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Acute Viral Hepatitis A - Clinical, Laboratory and Epidemiological Characteristics

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Abstract
Infection with hepatitis A virus is still one of the most common causes of hepatitis worldwide. The clinical manifestation of acute hepatitis A (AHA) in adults can vary greatly, ranging from asymptomatic infection to severe and fulminant hepatitis. The aim of this study was to describe the demographic, clinical characteristics, laboratory features and hospital outcome of adult patients with AHA over a consecutive period of 4 years within an area from Eastern European country. Two hundred and two adult patients diagnosed with AHA were retrospective, observational and analytic analized over a period of 4 years. Based on prothrombin time less than 50, the study group was stratified in medium (79.2%) and severe forms (20.8%). The hemorrhagic cutaneous-mucous manifestations (6.93%) associated with the severe forms of AHA (OR =12.19, 95%CI -3.59 - 41.3, p =0.001). We found statistically significant differences for PT (p <0.001), INR (p <0.001), TQ (p <0.001), ALAT (p <0.001), ASAT (p <0.001), ALP (p <0.001) and platelets (p =0.009) between severe and medium AHA forms. We found that TQ, INR, ALAT and ASAT have the highest diagnostic values, statistically significant (p <0.05) for severe AHA forms. The severe AHA forms were associated with hemorrhagic cutaneous-mucous manifestations (OR=12.19, p =0.001). The present study revealed that TQ, INR and ALAT have the highest diagnostic values and are statistically significant for severe AHA forms.

Keywords*:* Hepatitis A; Prothrombin time; ALAT; adult.

Introduction

Infection with hepatitis A virus (HAV) is still one of the most common causes of hepatitis worldwide [1].

HAV infections account for 1.5 million cases of hepatitis each year, with a supposed underreporting rate of up to 80% [2,3].

The HAV is a small non-enveloped, single-stranded RNA-virus, classified as a member of the Hepatovirus genus, of the family Picornaviridae [4].

There are large variations in endemicity, age at time of infectious and frequency of hepatitis caused by HAV. The shift from high to intermediate or even low endemicity leads to a change in the age of persons susceptible to HVA, from children to adolescents or adults [5].

The different patterns of HAV infection observed worldwide are determined by the association of HAV infection risk with levels of hygiene, the age-dependent clinical expression and the lifelong immunity.

HAV replicates in hepatocytes, interferes with liver function and induces an immune response causing liver inflammation [6]. In humans, HAV generates acute hepatocellular damage mediated by the host immune response and not directly by the virus, because HAV in not a cytopathic virus [7].

The expression of clinical symptoms varies greatly with the age of the infected persons and the host immunity, ranging from asymptomatic infection to fulminant hepatitis [5,6]. In most patients HAV infection is benign. The risk of fulminant hepatitis is 0.14-0.35% [VHA 71], increasing to 1.8% in patients over 49 years old [7].

The adults with HAV infections developing a severe hepatitis have an increased risk for prolonged cholestasis, intrahepatic or extrahepatic complications or even fulminant hepatitis [8].

The standard diagnosis of acute hepatitis A is based on the detection of the immunoglobulin M (IgM) antibody to HAV (anti-HAV) in patients who present with clinical features of hepatitis [5].

Although, IgM anti-HAV is used as the primary marker of acute hepatitis A (AHA) infection, the serologic test based on this marker is associated with a false-negative rate of 4-13% during the window period [9].

The aim of this study was to describe the demographic, clinical characteristics, laboratory features and hospital outcome of adult patients with AHA over a consecutive period of 4 years within an area from Eastern European country, where vaccination against HAV is not compulsory.

Material and Method

The present study is retrospective observational and analytic, conducted at the Infectious Diseases Hospital from Cluj-Napoca over a period of 4 years (2008-2011), on adult patients diagnosed with acute hepatitis A (AHA).

The study protocol was approved by the Ethics Board of the "Iuliu Haieganu" University of Medicine and Pharmacy from Cluj-Napoca, in accordance with the Declaration of Helsinki, and the written consent of all pacients was obtained.

Inclusion criteria: in the present study, patients over 18 years were included, diagnosed with AHA according to the CDC 2008 criteria (IgM anti-HAV in a patient with suggestive clinical symptomatology, which associates jaundice or values of alanine aminotransferase (ALT) higher than 200 UI/l [10].

Exclusion criteria: patients with HIV infection, as well as those infected with other hepatitis viruses (B, C, D, CMV, EBV) were excluded from the study.

For each patient an individual evaluation sheet was designed, including demographic data (age, gender, place of residence), patient's history, clinical, laboratory examinations in dynamics (biochemical, haematological, virological, immunological parameters) and imaging investigation. Consequently appropriate therapy was initiated according to the existing protocols in our hospital and in the country. The patients were followed-up for a period of 3-6 months after their discharge.

On the basis of prothrombin time (PT) and INR (international normalized ratio), regarded as essential elements of the hepatocellular injury, and as well as on the basis of the presence or absence of the neurological clinical signs, a stratification of patients into 2 groups was developed:

- Severe AHA forms – included case with PT values <50%, INR >1.5 and of TQ (Quick time) >16 seconds with or without neurological manifestations.
- Medium AHA forms – included patients with PT values >50%, INR <1.5 and of TQ <16 seconds, without neurological manifestations.

Laboratory test. A routine chemistry test (Konelab 20I, Cobas C311), complete blood count and coagulation studies (Pentra 60C, SysmexCA 1500) were performed. To detect serum IgM anti HAV by enzyme immunoassay we used EIAgen anti HVA IgM kit (Adaltis, Milano, Italy).

Statistics. The SPSS (v.15) program was used for the statistic analysis and the description of the data. The normality distribution of the quantitative data was certified with Kolmogorov-Smirnov test. The acceptable error threshold was α=0,05. On the purpose to compare the corresponding means of two independent groups the Student (t-test) was used in the event that the variables were normally distributed. The nonparametric Mann-Whithney and Kruskall-Wallis tests were used in order to compare the mediums of the two independent groups, where the variables had an abnormal distribution.

The Pearson correlation coefficient (for the continuous qualitative variables normally distributed) was calculated for the correlation analysis or the Spearman correlation coefficient (for the continuous qualitative variables that do not have a gaussian distribution). The significance tests were used in order to estimate the correlation coefficients (with α=0.05) and the Colton rules for the empirical interpretation were also used. In order to describe the continuous quantitative data with a normal distribution, we used the arithmetic mean ± the standard deviation (SD), yet for those which did not have a gaussian distribution, the median and the range. In order to determine the sensitivity (Sn) and specificity (Sp) of some bioumoral parameters the ROC curve was used and the area from under the curve (AUC) was calculated. The ROC curve illustrates the graphic relation between Sn and Sp for certain possible cut-off values. There are considered as cut-off points the optimal values from the point of view of the fiability of analysed parameters. The values of AUC close to 1 point out an increased accurately diagnose.

Results

Based on the inclusion criteria, in the present study were included 202 patients, representing 46.22% of the total 437 AHA cases hospitalized between 2008 and 2011.

It is remarked that within the analyzed lapse, an annual and relatively homogenous distribution of AHA cases, with the exception of the year 2010, when an epidemic peak of 104 cases (51.48%) was recorded, probably due to a regional epidemy, argumented with the positive epidemiological inquiry on the majority of cases (Figure 1).

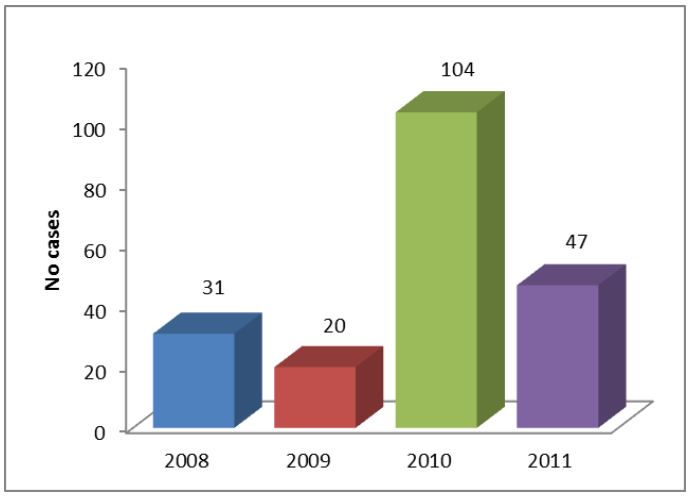

Figure 1. Annual distribution of AHA cases

The monthly distribution of the cases highlights an increased incidence of AHA during autumn months for the years 2008, 2009 and 2011, with a medium monthly value of 3.4 cases in this months, in comparison with 2.2 cases in the rest of the months of these years. In the year 2010 the maximum morbidity was recorded during the summer-autumn months, with a monthly average of 21.5 cases, in comparison with 2.25 cases recorded in the rest of the months âof that year. The data is presented in Figure 2.

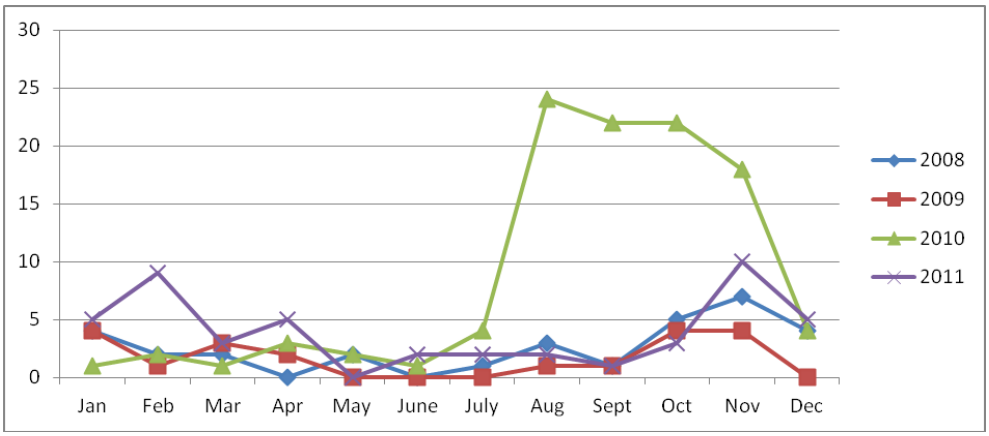

Figure 2. The monthly distribution of AHA cases

The main characteristics of the cases included in the study are presented in Table 1.

Table 1. Characteristics of AHA patients included in the study

Characteristics	Values
Demographics	
- age (years) - median ± range	34.06 ± 11.48
- gender – Male (%)	55.44
- urban area (%)	61.88
Clinical onset to admission interval (days) – mean ± DS	7.10 ± 4.19
Clinical manifestations	
- dyspeptic syndrome (%)	72.07
- asteno-adynamic syndrome (%)	87.62
- icteric syndrome (%)	86.63
- flu-like syndrome (%)	53.46
- hemoragipar (cutaneous- mucous) syndrome (%)	6.93
Hepatomegaly (%)	67.82
Splenomegaly (%)	5.46
Clinical forms of disease	
- severe AHA (%)	20.80
- medium AHA (%)	79.20
Average hospitalization time (days) – mean ± DS	11.45 ± 4.62
Outcome	
- Relapse /biphasic evolution (%)	7.92
- Colestasis (%)	4.45
Mortality	0

The median age of the patients included in the study was 34.06 ± 11.48 years, without statistically significant differences (p=0.982) on the whole 4 years. The distribution by age groups reveals a predominance of AHA at the age groups of 18-29 years, respectively 30-39 years, with a total of 147 (72.70%) of cases, data is presented Figure 3.

In the present study it was found a good correlation, statistically significant, between the patients' age and the interval between clinical onset to admission (r = 0.32, p = 0.05), as well as between the age and the duration of hospitalization (r = 0.35, p = 0.01) of the AHA cases, data presented in Figure 4. It was not found a statistically significant association between age and AHA clinical manifestations at onset (OR = 0.398, 95% CI – 0.14-1.13, p = 0.13).

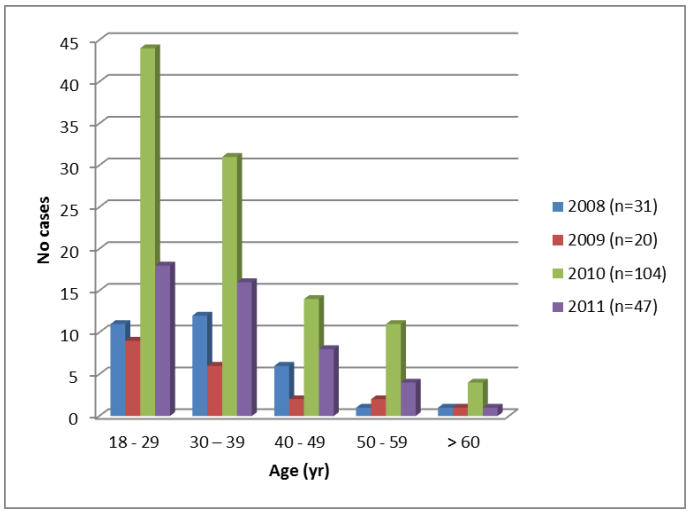

Figure 3. Age goups distribution of pacient with AHA

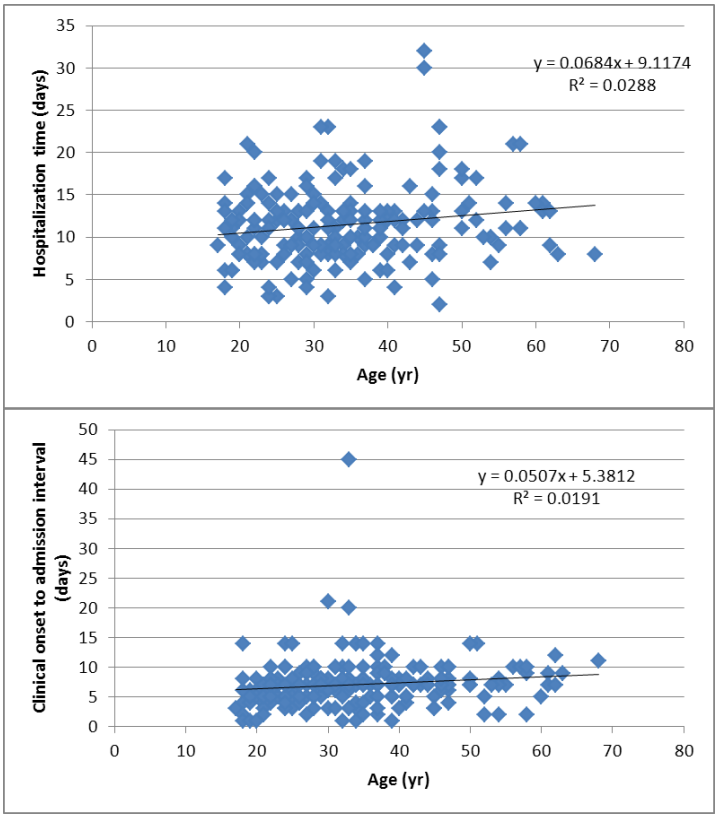

Figure 4. Correlation between the patients' age and clinical onset to admission interval and the hospitalization period (days)

The present study reveals a predominance in the male patients (male/female - 1.2) in addition to those from the urban area (urban/rural - 1.6), noticing a change of AHA trend from the rural area to the urban in the 4 years of observation.

After onset-admission interval, with a mean of 7.10 ± 4.19 days, the majority of patients presented at their admission to hospital dyspeptic manifestations (72.07%), jaundice (86.63%) and

asteno-adynamia (86.72%), without a significant statistical association between their presence and the clinical forms of disease (p >0.05).

The main laboratory examinations performed in patients with AHA, on admission and discharge, are shown in Table 2.

Reffering to the presence of liver injury in AHA, an increased value of ALAT is observed at the admission as compared with ASAT (ALAT/ASAT - 1.78), more than 80% of the patients having values of ASAT varying between 20–100 x NV.

The ALAT and ASAT values were significantly higher in patients with dyspeptic syndrome (p=0.04, p=0.02) as well as in the patients with flu-like manifestations (p =0.005, p =0.001).

The serum level of ALAT and ASAT did not present significant statistical differences depending on the age (p =0.26, p =0.18), hemorrhagic manifestations (p =0.43, p =0.10) and jaundice (p =0.16, p =0.18).

The impairment of the synthetic function of the liver (IP, INR, TQ) did not present significant statistical differences depending on the age (p =0.25, p =0.15, p =0.55).

A percentage of 5.94% of patients were without jaundice, the majority of them with an age below 40 years and with a medium value of ALAT below 20 x NV.

Table 2. Laboratory characteristics of the patients with AHA

Parameters	Values
At admission	
ALAT (UI/dL)	2006 ± 1165
5- 20 x NV (%)	12.37
20 – 100 x NV (%)	81.68
> 100 x NV (%)	5.94
ASAT (UI/dL)	1128 ± 884.4
PT (%)	72.59 ± 18.07
TQ (s)	18.70 ± 4.40
INR	1.34 ± 0.34
Total BR (mg/dL)	6.95 ± 4.24
< 1mg/dL (%)	5.94
1 - 15 mg/dL (%)	89.60
> 15 mg/dL (%)	4.45
Direct BR (mg/dL)	5.37 ± 3.35
ALP (UI/dL)	581.74 ± 265.98
GGT (UI/dL)	289.52 ± 192.31
Hypoalbuminemia (%)	13.36
Thrombocytopenia (%)	19.80
Leukopenia (%)	9.90
At discharge	
ALAT (UI/dL)	328.03 ± 168.31
< 5 x NV (%)	43.06
ASAT (UI/dL)	106.10 ± 59.83
PT (%)	85.15 ± 9.00
INR	1.11 ± 0.13
Total BR (mg/dL)	2.49 ± 2.24
< 1(mg/dL)	21.78
ALP (UI/dL)	356 ± 269

ALAT – Alanine aminotransferase, NV – Normal Value (40UI/dL) ASAT – Aspartate aminotransferase, PT – Protrombin Time, TQ - Quick time, INR – International Normalized Ratio, BR – Bilirubin, ALP – Alkaline phosphatase, GGT – Gamma glutamyltranspeptidase. Hypoalbuminemia - Albumin < 3.5 g/dL, Thrombocytopenia - Platelet <150.000/mm3, Leukopenia - Leukocytes < 3700/mm^3. The arithmetic mean ± standard deviation (SD) was used for describing the normally distributed continuous quantitative data, while for those that did not have a Gaussian distribution the median and range were used.

Significant differences of GGT (p =0.01) were found depending on the age of the patients and for Total BR (p = 0.004) depending on the patients' gender, with increased values of males.

At admission in the hospital, the univariate analysis of the biological parameters was performed. A negative correlation, highly statistically significant between PT and ALAT (r = -0.54, p < 0.0001), respectively ASAT (r = - 0.60, p < 0.0001) was observed.

The follow-up revealed that 7.92% of the pacients presented relapse, and 4.45% have evolved with cholestasis, with values of total BR >3mg%, for more than three months period. Ultrasonography confirmed hepatomegaly and splenomegaly and detected acalculous cholecystitis in 16.33 % of cases.

According to the stratification criteria, 20.8% of the patients have presented severe forms of AHA. The present study demonstrated that there is a significant statistical association between the severe AHA forms and the mean interval (under 7 days) between the clinical onset to admission (OR = 5.99, 95%CI [2.03-17.7], p = 0.0004). The hemorrhagic cutaneous-mucous manifestations were present at 6.93% of the patients, existing a significant statistical association between their presence and the severe forms of AHA (OR = 12.19, 95%CI [3.59 - 41.3], p =0.001).

The main laboratory examinations performed in patients with severe and medium AHA forms, at admission and discharge are shown in Table 3.

Table 3. Laboratory characteristics of patients with medium and severe AHA forms

Parameters	Severe AHA form n = 42	Medium AHA form n = 160	p-value
At admission:			
PT (%)	49.30 ± 2.60	82.24 ± 15.38	< 0.001*
TQ (s)	25.10 ± 5.90	16.24 ± 2.52	< 0.001*
INR	1.72 ± 0.10	1.18 ± 0.19	< 0.001*
ALAT(UI/dL)	3204 ± 1179	2036 ± 775.45	< 0.001*
ASAT (UI/dL)	2221 ± 1001	1957 ± 438.79	< 0.001*
Total BR (mg/dL)	7.62 ± 2.25	7.46 ± 12.60	0.001*
ALP (UI/dL)	548 ± 777	644.65 ± 362.09	< 0.001*
GGT (UI/dL)	225.0 ± 351.0	343.29 ± 217.35	0.191
Platelet ($x10^3$ /mm^3)	172 ± 192	249.12 ± 63.83	0.009*
Albumin (g/dL)	3.28 ± 0.45	3.66 ± 0.44	0.15
At discharge:			
PT (%)	87.00 ± 10.91	86.10 ± 10.05	< 0.001*
INR	1.08 ± 0.08	1.10 ± 0.10	< 0.001
TQ (s)	15 ± 0.77	15.65 ± 1.31	0.019
ALAT (UI/dL)	271 ± 133.36	347 ± 178.17	0.85
ASAT(UI/dL)	70 ± 30.73	103 ± 52.06	0.39
ALP (UI/dL)	394.80 ± 286.12	365.24 ± 219.34	0.6
GGT (UI/dL)	123.60 ± 57.77	166.53 ± 153.84	0.12

n - patients number, * - statistically significant, PT – Protrombin Time, TQ - Quick time, INR – International Normalized Ratio, ALAT – Alanine aminotransferase, ASAT – Aspartate aminotransferase, BR – Bilirubin, ALP – Alkaline phosphatase, GGT – Gamma glutamyltranspeptidase. The arithmetic mean ± standard deviation (SD) was used for describing the normally distributed continuous quantitative data, while for those that did not have a Gaussian distribution the median and range were used.

Comparing the patients with medium and severe AHA form of disease, significative differences were observed for the following parameters on admission: PT, TQ, INR, ALAT, ASAT, Total BR, ALP and platelet counts.

The analysis of the same two groups of pacients regarding the biological parameters at discharge, showed significant differences only for PT, INR and TQ.

We used ROC curves and AUC for the main biological parameters to establish the threshold values (cut-off), the sensitivity and specificity for severe AHA forms.

We found that TQ and INR have the highest diagnostic values and are statistically significant for severe AHA forms with AUC (0.99, 0.99) at values of sensitivity (95%, 90.5%) and specificity

(98%, 99%), at cut off values of 21.45 seconds for TQ and 1.61 for INR ($p < 0.05$). ALAT and ASAT proved to be also predictive for severe AHA forms (Table 4 and Figure 5).

Table 4. Comparison of sensitivity, specificity and AUC of biological parameters in patients with severe versus medium AHA forms

Parameters	Cut –off	Sn (%)	Sp (%)	AUC	SE	95 % CI of AUC		p - value
TQ	21.45	95	98	0.99	0.007	0.97	1.00	< 0.001*
INR	1.61	90.5	99	0.99	0.002	0.99	1.00	< 0.001*
ALAT	840	89	88	0.72	0.07	0.58	0.86	0.004*
ASAT	236.5	95	94	0.70	0.07	0.55	0.86	0.008*
Total BR	1.66	95	96	0.62	0.07	0.48	0.77	0.04
Platelet	107	96	98	0.63	0.07	0.18	0.45	0.008

Sn – Sensitivity, Sp – Specificity, AUC – Area Under the Curve, SE – Standard Error, 95% CI - Confidence Interval, * - statistically significant

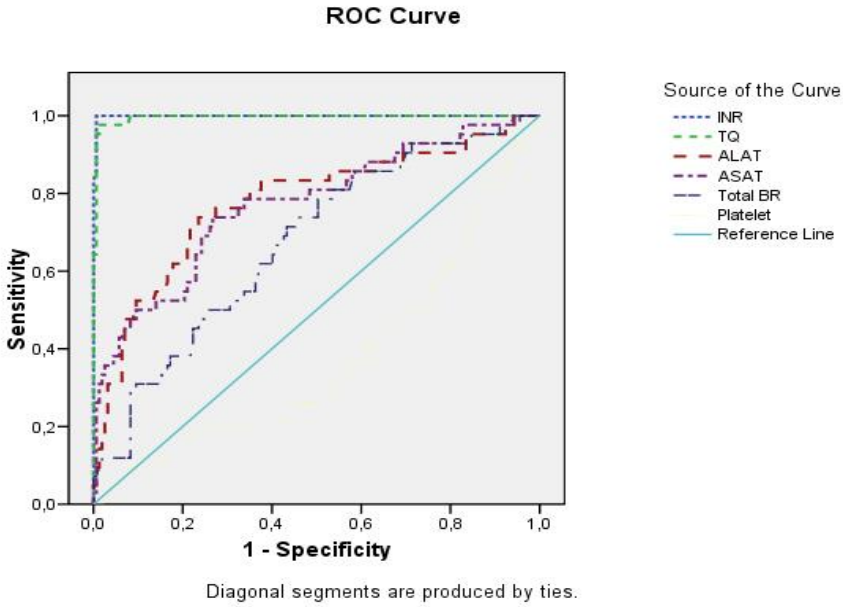

Figure 5. ROC curve for INR, TQ, ALAT, ASAT, Total BR and Platelets

Discussion

Acute hepatitis A infection is usually a mild disease, but adults have an increased susceptibility for severe clinical course and complications.

Romania reported for the year 2010 an incidence of 16.27 AHA cases at 100.000 inhabitants, similar to that from Latvia (13.26 cases) but inferior to those from Slovakia (26.75) and Bulgaria (31.19) [11].

During the 4-years study period (2008-2011), a relatively homogenous annual distribution of cases of AHA can be noticed, with the exception of the year 2010, when an epidemic peak with 51.48% of the cases was recorded, more likely due to a regional epidemy.

The present study reveals an annual seasonal variation of the AHA cases, with a more increased incidence in the autumn months for the years 2008, 2009 and 2011, with the exception of the year 2010 when the maximum morbidity was recorded during the summer-autumn months, with a

monthly average of 21.5 of the cases in comparison to 2.25 cases recorded in the rest of the months of the year.

A similar aspect was reported in Latvia, where after 8 consecutive years in which less than 100 cases/year were recorded, in the year 2007 a regional epidemy was described, with a maximum incidence of the cases during the autumn months [12].

Choi and his collaborators, during a 7 years study, also reported a maximum incidence of the AHA cases during the summer-autumn months [13].

In another study from 2004 Battikhi at al reported a maximum incidence of AHA during the spring-summer months. [14].

Demographic analysis of our study patients reveals that 72.7% of them were under 40 years old. Choi reported an incidence of 87.7% of AHA at the age group of 21-40 during an urban epidemy in Korea [13]. The same predominant involvement of the young adult (89%) was reported by Moon, in his study from 2010 [4]. Bember in a study concerning AHA in London's population revealed an increased incidence at the age group of 15-45 years [15].

Our study proved that patients of the male gender were predominantly affected (55.44%), more likely due to occupational risc and the disregard for the profilaxy measures, aspect certified by other authors too [4,14,16].

In contrast to that, Tong and Kuntz point out the fact that both genders are equally affected [17,18].

An important feature of the onset of AHA is represented by the polymorphism of clinical manifestations, aspect encountered in the studied group [3]. The majority of patients from the study group presented dyspepsia (72.07%), jaundice (86.63%) and asteno-adynamia (87.62%), as well as flu-like manifestations. Other authors also reported a similar incidence of these clinical AHA manifestations [13,17,19,20].

Hepatomegaly has been observed at 67.82% and splenomegaly at 3.46% of the patients, percentages comparable with the ones from the literature [7,17].

We found acalculous cholecystitis in 16% of patients with AHA, close to 21% of cases reported by MacKinney-Novello et al [7].

Our study has determined that more than 80% of the patients presented ALAT values between 800-4000UI/dL, similiar values being reported by other studies [4,9,13,17].

The high levels of ALAT and ASAT in AHA are the consequence of a major inflammatory process and their main source was the liver. The increase of ASAT and ALAT serum values express both liver cell destruction and changes of hepatocyte permeability [21].

In the literature there are data showing that the high values of ALAT and ASAT are not correlated with the disease prognosis [22].

Regarding the value of ASAT and ALAT, Nagaki et al have not reported significant differences in these parameters in patients with fulminant hepatitis versus severe and medium forms of acute hepatitis [23].

In our study the univariate analysis shows that a statistically significant but negatively correlation between IP and ALAT ($r = - 0.54$, $p < 0.0001$), respectively ASAT ($r = - 0.60$, $p < 0.0001$).

Comparing the patients with severe and medium AHA forms, by considering the laboratory parameters on admission, statistically significant differences were detected for PT ($p <0.001$), INR ($p <0.001$), TQ ($p <0.001$), ALAT ($p <0.001$), ASAT ($p <0.001$), ALP ($p <0.001$),) and platelets ($p=0.009$).

Sainokami et al found significant differences for PT, ALAT, ASAT, platelets in patients with severe and moderate forms of acute hepatitis A [24].

Other authors [23,25,26] have reported significantly lower values of PT in patients with acute hepatitis with fulminant evolution in comparison to those with moderate evolution, probably secondary to the impairment of the synthesis function of the liver [27].

Fujiwara et al suggested that both viral and host factors have to be taken into consideration when analyzing the mechanisms responsible for the severity of type A hepatitis [28].

Our study revealed the fact that the severe AHA forms were associated with hemorrhagic cutaneous-mucous manifestations (OR=12.19, 95%CI - 3.59-41.3, $p = 0.001$) aspect mentioned by Moon [4].

In our study group hypoalbuminemia was discovered at 13.36% of patients. Moon consider hypoalbuminemia as a severity indicator, as well as increased total bilirubinemia [4].

The most frequent complications in acute hepatitis A are: biphasic evolution (relapse), prolonged cholestasis, hematological abnormalities and extrahepatic manifestations.

The biphasic evolution, most likely immunological mediated observed in the analysed group was 7.92%, inferior to the one communicated by Tong (11.9%) [17].

A percent of 4.45% of the patients evolved with cholestatic forms. Prolonged cholestasis was also reported by other authors in 4.7% of patients with hepatitis A infection The cholestasis produced during the viral infection might be induced by the reduction of bile salt transporter function due to the proinflammatory cytokines [29].

In our study group the complications found were thrombocytopenia (19.80%) and leukopenia (9.90%). Akarsu et al reported similar hematological changes in AHA [30].

Our study revealed that TQ, INR, ALAT and ASAT are signifiquant predictor factors for severe AHA forms.

All our patients had a favorable outcome, after an average hospitalization time of 11.45 ± 4.62 days. No deaths were recorded during those 4 years.

Conclusions

Our study revealed an annual and relatively homogenous distribution of AHA cases, with the exception of the year 2010, when an epidemic peak of 104 cases (51.48%) was recorded. Most patients of our study group (72.7%) were under 40 years. The big majority of cases (79.2%) presented medium severity forms. The severe AHA forms were associated with hemorrhagic cutaneous-mucous manifestations (OR=12.19, 95%CI -3.59 - 41.3, p =0.001). The univariate analysis proved a negatively statistically significant correlation between IP and ALAT/ASAT. We found that TQ, INR and ALAT have the highest diagnostic values and are statistically significant for severe AHA forms.

Conflict of Interest

The authors declare that they have no conflict of interest.

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