ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Performance of a calculator for diagnosing the cause of liver damage

Narcisa Petrović-Subić[1], Miroslav Kojić[2], Slobodan M. Janković[1], Srđan M. Stefanović[1]

[1]University of Kragujevac, Faculty of Medical Sciences, Department of Pharmacology and Toxicology, Kragujevac, Serbia;
[2]Military Medical Academy, Clinic for Infectious and Tropical Diseases, Belgrade, Serbia

SUMMARY
Introduction/Objective Making a calculator that would recognize patterns of abnormal liver function tests and link them to the most probable etiology could help clinicians in their initial orientation towards a definitive diagnosis in patients with liver damage.
The aim of our study was to design, construct, and validate a calculator that based on a pattern of abnormalities in liver function tests of a patient with liver damage would propose the most probable etiology.
Methods Patterns of abnormal liver function tests for certain etiology of liver damage were extracted from distributions of actual values taken from reports in medical literature about patients whose etiology of liver damage was proven by reliable diagnostic tests. After setting up the calculator with the patterns extracted, its diagnostic value was checked under real-life conditions, on a sample of patients with liver damage whose etiology was established by the gold standard of diagnostics (biopsy or else). The calculator validation study was carried out at the Military Medical Academy in Belgrade during a two-year period (2015–2016).
Results For all tested diagnoses, the calculator demonstrated a highly significant difference between the area under the receiver-operator curves' values and the value of 0.5 (p < 0.001), and high level of sensitivity (more than 90%, except for the model for chronic hepatitis) as well as relatively high specificity (more than 75%) were noted, indicating good ability of the calculator to detect etiology of liver damage.
Conclusion New calculators showed satisfactory sensitivity and specificity for revealing major liver damage etiologies.
Keywords: medical calculator; sensitivity; specificity; etiology

INTRODUCTION

In patients with identified liver dysfunction, evaluation of a pattern of abnormal liver function tests is usually the first step towards recognizing etiology of liver disease and establishing prognosis. In asymptomatic patients, elevation of liver enzymes is frequently the first evidence of liver disease [1]. However, the lack of specificity may limit the diagnostic value of isolated liver function tests. Alkaline phosphatase (AP) could be elevated in both bone and liver disorders, and aminotransferases could be elevated in cardiac diseases, skeletal muscle as well as in liver diseases. During chronic diseases such as alcoholic liver disease, serum albumin can be affected by many factors not directly related to the main cause of illness (e.g. malnutrition, malabsorption, chronic inflammation). Elevated serum values of gamma-glutamyltransferase (GGT) could reflect the liver, biliary tract and pancreas diseases [2, 3]. A prolonged prothrombin time (PT) is not specific for liver diseases and is seen in different congenital deficiencies of coagulation factors, as well as in acquired conditions. Liver function tests also lack sensitivity, and in certain liver diseases like cirrhosis, the early phase can be present without liver test abnormalities. Single liver function tests are not providing sufficient data and may not provide a specific diagnosis. A combination of tests and a pattern of abnormalities can suggest a general category of hepatic dysfunction [3].

The Model for End-Stage Liver Diseases (MELD) calculator uses laboratory parameters (creatinine, bilirubin, and international normalized ratio (INR)) in order to project the state of the chronic liver disease at a given moment, as well as the need for transplantation. The Pediatric Model for End-stage Liver Diseases score is a modified formula for children up to 12 years of age. The original version was devised at the Mayo Clinic, but it has several adaptations [4, 5]. FibroTest®, Fibrosure® and Enhanced Liver Fibrosis® are mathematical formulas used for rating liver fibrosis [6]. A scoring system for nonalcoholic fatty liver disease (NAFLD) was designed and validated by the Nonalcoholic Steatohepatitis (NASH) Clinical Research Network. The NAFLD Activity Score is used for the assessment of any degree of the NAFLD and is under critical evaluation in many recent studies [7]. Maddrey Discriminant Function (MDF) and Glasgow Alcoholic Hepatitis Score (GAHS) are used for defining severity and predicting mortality in patients with alcoholic hepatitis (AH) [8]. International

Correspondence to:
Narcisa PETROVIĆ SUBIĆ
Džordža Vašingtona 4/10
11000 Belgrade
petrovicnarcisa3@gmail.com

Autoimmune Hepatitis Group developed a scoring system for diagnostic, differential diagnostic, and prognostic purposes in patients with autoimmune hepatitis (AIH). There are several adaptations of the initial scoring system. The Roussel Uclaf Causality Assessment Method (RUCAM) was designed to assess likelihood causality in cases of suspected drug induced liver injury (DILI) [9]. However, none of the earlier calculators were designed to reveal the etiology of liver damage, which remains to be established by elaborate diagnostic algorithms.

Making a calculator that would recognize patterns of abnormal liver function tests and link them to the most probable etiology could help clinicians in their initial orientation towards the definitive diagnosis in a patient with liver damage. The prerequisite for such a calculator would be revealing connections between the patterns of abnormal liver tests and a specific etiology, which could only be made by systematic search and analysis of published clinical studies, case series, and case reports, that involve liver function tests in patients with an established etiology of liver damage by means of the gold standard of diagnostics (usually liver biopsy).

The aim of our study was to design and construct a calculator that based on a pattern of abnormalities in liver function tests of a patient with liver damage would propose the most probable etiology. Diagnostic accuracy of the calculator will be tested on a sample of real patients suffering from various types of liver damage whose etiology was established by the gold standard of diagnostics.

METHODS

This retrospective observational, cross-sectional study was designed as a test for the diagnostic accuracy of an instrument (calculator) for rapid diagnostic orientation in patients with liver damage.

The main principle by which the calculator was constructed was comparing the pattern of abnormal liver function tests (i.e. a certain combination of abnormal values of laboratory parameters) in a patient with distributions of patterns characteristic for certain causes of liver damage obtained from the systematic search of published studies. Patterns of abnormal liver function tests for a certain etiology of liver damage were extracted from distributions of actual values taken from reports in medical literature about patients whose etiology of liver damage was proven by reliable diagnostic tests (gold standards for each specific diagnosis). Comprehensive and systematic literature search in the MEDLINE database dealing with abnormal liver chemistries was conducted. The search results included 5,867 publications from the categories of clinical trials, case series, or case studies. The calculator was based on a randomly chosen sample of 1,100 publications, whose results were further weighted according to the size of a patient sample. The calculator outputs were obtained on the basis of the analysis of a large number (more than 1,000) of individual model results obtained by random sampling of input variable values ("bootstrapping"). The input vari-

ables were the following: serum alanine aminotransferase (ALT) (IU/L) and aspartate aminotransferase (AST) (IU/L) levels, serum bilirubin (mmol/L), AP (IU/L), GGT (IU/L) serum albumin values (g/L), PT, long-term alcohol intake, drug or narcotics (xenobiotics) exposure, diabetes, hyperlipidemia, obesity, thyroid-stimulating hormone values, intense physical effort. The calculator provides output in the form of the most probable etiology of liver damage, or diagnoses, ranked by the probability of causation: toxic and drug-induced hepatitis (TDIH), chronic hepatitis (CH), AH, nonalcoholic steatohepatitis, acute hepatitis, AIH, metabolic liver disease, hyperthyroidism, heart diseases, and myopathies. The calculator was built in Microsoft Excel, Version 2007, using Boolean operators, the "if – then" function, and other general functions of the program.

The calculator functions according to the principle with what degree of positivity of the clinical condition parameters in patients with a liver lesion coincide with a degree in which such changes of parameters are described in scientific medical literature. Clinical condition parameters are valued binary (1 – there is a significant change; 0 – there is no significant change), as well as parameter values within a certain described clinical entity (1 – a significant change is described; 0 – no significant change is described). Depending on what percentage of studies from the total number of published studies describing a particular parameter change has determined that the parameter has changed and vice versa, i.e. if it exceeds a certain percentage threshold (of a positive or negative finding), such a parameter is assigned a value of 1 (over the threshold of positive values), 0 (over the threshold of negative values), or no value is assigned. Finally, the combination of individual parameter values in a patient is compared with the achieved combination of parameter values described in the literature for a certain diagnosis; therefore, the calculator provides the result that the clinical picture corresponds to a certain diagnosis, i.e. points to the diagnosis that most closely corresponds to the clinical picture of the patient.

Respecting established methodology and available published randomly chosen sample data, calculators for TDIH, CH; AH, nonalcoholic steatohepatitis, and AIH were set up. Established calculators are presented in Table 1.

After setting up the calculator, its diagnostic value was checked under real-life conditions, on a sample of patients with liver damage whose etiology was established by the gold standard of diagnostics (biopsy or else).

The inclusion criteria for the validation set of the patients were as follows: a) older than 18 years of age; b) male or female sex; c) patients with abnormal liver function test values in whom a definitive etiology of abnormal values was set on the discharge list and/or the report of the appropriate specialist (or it was concluded that liver damage was not the cause of abnormal liver function tests).

The exclusion (non-inclusion) criteria were the following: a) patients with incomplete medical documentation in whom the values of the input model variables could not be determined; b) patients with normal liver function test values; c) patients under 18 years of age; d) pregnant

and lactating women; e) patients who did not sign the informed consent.

In total, out of more than 1,000 screened patients, the validation set included 145 who fulfilled inclusion and did not have exclusion criteria.

The calculator validation study was conducted from September 1, 2015 to February 28, 2016 at the Military Medical Academy in Belgrade, Serbia. The data were collected from the medical records. Anonymity of the data used for the study was ensured by the study protocol and procedures. The patients were included in the validation group according to the "convenient" sample principle, since, due to limited resources of the researchers, it was not possible to choose a simple or cluster random sample. However, the sample was consecutive, i.e. all patients treated at the study site during the study time span were included in the sample. In order to avoid bias, the author who administered the calculator was blinded for results of the gold standard of diagnostics. The study was approved by the Professional Board of the health facility where the study was conducted, and the Helsinki Declaration was followed as a guidance.

All the data was summarized with adequate descriptive statistics. Numbers and percentages were used for categorical variables, while age in years as a continuous variable was presented as ranges (minimum–maximum values), medians, and interquartile ranges (IQRs, 25th–75th percentile) since the distribution had not been normal according to Kolmogorov–Smirnov testing. The difference between men and women in age ranges (groups) was explored using the Mann–Whitney U-test. The receiver operating characteristic (ROC) curves were constructed based on the percentage of overlap between the patterns of abnormal liver test for a certain diagnosis and actual abnormal liver test values of the patients. The areas under the curves (AUCs) and cut-off values (Manhattan distance) with corresponding sensitivity and specificity, positive (PPV) and negative predictive values (NPV), positive and negative likelihood ratios (LRs), as well as pre-test and post-test odds were calculated for each relevant diagnosis. Relative contribution of the input parameters to the most frequent diagnoses was tested by logistic regression. The significance level was set at 0.05. All analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) and the online Manhattan distance calculator (available at: http://molpath.charite.de/cutoff/).

RESULTS

A total of 145 patients, 84 males (57.9%) and 61 females (42.1%), with the median age of 50 years (range 18–76; 25–75% IQR = 35–78), were enrolled in the study. The median age of the female participants was 52 years (range 18–70; 25–75% IQR = 40–60) while that of the male patients was 47.5 years (range 22–76; 25–75% IQR = 35–57.5). A significant difference between females and males in terms of age was not observed: Mann–Whitney test = 2258.5, Z = -1, p = 0.224.
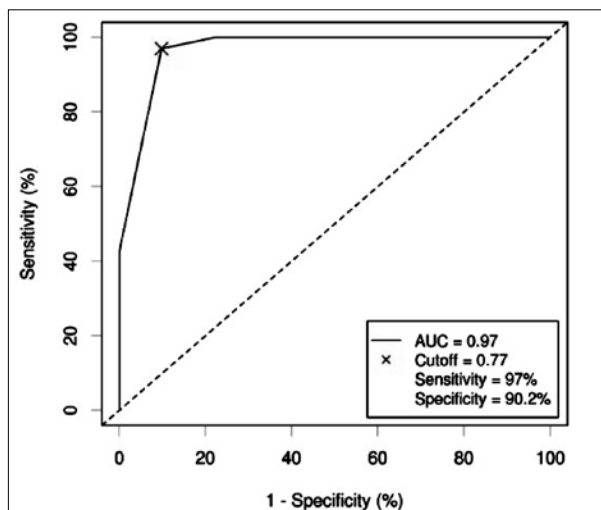

Figure 1. Receiver operating characteristic curve for toxic and drug-induced hepatitis
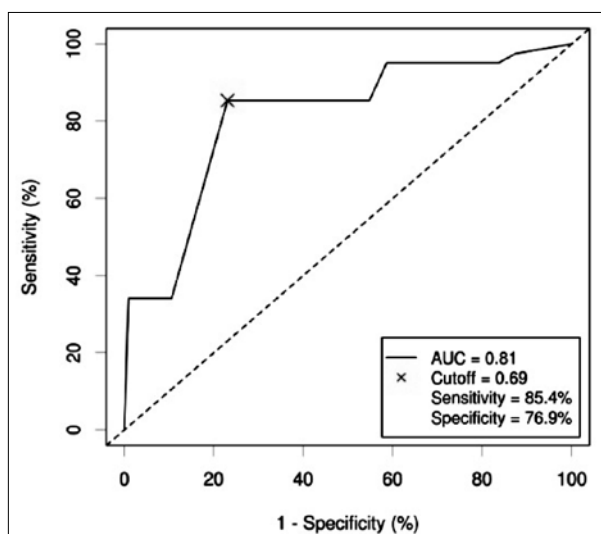AUC – area under the curve

Figure 2. Receiver operating characteristic curve for chronic hepatitis
AUC – area under the curve

Actual clinical diagnosis (as established by the "gold standard") in the sample were expressed as a number/percentage of the total: CH (41/28.3%), TDIH (33/22.8%), nonalcoholic steatohepatitis (15/10.3%), AH (11/7.6%), and AIH (11/7.6%). The ROC curves for three of the most relevant diagnoses are presented in Figures 1, 2, and 3.

ROC curves of the other diagnoses, i.e. for NASH, and AIH, also showed similar results: AUC 0.98, 0.97; cut-off values 0.65, 0.77; sensitivity 93.3%, 100%; specificity 100%, and 88%, respectively.

For all tested diagnoses, the calculator demonstrated highly significant difference between the AUC values and the value of 0.5 (p < 0.001) and high level of sensitivity (more than 90%, except for the model for CH) as well as relatively high specificity (more than 75%) were noted, indicating the good ability of the calculator to detect the etiology of liver damage. The additional results of validation of the calculator are shown in Table 2.
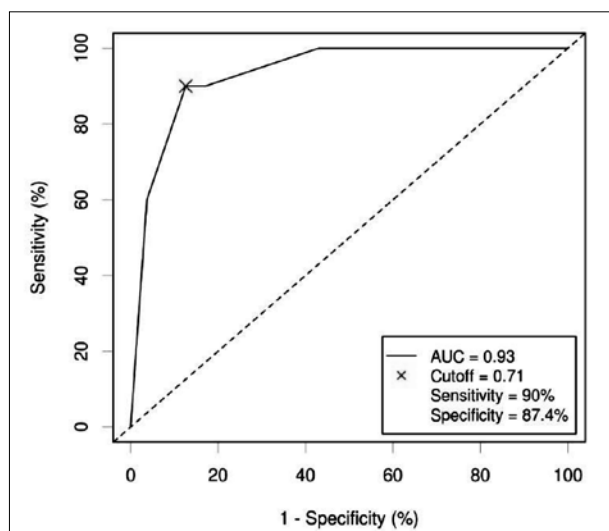
Figure 3. Receiver operating characteristic curve for alcoholic hepatitis
AUC – areas under the curve

DISCUSSION

Validation of our calculator on the sample set of the patients gave satisfactory results. Given the relatively low prevalence of the tested diagnoses of hepatic damage in our patients, the obtained values of PPV and NPV point to good performance of the calculator for almost all etiologies, except for the NASH (Table 2). The calculator was the most sensitive for TDIH, AIH, and NASH, while specificity was the highest for AIH and TDIH. Likelihood ratios as well as values of post-test odds indicate that the calculator increases significantly the probability of an etiology to which a pattern of liver test results in an individual patient correspond, particularly when it comes to CH and TDIH (Table 2). For the five diagnoses listed in Tables 1 and 2, the calculator could be considered as having sufficient diagnostic accuracy.

Basic etiological factors in AH are oxidative stress, metabolic disorders, and inflammatory responses [10]. Liver enzymes' modifications are typical of alcohol abuse. The pattern entered into our calculator consisted of abnormal levels of GGT, AST, ALT, bilirubin, AP, serum albumin, and PT in patients with evidence of alcohol abuse. A typical pattern of laboratory abnormalities in alcoholic liver disease observed by other authors was elevated AST and ALT (AST:ALT ratio exceeds 2); the values of AP and GGT levels are usually elevated to a variable degree; serum albumin, PT, and serum bilirubin values are usually normal until the occurrence of significant liver damage. Hypoalbuminemia occurs due to the decreased hepatic synthetic function as well as coexisting protein-energy malnutrition. The level of hyperbilirubinemia and abnormal PT reflects the severity of AH and is of prognostic value [11, 12, 13]. Available scoring systems for assessing the severity and

Binary logistic regression model for TDIH (Cox–Snell $R^2 = 0.202$; Nagelkerke $R^2 = 0.326$; Hosmer–Lemeshow test p = 0.050) did not reveal significant contribution of input parameters to the diagnosis, although the age and AST showed a strong tendency (p < 0.1). On the other hand, the binary logistic regression model for CH (Cox–Snell $R^2 = 0.466$; Nagelkerke $R^2 = 0.640$; Hosmer–Lemeshow test p = 0.180) showed significant contributions of AST [odds ratio = 1.005 (1.000–1.009), p = 0.036] and ALT [odds ratio = 0.984 (0.970–0.997), p = 0.021], although in opposite directions. The binary logistic regression model for AH (Cox–Snell $R^2 = 0.193$; Nagelkerke $R^2 = 0.699$; Hosmer–Lemeshow test p = 1.000) did not reveal a significant contribution of any of the input parameters to the diagnosis.

Table 1. Established calculators; calculators for the diagnoses of toxic and drug-induced hepatitis, chronic hepatitis, alcoholic hepatitis, nonalcoholic steatohepatitis, and autoimmune hepatitis are presented as a combination of individual input parameters

Diagnosis	Value of input parameters that determine the diagnosis											
	ALT	AST	BIL	AP	GGT	SA	PT	DRUG	ALCO	DM	OB	HL
Toxic and drug-induced hepatitis	1	1	1	1	1	0	0	1	0	0	0	0
Chronic hepatitis	1	1	1	0	0	1	1	0	0	0	0	0
Alcoholic hepatitis	1	1	1	1	1	1	1	0	1	0	0	0
Autoimmune hepatitis	1	1	0	0	0	0	0	0	0	0	0	0
Nonalcoholic steato-hepatitis	1	1	0	1	1	0	0	0	0	1	1	1

ALT – alanine aminotransferase; AST – aspartate aminotransferase; BIL – serum bilirubin; AP – alkaline phosphatase; GGT – gamma-glutamyl transferase; SA – serum albumin; PT – prothrombin time; DRUG – drug or narcotics (xenobiotics) exposure; ALCO – long-term alcohol intake; DM – diabetes mellitus; OB – obesity; HL – hyperlipidemia

Table 2. Results of calculator validation

Diagnostic value	Actual diagnosis (gold standard)				
	CH	TDIH	NASH	AH	AIH
PPV	0.59	0.75	1.00	0.35	0.42
NPV	0.93	0.99	0.99	0.99	1.00
Prevalence	0.28	0.23	0.10	0.07	0.08
Positive LR (conventional/weighted for prevalence)	3.70/1.46	9.90/2.96	Infinity	7.14/0.54	8.33/0.72
Negative LR (conventional/weighted for prevalence)	0.19/0.07	0.03/0.01	0.07/0.01	0.11/0.01	0.00/0.00
Pre-test odds	0.39	0.29	0.12	0.07	0.09
Post-test odds	1.43	2.87	Infinity	0.50	0.75

CH – chronic hepatitis; TDIH – toxic and drug-induced hepatitis; NASH – nonalcoholic steatohepatitis; AH – alcoholic hepatitis; AIH – autoimmune hepatitis; PPV – positive predictive value; NPV – negative predictive value; LR – likelihood ratio

prognosis of AH are Modified MDF based on PT and serum bilirubin concentration; GAHS that uses variables including age, blood urea, peripheral blood leukocyte count, serum bilirubin, and PT; the MELD score using bilirubin, creatinine, and INR levels; the Lille model which combines six variables (age, renal insufficiency, albumin, PT, bilirubin, and evolution of bilirubin on day 7). Scoring systems include differing cut-offs, various clinical and laboratory parameters; combining more than one scoring system, as well as establishing new scoring models, could improve the current practice [8].

CH is symptomatic, biochemical, or serological evidence of continuing or relapsing hepatic disease for more than six months. Histologically it is manifested as inflammation, necrosis, and fibrosis. Liver diseases leading to CH are viral, autoimmune, alcoholic, drug-induced, and cryptogenic. There are many histological scoring systems used in assessing grading and staging of liver biopsies from patients with CH: Knodell Histology Activity Index (HAI), the Scheuer scoring system, Ishak's system, METAVIR system, and Ishak modified HAI [14]. There are also commercial serum marker systems used to detect fibrosis in the liver, such as FibroTest (multiparameter test that includes haptoglobin, bilirubin, GGT, apolipoprotein A-I, and alpha-macroglobulin) or Enhanced Liver Fibrosis (ELF™) test (Siemens Healthcare GmbH, Erlangen, Germany). "Egy-Score" has been developed for the noninvasive assessment of hepatic fibrosis and cirrhosis. Egy-Score has shown good sensitivity, specificity, PPVs and NPVs, and AUROCs for predicting significant fibrosis ($\geq$ F2), severe hepatic fibrosis ($\geq$ F3), and cirrhosis (F4) [15]. Liver stiffness measurement (LSM) can be used to assess liver fibrosis in patients with CH. Our biochemical calculator used the following pattern of abnormal liver test values for diagnosing CH: AST, ALT, total bilirubin, serum albumin, and PT. An abnormal bilirubin level could signalize the disease is severe or advanced. Serum albumin and PT determine the severity; low serum albumin level and or prolonged PT may suggest cirrhosis and even portal hypertension. Non-invasive methods can now be used instead of liver biopsy to assess liver disease severity prior to therapy at a safe level of predictability [16].

The diagnosis of AIH is based on clinical, biochemical findings, the presence of histological image, autoantibodies, and abnormalities of serum globulins [17]. In our study, we observed abnormal levels of transaminases, AST and ALT. Elevation of liver transaminases (less than 500 UI/L) with normal AP is typical in AIH. An abnormal level of AP, which is disproportional to transaminase elevation, is unusual and requires an investigation of other causes of liver disease such as drug-induced disease, primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). International Autoimmune Hepatitis Group has proposed a scoring system of which there are several adaptations. A simplified scoring system uses serum antibodies, serum IgG levels, liver histology data and data on absence of viral hepatitis. The original revised scoring system has greater sensitivity for AIH (100% *vs.* 95%), whereas the simplified scoring system has specificity 90% *vs.* 73% and accuracy

(92% *vs.* 82%), using clinical assessment as the gold standard. AIH may overlap with PBC or PSC. AIH could be combined with NAFLD and these patients are more likely to develop an adverse clinical outcome with poor survival. There is a subtype of DILI with autoimmune background. AIH will attract more attention because many serious issues related to it remain to be elucidated [17, 18, 19].

Diagnosis of drug-induced liver disease (DILD) is based on history, blood tests, imaging examinations, and, if applicable, liver biopsy. There are no specific laboratory tests, histological presentations, or clinical signs and symptoms enabling the diagnosis of DILD. Signs and symptoms vary with the drug, host, and severity of damage [20]. The manifestations of drug-induced hepatotoxicity are highly variable, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure. CIOMS/RUCAM score reflects the likelihood that the hepatic damage is due to a specific medication. Limitations of such scoring algorithms are poor inter-rater reliability and arbitrary scoring, for example, for alcohol use [21]. Significant increase in scientific studies investigating this disorder in the last few years is making DILD an emerging safety issue. The United States Food and Drug Administration (FDA) established the Liver Toxicity Knowledge Base (LTKB) at the FDA's National Center for Toxicological Research [22]. Based on the daily dose, lipophilicity, and formation of reactive metabolites, a DILD score algorithm has been developed. It provides a scale for assessing the severity of DILD risk in humans, associated with oral medications [23]. Patients with DILD at high risk for acute liver failure could be identified by Hy's Law. Limitations are low sensitivity but high specificity. Due to the current lack of sensitive and specific clinical tests to diagnose, predict and monitor drug-induced injury to the liver, EMA has opened a project in order to set up new biomarkers to enable earlier diagnosis, predict outcome and prognosis of DILD [24, 25]. By using well-established liver serum parameters in our study, we observed abnormal levels of ALT, AST, total bilirubin, GGT, and AP in DILD.

NAFLD is one of the most common liver diseases that includes steatosis, steatohepatitis, and NASH and can progress to cirrhosis, liver failure, or hepatocellular cancer. Liver histology is the gold standard for diagnosing NASH [26]. Since biopsy is invasive, risky, and connected to errors in obese patients, noninvasive alternatives have been established [27]. The pattern entered into our calculator consisted of abnormal levels of AST, ALT, AP, GGT associated with hyperlipidemia, obesity, and abnormal glucose metabolism (diabetes mellitus). Existing noninvasive models and scores combine clinical data (age, degree of obesity and diabetes, family history, AST:ALT ratio > 1), measures of elasticity and blood test variables (pointers of collagen metabolism, cell death (M30 CK-18), insulin resistance (adiponectin and resistin), or oxidative stress markers (thioredoxin, lipid peroxides), but have still not reached a wide clinical acceptance [28, 29].

Main limitation of our study was a relatively small number of patients with certain diagnoses, so validation could have been conducted for a limited etiological spectrum. In

addition, low prevalence of certain diagnoses could have led to an overestimation of diagnostic accuracy of the calculator in that regard. Further studies are needed to have complete picture of diagnostic value of this calculator. The calculator could be improved in the future if the full spectrum of retrieved studies is taken into account, as more complete data about laboratory parameters could increase precision of the estimate of diagnostic accuracy and its scope may be widened with a number of other diagnoses.

rely on this calculator for making a definitive etiological diagnosis of liver damage; it should rather be considered an auxiliary, not quite precise tool for rapid screening of such patients and directing further diagnostics including the gold standard, as necessary. In the future, this calculator should become available to clinicians as a free application on smart phones, so that they can be able to use it easily and rapidly whenever they first encounter a patient with abnormal liver tests.

CONCLUSION

In conclusion, our calculator showed satisfactory sensitivity and specificity for major liver damage etiologies. It is clear that the calculator is not a substitute for elaborate diagnostic algorithms and methods already used for finding a cause of liver damage, but it could be a useful tool for rapid orientation when first faced with a patient whose liver function tests are abnormal. Clinicians should not

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Перформансе калкулатора за дијагностику узрока оштећења јетре

Нарциса Петровић-Субић[1], Мирослав Којић[2], Слободан М. Јанковић[1], Срђан М. Стефановић[1]

[1]Универзитет у Крагујевцу, Факултет медицинских наука, Катедра за фармакологију и токсикологију, Крагујевац, Србија;
[2]Војномедицинска академија, Клиника за инфективне и тропске болести, Београд, Србија

САЖЕТАК
Увод/Циљ Израда калулатора који би препознао обрасце абнормалних тестова функције јетре и повезао их са највероватнијом етиологијом могла би да помогне клиничарима код прве оријентације ка дефинитивној дијагнози код болесника са оштећењем јетре. Циљ наше студије био је да дизајнирамо, конструишемо и валидирамо калкулатор који на основу обрасца абнормалних тестова функције јетре код болесника са оштећењем јетре предлаже највероватнију етиологију.

Методе Образац абнормалних тестова функције јетре за одређену етиологију оштећења јетре преузет је из дистрибуције стварних вредности које су преузете из медицинске литературе о болесницима чија је етиологија оштећења јетре доказана поузданим дијагностичким методама. После постављања калкулатора, његова дијагностичка вредност је проверена у стварним условима, на узорку болесника са оштећењем јетре чија је етиологија установљена златним стандардом дијагностике (биопсија или друго). Студија валидације калкулатора обављена је на Војномедицинској академији у Београду током двогодишњег периода (2015–2016).

Резултати За све тестиране дијагнозе, калкулатор је показао веома значајну разлику између површине испод *ROC* (*Receiver operating characteristic*) крива и вредности од 0,5 (*p* < 0,001), а уочен је и висок степен сензитивности (више од 90%, осим калкулатора за хронични хепатитис), као и релативно висока специфичност (више од 75%), што указује на добру способност калкулатора да открије етиологију оштећења јетре.

Закључак Нови калкулатори показали су задовољавајућу осетљивост и специфичност за откривање главних етиологија оштећења јетре.

Кључне речи: медицински калкулатор; сензитивност; специфичност; етиологија