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Computing tools for analysing the pathological levels of serum transaminases

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Abstract
Aim: Serum transaminases are frequently tested for diagnostic purposes by comparing them with the considered normal values. The aim of this study was to carry out a detailed analysis on the pathological values of serum transaminases, recorded in the medical practice of the Cluj area. *Material and method*: A cross-sectional study was conducted with trainee doctors working in Cluj-Napoca hospitals, between 2004 and 2010. The common database, the descriptive statistic and tools for an extended analysis were conducted in Excel. *Results:* In the survey's cumulative sample of 1 725 hospitalised patients, 52.6% were male, 63.1% from urban area, with a mean age of 28.5 years and hospitalized for 12.7 days on average. During a hospitalization, the serum enzymes were repeated up to 15 times. Median levels ranged from 265 to 960 IU/L for alanine transaminase (ALT) and from 117 to 685 IU/L for aspartate transaminase (AST). The main diagnoses were hepatitis A (51.2% of cases), acute or chronic hepatitis B (17.4%) and C (6%). Levels four times higher than threshold values were reached only in the first quartile for ALT, and from the second in the case of AST. *Conclusion*: The serum transaminases are frequently monitored during a hospitalization, mainly leading to a diagnosis of primary or secondary hepatitis. However, one in six patients remains without a complete diagnosis and for a quarter of patients the diagnosis accuracy is questionable. More evaluations are needed for selecting appropriate measures to improve the diagnostic performance.

Keywords: Computing tools; Serum transaminases

Introduction

The value of transaminase assay is largely based on the diagnosis of liver dysfunction. Thus, the hepatic cytolysis syndrome is evaluated through the levels of alanine transaminase (ALT) and aspartate transaminase (AST), and the cholestasis syndrome is highlighted by alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT) levels [1]. The use of serum transaminase levels is also effective in exploration of metabolic syndrome, dementia, stroke, colorectal adenoma, frailty,

disability or sarcopenia [2-4]. The comparative approach remains the method usually used to characterize a patient in diagnostic terms.

In the current medical practice, the only information used concerning these serum enzymes is represented by the results (normal or pathological) compared to the range of values considered as normal by the laboratory that performed the tests. However, the reference values that always relate to a given population require the consideration of geographical factors or even the repetitive nature of these values, especially those of ALT [5]. In Romania, Ambrosy et al. showed that elevated ALT values predicted mortality in hospital, regardless of known prognostic indicators [6]. These associations are also found in other several studies [7, 8]. Such a diagnostic parameter should be much better characterized for achieving better practical performances.

In this sense, we have carried out a detailed analysis through available computer tools to extend the information that can be obtained for the characterization of the serum transaminases pathological levels, recorded in the usual medical practice from the Cluj geographical area. At the same time, this detailed descriptive analysis was developed as a practical model of clinical epidemiology and a teaching model for postgraduate training of medical doctors.

Material and Method

The Study Sample

The type of study. To analyse the pathological values observed in the medical practice in the Cluj area, we conducted a cross-sectional study during 2004 - 2010 period. The data were collected by medical interns in different specialties (epidemiology, hygiene, public health, neonatology, laboratory, infectious diseases, pneumology, cardiology, family medicine) who attended a module in Epidemiology, during their residency training program. The development and coordination of the study was ensured by the associate professor responsible for the doctors' internship in Epidemiology.

Inclusion criteria. The sample was conveniently comprised of patients who were selected by each trainee doctor, during their clinical practice in Cluj-Napoca hospitals. The criteria for patient inclusion were: being hospitalized (irrespective of the duration of hospitalization), having at least one assay of ALT with pathological values, or in the case of repeated tests, the first one should have had a pathological value. Pathological values were considered those who have exceeded the cut-off value of 45 IU/L, taking into account the differences between laboratories (maximum values ranging from 35 to 45 IU/L) related to device calibration, some taking account the age and gender, others not.

The cases which did not have an analysis of ALT, those with values equal or less than cut-off value (45 IU/L) of the first ALT determination and the readmissions after discharge in which ALT had pathological values were excluded.

The parameters recorded for each patient were: sex, age (in years, for children under one year, in months and for children up to 6 years, in years and months), residence area (urban or rural), hospitalization duration (in days), the year and month of hospitalization, the main diagnosis associated with the pathological level of serum transaminases, the values of all enzyme assay for hepatic cytolysis and biliary stasis, in chronological order during hospitalization, these being ALT, AST, ALP and GGT in IU/L and if it was the case, the death. The intervals for normal values in the region were considered to be 0-45 IU/L for ALT and AST, 35-105 IU/L for ALP and 0-50 IU/L for GGT.

The Enzymes Levels' Analysis

The database. We created a single database in Excel, after every physician recorded the data for his patients. Data verification and validation were assured by the study coordinator for each doctor as the data was registered. Thus, the correctness of the data was evaluated, the errors corrected, and the cases with incomplete data and the repetitive admissions for the same patient were excluded.

Registration of cases in the database was continuously done throughout the study period. Phase analysis and validation of the recorded data were conducted for each period of inclusion and registration, corresponding to the teaching Epidemiology modules, and cumulatively for all cases.

Statistical analysis. Descriptive statistics were performed in Excel and included proportions, average, median, quartiles, minimum and maximum, range, quartile coefficient of dispersion and linear regression.

The informatics tools. The functions for the basic descriptive statistics such as average, range, minimum, maximum, median and quartiles were found in the Excel menu for functions. These gave the results directly for each variable we analyzed. The quartiles divided the number of determinations results arranged in increasing order into four equal parts. Each quartile showed the rank of the sample to which the results of each quartile (i.e. ¼, ½, and ¾ of values) are distributed, starting from the lowest value recorded in the sample. For calculation, the formula for the first quartile was Q1 = N* ¼, for the second was Q2 = N * ½, and the third Q3 = N * ¾, where N is abbreviated the number of subjects in the sample and Q, the quartiles [9]. Quartiles functions were accessed from the Excel menu for formulas, by selecting the "Quartile" functions, stating the value string, "Array" and quartile number 1, 2, or 3, displaying the values corresponding to the parameter that was determined.

The linear regression formula as y = a + bx (where y is the dependent variable, x the independent variable, and a,b are the regression coefficients) allowed us to explore the association between two variables [9]. It is done in the scatter plot graphic representation and the command "add trendline" with the selection of "Equation" and "R-squared value." These allowed us to have the information derived from the equation of the regression line and the correlation coefficient.

Quartile coefficient of dispersion (QCD) or quartile variation coefficient, showed the degree of variability of the results of a skewed distributed parameter recorded in the analyzed population and allowed us to compare different variables, because they are independent of the measurement unit. It took into account the quartile deviation (or semi inter-quartile range) which is Qd=(Q3 - Q1)/2 and the average of the quartiles (or midhinge) computed by Qm=(Q1 + Q3)/2 [10]. Finally the QCD formula: [(Q3 - Q1)/(Q1 + Q3)]*100, represented the derivate of the ratio between the two dispersion's parameters. In computer software is not found such as, but is calculated by interquartile range in the statistics menu and selecting "Interquartile range".

Results

In total, between 2004 and 2010, resident doctors selected 1 908 cases, of which 14 were excluded for incomplete data, 130 were repeated admissions and 39 had ALT less than 45 IU/L. Finally, after excluding 183 cases, the sample size was 1 725 patients. These patients were 52.6% male, 63.1% from urban area, with a mean age of 28.5 years (range 0.1-90 years) and hospitalized in average for 12.7 days (range 1-61 days) (Table 1). The primary diagnosis associated with pathological ALT was most frequently hepatitis A (51.2% of cases), acute or activation of chronic hepatitis B (17.4%) or C (6%), as well as unspecified hepatitis (17.2%). Unspecified hepatitis were cases that were diagnosed as hepatitis, but the aetiology has not been established during hospitalization. More rarely, secondary hepatitis caused by cytomegalovirus (0.2% of cases), Epstein Barr virus (3.6%), or toxic (0.2%) and reactive hepatitis (0.5%), without specifying their origin, were diagnosed. Three patients died after hospitalization between 3 to 18 days, being diagnosed with B (two cases) or unspecified (one case) hepatitis.

On average, serum enzyme assays have been repeated up to 15 times during a hospitalization, most frequently for ALT and AST (Figure 1). Patients' median serum levels of ALT (range: 265 to 960 IU/L) and AST (range: 117 to 685 IU/L) have had a decreasing evolution, indicating the cytolysis reduction. Differentially, the mean values of the 11th to 15th determinations had large variation for both enzymes, but they were determined for a small number of patients. These patients were aetiologically diagnosed with hepatitis B. The median levels of ALP (range: 344 to569.5 IU/L) and GGT (range: 76 to 251 IU/L) were slowly decreasing, with a final increase of the ALP in a small number of patients, also diagnosed with hepatitis B.

In the boxplot logarithmic (log10) representation that presents the majority of information about the enzymes' levels, we included only the first 7 determinations who had on average more than 50 cases tested, in order to avoid the deformation due to particular cases (Figure 2). For the main serum enzymes, the ALT, the minimum values fell below the cut-off value of 45 IU/L, already to the second

test and remained, for the others, further reduced. A level four times the upper normal limit (180 IU/L) was reached only from the first quartile. For the ASTs, only from the second quartile the values were four times higher, while the minimum was in the range of normal values. In the case of ALP, the minimum was above the pathological level starting with the fifth determination and levels more than four times the upper normal limit were from the second quartile. For GGTs, the minimum values were within the normal range and levels four times higher than the upper normal values were only from the third quartile.

Table 1. The main characteristics and the diagnosis established for the patients included in the study

Parameters		Patients		Average age (range) (years)	Average hospitalization (range) (days)
		Number	Proportion (%)		
Residence area	Urban	1089	63.1	30.2 (0.1-88)	12.9 (1-51)
	Rural	636	36.9	25.5 (0.1-90)	12.3 (1-61)
Gender	Male	908	52.6	28.4 (0.1-86)	12.9 (1-61)
	Female	817	47.4	28.6 (0.3-90)	12.5 (1-50)
The main diagnosis	Hepatitis A	883	51.2	19.9 (0.1-88)	12.1 (1-61)
	Hepatitis B	301	17.4	38.7 (0.4-90)	17.5 (2-51)
	Hepatitis C	104	6	48.6 (1-80)	15.4 (1-40)
	Hepatitis non-A, non-B, non-C	63	3.7	41.7 (0.7-75)	10.3 (2-25)
	Unspecified hepatitis	297	17.2	35.3 (0.1-86)	10.3 (1-42)
	Toxic hepatitis	4	0.2	53.8 (30-76)	2 (1-3)
	Reactive hepatitis	8	0.5	42.3 (2-74)	9.6 (6-13)
	Cytomegalovirus hepatitis	3	0.2	21 (5-34)	12.3 (7-15)
	Epstein Barr hepatitis	62	3.6	18.9 (0.9-59)	8.4 (3-17)
Total cases		**1725**	**100**	**28.5 (0.1-90)**	**12.7 (1-61)**

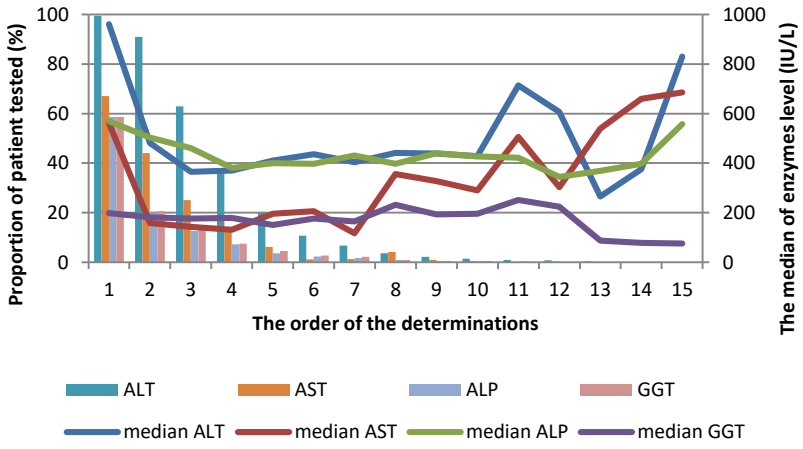

Figure 1. The number of tests, the proportion of patients with enzyme assays performed and the median value for each test performed during patients' hospitalization

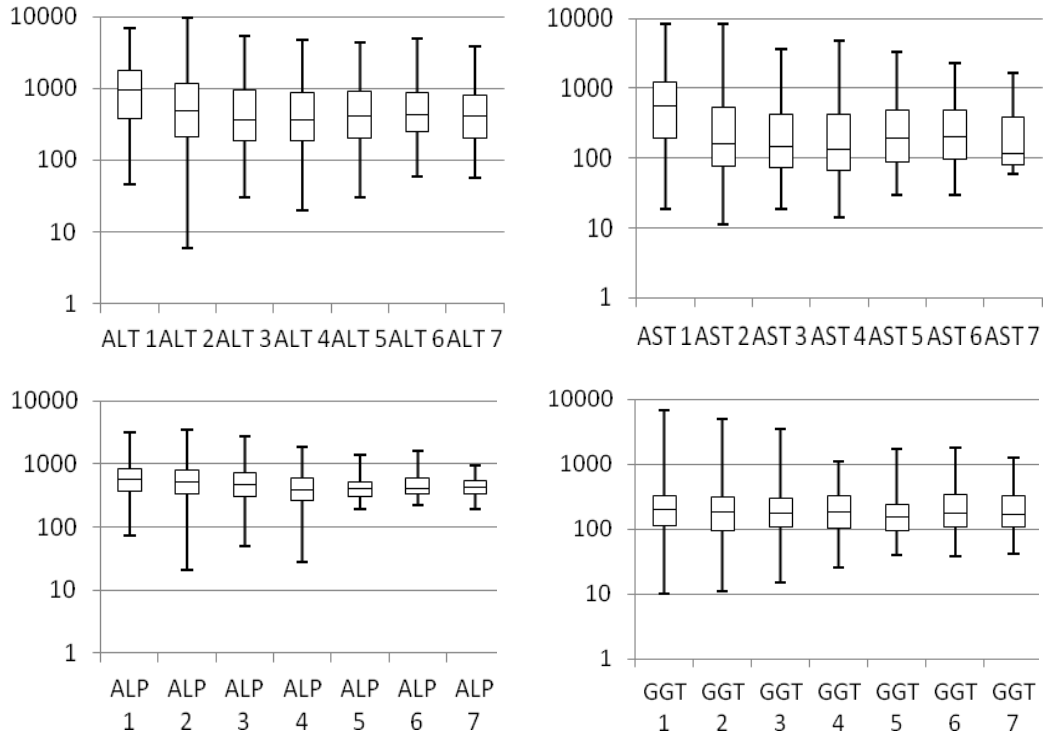

Figure 2. Boxplot in logarithmic (as log10) representation for the first seven assays including the minimum, maximum, the median, and the first and third quartiles for the levels of the four enzymes: alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT)

For the main diagnosis, the mean ALT values were the highest in patients with hepatitis A and B (primary infection and activation of chronic hepatitis) and the lowest in those with Epstein Barr hepatitis (Figure 3). In evolution, the ALT's decrease was more marked in patients with hepatitis A, much slower in those with hepatitis B and C, and with recrudescence in patients with unspecified hepatitis and non-A, non-B, non-C hepatitis (HNABC). The model followed by AST is similar, but with more discrete recrudescence, which was also present in the case of B hepatitis. The ALP had the highest values in cases with hepatitis A, C and Epstein Barr, the progression was slowly going downward and was varying in the case of unspecified and C hepatitis. The greatest values of GGT were for unspecified hepatitis, hepatitis C and HNABC, with little evolutionary differences and somehow broader in patients with C and unspecified-hepatitis.

The linear regression for the values of the first assay (ALTs had pathological values in all patients) shows a good association between ALT and AST, for a correlation coefficient of 0.836. The increasing levels of ALT did not associate with increasing levels of ALP and GGT (Figure 4). This suggests the high amplitude of the hepatocellular lesion process and the lower degree of cholestasis in the liver pathological process.

Quartile coefficient of dispersion (QCD), for each of the laboratory test performed during the patients' hospitalization, shows the highest variability for AST values (QCD maximum 76.8%), followed by the ALT (QCD: 69.6%), especially at first determinations (Figure 5). Conversely, the lowest variability, i.e. the highest stability, had ALP (QCD: 40.3%) followed by GGT (QCD: 52.9%).

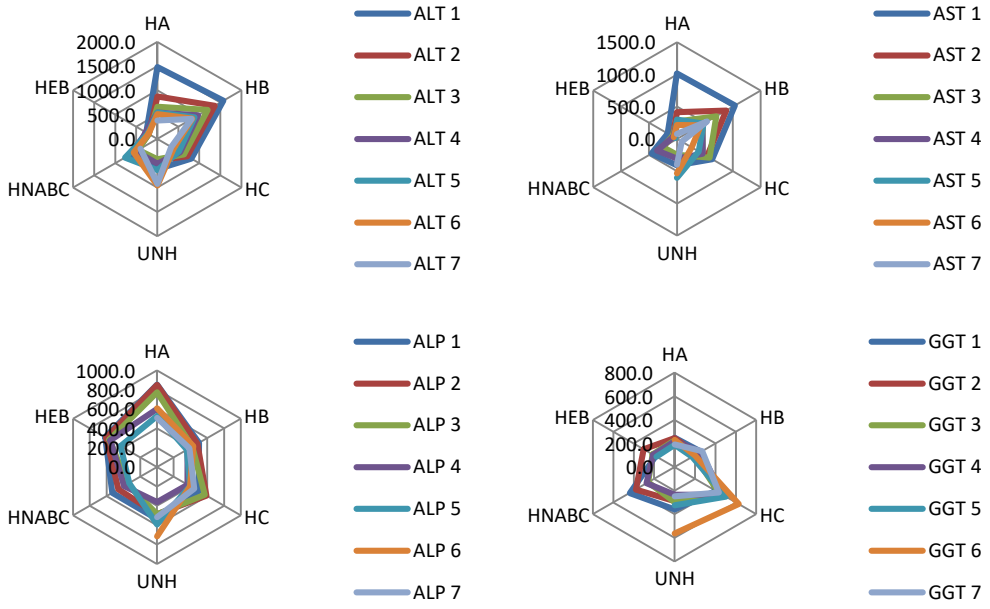

Figure 3. The average levels of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT) for the first seven assays, by diagnosis (Abbreviations: HA= hepatitis A; HB =hepatitis B; HC= hepatitis C; HNABC = hepatitis non-A, non-B, non-C; UNH = unspecified hepatitis, HEB= hepatitis Epstein Barr)

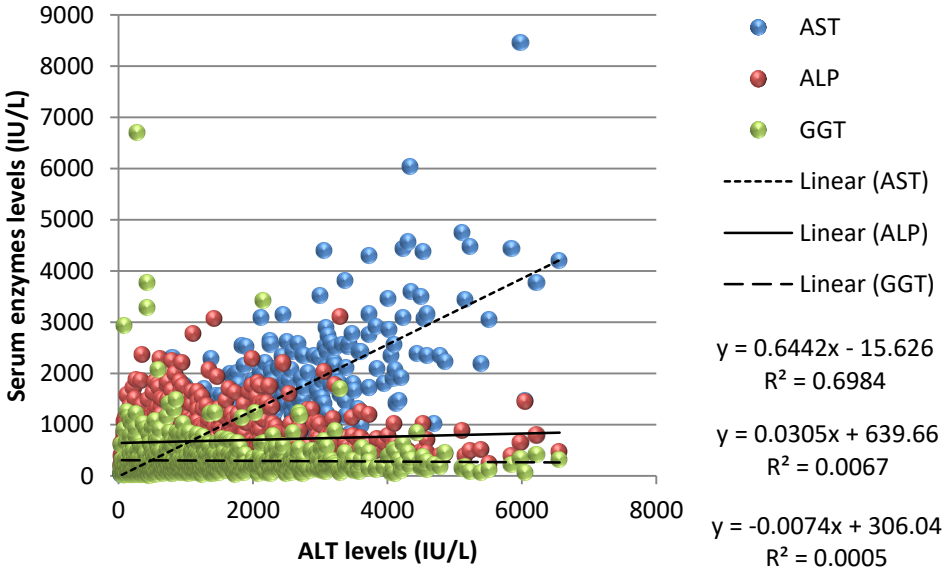

Figure 4. The linear regression between the levels of alanine transaminase (ALT) and of the others three enzymes analysed in the study: aspartate transaminase (AST), alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT)

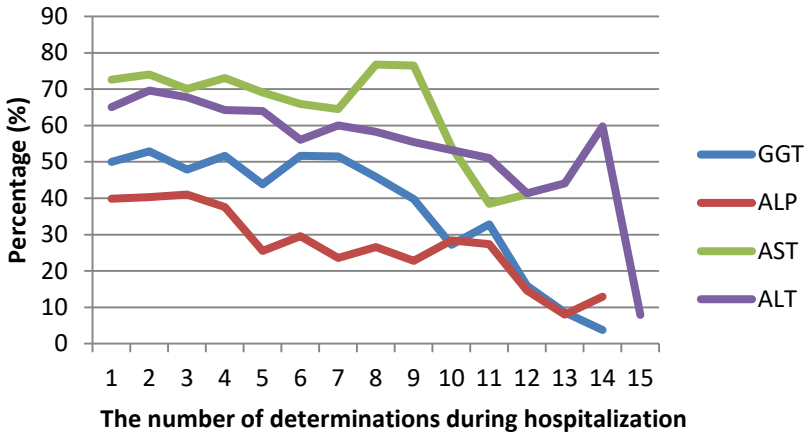

Figure 5. The quartile coefficient of dispersion for the levels of the four analyzed enzymes, of all assays made during the hospitalization of patients enrolled in the study

Discussion

The presented study did not include the cases recorded after 2010, in order to maintain the patients' homogeneity after diagnosis, which would have been affected by the decrease in the number of primary acute hepatitis cases, for both A (from more than 300 per 100000 inhabitants to less than 30) and B (from more than 30 per 100 000 inhabitants to 1.9), as a result of the population vaccination program and hygiene compliance mainly in children's collectives [11-13]. Consequently, the number of cases with chronic hepatitis became larger, numerically dominating all other causes and this would have changed the sample's structure trough the cases' diagnosis. At the same time, in our study sample, the patients were diagnosed mainly with A and B hepatitis, while at national and regional levels, the incidence was decreasing and also the seroprevalence in population studies conducted in the same period [13, 14].

In the regional practice we observed many cases with an incomplete diagnosis as unspecified, toxic or reactive hepatitis, not having the information about the causal factor. Drug-induced liver injury (DILI) is at present responsible for the majority of acute liver failure cases and it is also the main cause for liver transplantation. About 2–10% of hospitalized patients present jaundice secondary to liver injury caused by medicines. The mechanisms for DILI are intrinsic liver injury and idiosyncratic liver injury. Hepatocellular DILI is characterized by an increase of the level of ALT more than two times the upper limit of normal, or when the ratio between ALT to ALP is higher than five; cholestatic DILI is characterized by the ratio of ALT to ALP below two. A ratio of ALT to ALP between 2 and 5 characterizes a mixed liver injury [15].

The serum enzymes characteristics encountered in the analyzed sample, in terms of levels and their evolution, fit only in part with the known patterns of disorders that primary or secondary alter the liver tissue [1, 16]. It was the case for more than a quarter of patients who did not have high level of enzymes, or the value dropped quickly at the second test or evolved with relapses. These aspects of heterogeneity may be due to different particularities and can be identified through investigative epidemiological studies.

Therefore, for the upcoming period we consider all these observations as justifiable evidence for re-evaluation of the current diagnostic methods involving the serum transaminases levels, in order to identify the explanatory factors for the cases characteristics in our region and make appropriate changes for increasing the medical performance in Cluj geographical area.

The main limits of our study were the large number of doctors who worked for short periods to select patients, to collect and record the data, and the differences between laboratories regarding the maximum values of serum transaminases.

Conclusions

In the hospital medical practice, the serum transaminases assays are frequently done and repeated for many times during a hospitalization. The pathological values of serum transaminases were recorded mainly in young adults who were diagnosed with various primary or secondary liver conditions, for whom they needed long-term hospitalization. However, one in six patients remained without a complete diagnosis targeting the aetiology. For more than a quarter of patients the serum transaminases levels and evolution did not fit with the known pattern of hepatic lesions making questionable the diagnosis accuracy. More studies are needed to investigate the explanatory factors of the cases heterogeneity in the region. Only in this way, appropriate measures can be selected for improving the diagnostic performance in the medical practice.

List of abbreviations

ALP: alkaline phosphatase
ALT: alanine transaminase
AST: aspartate transaminase
GGT: gamma glutamyl transpeptidase
HA: hepatitis A
HB: hepatitis B
HC: hepatitis C
HEB: hepatitis Epstein Barr
HNABC: hepatitis non-A, non-B, non-C
IU/L: international units per litter
QCD: Quartile coefficient of dispersion
UNH: unspecified hepatitis

Conflict of Interest

The authors declare that they have no conflict of interest.

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