65–11.38) and 3.78 for adolescents (95% CI, 1.60–8.97), compared with infants.

Of the entire cohort (N=1,226), 767 patients (62%) had at least one predefined CBC abnormality involving hemoglobin, platelet count, ANC, or a combination of these parameters. Among patients with any CBC abnormality, 28% had malignancy (20% hematologic and 8% solid), compared with 2% among patients without these CBC abnormalities (1% hematologic and 1% solid). CBC abnormalities were strongly associated with both hematologic malignancy (OR, 16.67; 95% CI, 8.33–33.33) and solid malignancy (OR, 8.33; 95% CI, 3.45–20.00).

Of the 225 patients diagnosed with malignancy, 212 (94%) had at least one of the predefined CBC abnormalities, and 106 (47%) presented with B symptoms or other predefined clinical features potentially suggestive of malignancy.

Among patients with B symptoms or other predefined clinical features potentially suggestive of malignancy, 44% had malignancy (34% hematologic and 10% solid), compared with 12% among patients without these features (8% hematologic and 4% solid). The presence of these clinical features was associated with both hematologic malignancy (OR, 6.67; 95% CI, 4.67–10.00) and solid malignancy (OR, 3.70; 95% CI, 2.17–6.25).

Figure 3 presents the predicted probabilities of hematologic malignancy, solid malignancy, and non-malignant diagnoses as a function of LDH level, based on the multinomial logistic regression model. LDH was modeled as an untransformed continuous variable. The overall model was statistically significant (χ^2=91.95; P<.0001), demonstrating a significant association between increasing LDH levels and the probability of malignancy. Predicted probabilities were estimated across the observed range of LDH values rather than at a single predefined LDH value.

Figure 4 presents the proportion of patients with malignancy according to the number of abnormal clinical and laboratory findings at each cumulative LDH threshold (≥1,500, >2,500, and >5,000 U/L). The evaluated abnormalities included CBC - ANC, platelet count, hemoglobin, and B symptoms or other predefined clinical features potentially suggestive of malignancy. The proportion of patients with malignancy increased with both increasing LDH thresholds and an increasing number of abnormal clinical and laboratory findings.

Discussion and Limitations

In this large cohort of hospitalized children with markedly elevated LDH levels (≥3 times the ULN), the most common etiologies were infectious diseases and malignancy. Although infectious disease was the most frequent diagnosis overall, increasing LDH levels were associated with an increasing likelihood of malignancy. Whereas the prevalence of malignancy in the general pediatric population has been estimated at 0.3%–1%,[22] and was approximately 0.6% at our institution, malignancy accounted for 10% of patients with LDH levels of 1,500–2,500 U/L, 46% of those with LDH >2,500 U/L, and 53% of those with LDH >5,000 U/L. Increasing age was also strongly associated with malignancy among children with markedly elevated LDH.

LDH reference ranges may vary between institutions according to laboratory methodology, assay characteristics, and population-specific reference values, limiting the generalizability of a single absolute LDH cutoff. To reduce the impact of this variability, we defined marked LDH elevation as ≥3 times the institutional ULN. The use of a relative rather than absolute threshold may facilitate comparison across institutions; nevertheless, differences in laboratory-specific reference ranges should be considered when interpreting our findings.

Our findings suggest that marked LDH elevation without an evident procedural or mechanical explanation may serve as a clinical warning sign for underlying malignancy. However, LDH should not be interpreted in isolation. CBC abnormalities and clinical features suggestive of malignancy were strongly associated with malignancy in our cohort. Among the 225 patients diagnosed with malignancy, 212 (94%) had at least one predefined CBC abnormality, and 106 (47%) presented with B symptoms or other predefined clinical features potentially suggestive of malignancy. Furthermore, the proportion of patients with malignancy increased as the number of abnormal clinical and laboratory findings increased across the evaluated LDH thresholds. These findings emphasize the

importance of integrating the degree of LDH elevation with clinical history and other laboratory findings rather than using LDH alone for clinical decision-making.

Our results are consistent with the limited pediatric literature available. Previous studies investigating LDH in children have generally focused on specific diagnoses, such as acute lymphoblastic leukemia (ALL) or *Mycoplasma pneumoniae* infection, and have demonstrated diagnostic or prognostic value primarily when LDH is considered together with other clinical or laboratory markers[13–16]. One previous study involving a relatively small cohort suggested that LDH alone had limited diagnostic utility unless markedly elevated.[23]

Unlike many previous studies, our cohort was not selected on the basis of suspected malignancy and included a broad range of diagnoses among hospitalized children with marked LDH elevation. Our study therefore provides a broader perspective on the differential diagnosis and potential clinical significance of markedly elevated LDH in children.

Our study has several strengths, including a large pediatric cohort, standardized laboratory methodology, and manual review of diagnoses based on electronic medical records and discharge summaries. Nevertheless, several limitations should be acknowledged. First, this was a retrospective, single-center study conducted at a tertiary pediatric medical center, which may limit generalizability to other settings and patient populations. Second, only hospitalized children were included because hospitalization allowed reliable ascertainment of the final diagnosis. Consequently, the cohort may represent children with more severe or persistent illness, and our findings may not be fully generalizable to children discharged from the ED or managed in general pediatric practice. Third, patients with LDH levels <1,500 U/L were not included; therefore, no conclusions can be drawn regarding the diagnostic utility of LDH at lower levels. Finally, although our analysis incorporated CBC abnormalities and presenting clinical features, other potentially relevant factors, including symptom duration and additional laboratory or imaging findings, were not systematically evaluated.

Overall, our findings suggest that markedly elevated LDH should prompt careful clinical reassessment. Such reassessment should integrate the degree of LDH elevation with the patient's clinical presentation and other laboratory findings, particularly CBC abnormalities and clinical features potentially suggestive of malignancy. In summary, we believe that markedly elevated LDH should be regarded as a supportive marker that warrants careful clinical reassessment rather than as an independent indicator of malignancy. When marked LDH elevation is identified without an evident explanation, reassessment may include revisiting the medical history and physical

examination for B symptoms or other features suggestive of malignancy and obtaining basic laboratory investigations, including a CBC, when appropriate. Although markedly elevated LDH alone is not sufficient to indicate malignancy, it should prompt consideration of malignancy within the differential diagnosis and should be interpreted in conjunction with the patient's clinical presentation and other laboratory findings

References

1. Krieg AF, Rosenblum LJ, Henry JB (1967) Lactate dehydrogenase isoenzymes a comparison of pyruvate-to-lactate and lactate-to-pyruvate assays. Clin Chem 13:196–203

2. Forkasiewicz A, Dorociak M, Stach K, et al (2020) The usefulness of lactate dehydrogenase measurements in current oncological practice. Cell Mol Biol Lett 25:35. https://doi.org/10.1186/s11658-020-00228-7

3. Argiles A, Mourad G, Mion C, et al (1991) Two-Dimensional Gel Electrophoresis of Urinary Proteins in Kidney Diseases. https://doi.org/10.1159/000418766

4. Wróblewski F, Gregory KF (1961) Lactic Dehydrogenase Isozymes and Their Distribution in Normal Tissues and Plasma and in Disease States. Ann N Y Acad Sci 94:912–932. https://doi.org/10.1111/j.1749-6632.1961.tb35584.x

5. Kopperschläger G, Kirchberger J (1996) Methods for the separation of lactate dehydrogenases and clinical significance of the enzyme. J Chromatogr B Biomed Appl 684:25–49. https://doi.org/10.1016/0378-4347(96)00133-8

6. Electrophoretic distribution pattern of lactate dehydrogenase in mouse and human muscular dystrophy - ScienceDirect. https://www-sciencedirect-com.beilinson.idm.oclc.org/science/article/abs/pii/0009898164901081?via%3Dihub. Accessed 26 Nov 2024

7. Drent M, Cobben NA, Henderson RF, et al (1996) Usefulness of lactate dehydrogenase and its isoenzymes as indicators of lung damage or inflammation. Eur Respir J 9:1736–1742. https://doi.org/10.1183/09031936.96.09081736

8. Kawamoto M (1994) Breast cancer diagnosis by lactate dehydrogenase isozymes in nipple discharge. Cancer 73:1836–1841. https://doi.org/10.1002/1097-0142(19940401)73:7%3C1836::aid-cncr2820730710%3E3.0.co;2-7

9. Wu J, You K, Chen C, et al (2021) High Pretreatment LDH Predicts Poor Prognosis in Hypopharyngeal Cancer. Front Oncol 11:641682. https://doi.org/10.3389/fonc.2021.641682

10. Finck SJ, Giuliano AE, Morton DL (1983) LDH and melanoma. Cancer 51:840–843. https://doi.org/10.1002/1097-0142(19830301)51:5%3C840::aid-cncr2820510516%3E3.0.co;2-7

11. Chen Z-H, Qiu M-Z, Wu X-Y, et al (2018) Elevated baseline serum lactate dehydrogenase indicates a poor prognosis in primary duodenum adenocarcinoma patients. J Cancer 9:512–520. https://doi.org/10.7150/jca.22305

12. Petrelli F, Cabiddu M, Coinu A, et al (2015) Prognostic role of lactate dehydrogenase in solid tumors: A systematic review and meta-analysis of 76 studies. Acta Oncol 54:961–970. https://doi.org/10.3109/0284186X.2015.1043026

13. Zahra SSA, Al-Shammary EH, Hameed IM (2021) Serum lactate dehydrogenase level in childhood acute lymphoblastic leukemia. Iraqi J Hematol 10:55. https://doi.org/10.4103/ijh.ijh_4_21

14. Zou M, Zhai Y, Mei X, Wei X (2023) Lactate dehydrogenase and the severity of adenoviral pneumonia in children: A meta-analysis. Front Pediatr 10:1059728. https://doi.org/10.3389/fped.2022.1059728

15. Diagnostic Value of Lactate Dehydrogenase and Uric Acid as Screening Tools for Malignancies in Children - PubMed. https://pubmed-ncbi-nlm-nih-gov.beilinson.idm.oclc.org/35477707/. Accessed 26 Nov 2024

16. Yanhong R, Shuai Z, Dan C, Xiaomin S (2024) Predictive value of lactate dehydrogenase for Mycoplasma pneumoniae necrotizing pneumonia in children based on decision curve analysis and dose–response analysis. Sci Rep 14:9803. https://doi.org/10.1038/s41598-024-60359-1

17. Frank JJ, Bermes EW, Bickel MJ, Watkins BF (1978) Effect of in vitro hemolysis on chemical values for serum. Clin Chem 24:1966–1970. https://doi.org/10.1093/clinchem/24.11.1966

18. Yücel D, Dalva K (1992) Effect of in vitro hemolysis on 25 common biochemical tests. Clin Chem 38:575–577

19. (2024) Guideline on haemoglobin cutoffs to define anaemia in individuals and populations. World Health Organization, Geneva

20. Fioredda F, Skokowa J, Tamary H, et al (2023) The European Guidelines on Diagnosis and Management of Neutropenia in Adults and Children: A Consensus Between the European Hematology Association and the EuNet-INNOCHRON COST Action. HemaSphere 7:e872. https://doi.org/10.1097/HS9.0000000000000872

21. Russo G, Parodi E, Farruggia P, et al (2024) Recommendations for the management of acute immune thrombocytopenia in children. A Consensus Conference from the Italian Association of Pediatric Hematology and Oncology. Blood Transfus 22:253–265. https://doi.org/10.2450/BloodTransfus.501

22. Volberding PA, Spicer CM, Cartaxo T, Aiuppa L (2021) Childhood Cancer and Functional Impacts Across the Care Continuum. National Academies Press, Washington, D.C.

23. Ross AD, Abrahamson E (2011) A review of the use of serum lactate dehydrogenase measurement in patients presenting to the paediatric emergency department. Arch Dis Child 96:A87–A87. https://doi.org/10.1136/adc.2011.212563.202

Statements and Declarations

Conflict of Interest Disclosures:
The authors have no conflicts of interest relevant to this article to disclose.

Funding/Support:
No external funding was secured for this study.

Authors' contributions:

Dr Tausky had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Tausky conceptualized and designed the study, coordinated and supervised data collection, performed the data analysis, and drafted the initial manuscript.

Prof Scheuerman and **Dr Levinsky** provided overall study supervision, contributed to study design and interpretation of the data, and critically revised the manuscript for important intellectual content.

Drs Atias, Mulla, Reisler, Lavie, B. Goldberg, L. Goldberg, Cohen, Katz, Koren, K. De-Levie, and Klinger contributed to data acquisition and interpretation, participated in manuscript revision for important intellectual content, and approved the final manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work

Access to data: Dr Tausky had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics Approval: The study was authorized by the Institutional Review Board of Rabin Medical Center (approval number RMC-0675-22). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its subsequence amendments. Waiver of informed consent was granted due to the retrospective nature of the study.

Tables and Figures

Table 1: Characteristics of Patients with LDH>1,500 U/L, (n=1,226)

Age Group	Infants (0-2 y)	Children (2-12 y)	Adolescents (12-18 y)	**Total**
Diagnosis, n (%)				
Infectious Disease	459 (62)	106 (30)	23 (18)	**588 (48)**
Malignancy - hematological	22 (3)	95 (27)	42 (33)	**159 (13)**
Malignancy - solid	19 (3)	39 (11)	8 (6)	**66 (5)**
Other Disease	88 (12)	54 (15)	20 (16)	**162 (13)**
Unknown Disease	60 (8)	9 (3)	5 (4)	**74 (6)**
Liver Disease	31 (4)	15 (4)	11 (9)	**57 (5)**
Non-malignant Hematological Disease	35 (5)	19 (5)	4 (3)	**58 (5)**
Rhabdomyolysis	6 (0.5)	16 (4)	9(7)	**31 (3)**
Heart Disease	15 (2)	1 (0)	1 (1)	**17 (1)**
Hemophagocytic Lymphohistiocytsis (HLH)	4 (0.5)	3 (1)	5 (4)	**12 (1)**
Bone Disease	2 (0)	0 (0)	0 (0)	**2 (0)**
Total	**741 (100)**	**357 (100)**	**128 (100)**	**1,226 (100)**

Occurrences presented as Number of Cases, Percentage - per age group.

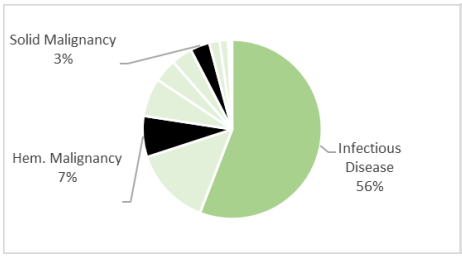


Fig. 1a: 1,500<LDH<2,500, n=970

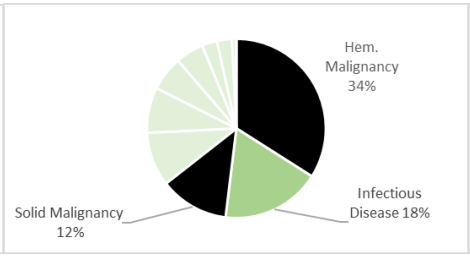


Fig. 1b: LDH>2,500, n=256

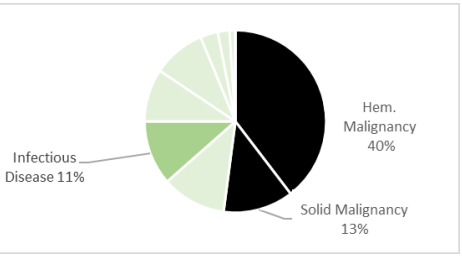


Fig. 1c: LDH>5,000, n=96

Figures 1: Etiologies by LDH Values >1,500 U/L

Figs. 1.a-c show the relative proportions of the different diagnoses according to LDH values - for hematological malignancy vs. non malignancy (OR=7.62, 95% CI=[5.31-10.93], p<0.0001, going up to OR=9.91, 95% CI=[6.06-16.22], p<0.0001), for solid malignancy vs. non malignancy (OR=5.94, 95% CI=[3.55-9.94], p<0.0001, going up to OR=6.63, 95% CI=[3.22-13.64], p<0.0001

Abbreviations: Hem., Hematological

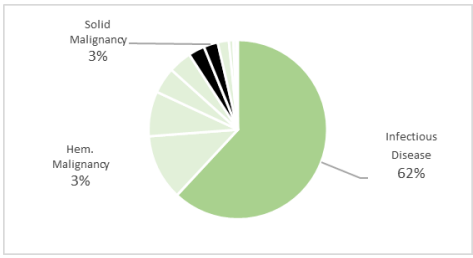


Fig. 2a: Infants (0-2 y) N=741

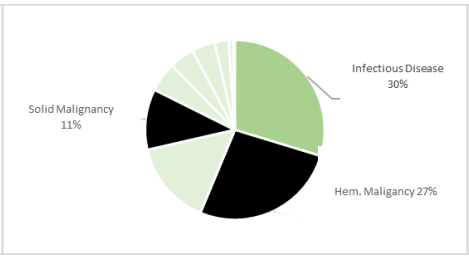


Fig. 2b: Children (2-12 y), n=357

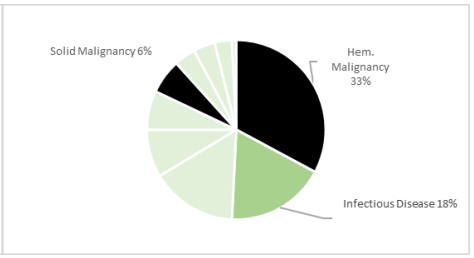


Fig. 2c: Adolescents (12-18 y), n=128

Figures 2: Different Etiologies by Age Group (LDH>1500 U/L)

Figs. 2a-c show the relative distribution of diagnosed diseases by patients' age group: for hematological malignancy vs. non malignancy - Children vs. Infants (OR=13.55, 95% CI=[8.32-22.07], p<0.0001) and Adolescents vs. Infants (OR=17.13, 95% CI=[9.83-30.19], p<0.0001), for solid malignancy vs. non malignancy - Children vs. Infants (OR=6.44, 95% CI=[3.65-11.38], p<0.0001) and Adolescents vs. Infants (OR=3.78, 95% CI=[1.60-8.97], p=0.0024)

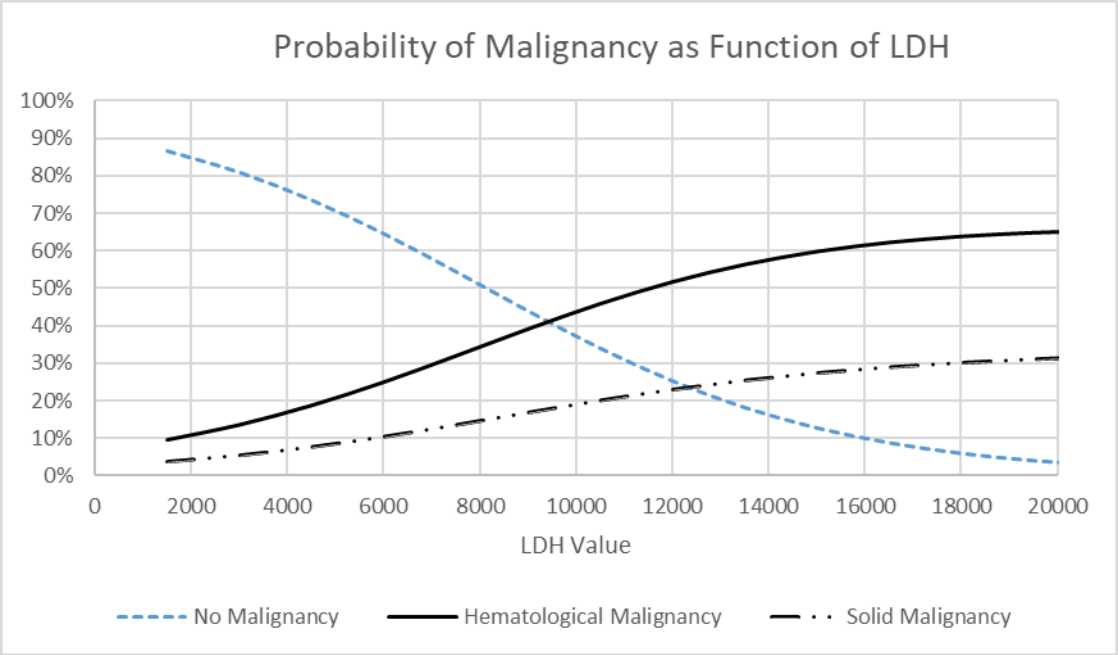


Figure 3: Probabilities of Hematological and Solid Malignancies as Function of LDH Value

By multinomial logistic model for hematological and solid malignancies as function of LDH value (Chi Sq.=91.95, $p<0.0001$ overall and for all coefficients)

Abbreviations: LDH, Lactate dehydrogenase

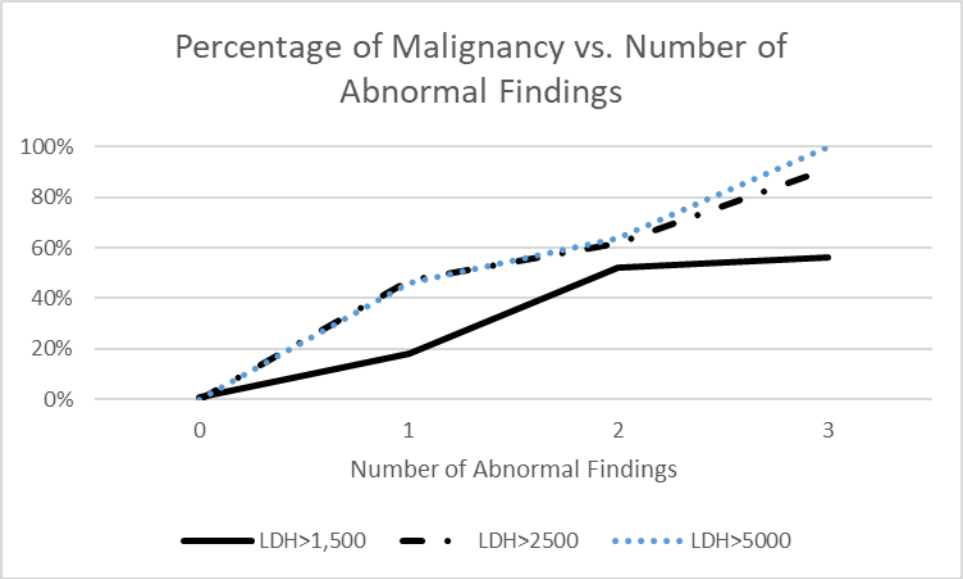


Figure 4: Percentage of Malignancy vs. Number of Abnormal Findings

Abnormal Findings: 1 ANC, 2 Platelets, 3 Hemoglobin, 4 B and other symptoms suggesting malignancy