ARTIFICIAL NEURAL NETWORKS AND LIVER DISEASES: AN ECONOMIC AND PRE-IMAGING DIAGNOSIS

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ABSTRACT

Background e Aims*: We investigated if an Artificial Neural Network ANN) is able to identify hepatobiliary disease in selected patients affected with several, already diagnosed, hepatobiliary diseases, using only clinical and few laboratory findings, to provide a tool for early and "pre-imaging"(i.e. without using radiologic techniques) diagnosis of patients in real-life context.*

Methods*: We used data from medical records of 270 patients affected with several hepatobiliary diseases. Patients were divided in three groups: G_{train} (with clinical paradigmatic characteristics), to train network; G_{test} ("clinically similar" to those of G_{train}) to test the trained network; and, finally, G_{val} significantly different from the above sets), to validate ANN diagnostic capabilities.*

Results*: After training, the network provided right answer 96% of times, while in remaining 4% network outputs were only partly wrong. Comparing sets G_{train} and G_{test}, we deduce that ANN is stable under minor modifications. Considering G_{val}, right answer was given 80% of cases, while remaining results were, again, enough correct, an evidence of ANN's stability under major modifications.*

Conclusions*: our ANN works well for patients with known hepatobiliary diseases. Next step will be to use ANN for patients with suspected hepatobiliary diseases, and to extend our ANN to other human diseases.*

Key words*: liver diseases, artificial neural network, differential diagnosis.*

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Introduction

Viruses, bacteria, or fungi, exposure to toxins, like alcohol or drugs, and autoimmunity are only few of the several possible etiological factors that contribute to the hepatocellular damage, characterizing liver diseases. Particularly, patients infected by major hepatotropic viruses present a continuous spectrum of hepatic pathology, from mild chronic hepatitis to end-stage cirrhosis and hepatocellular carcinoma. According to the statistical data from the Italian Ministry of Health, from 1980 to 2003 (the last available data), liver diseases, especially cirrhosis, have been consistently listed as one of the top ten fatal diseases (7th position), among the highest in Europe and industrialized countries, leading more than 15,000 fatalities every year[(1)]. On a worldwide scale, liver cancer, one of the most life-threatening solid tumours, remains the 5th most frequent cancer, with an incidence of about 560,000 new cases every year, and the 2nd most common cause of cancer-related deaths[(2)]. Besides, liver diseases are not easily diagnosed, as the liver is able to keep on its normal activity even if partially damaged. So, there is even more urgent need to diagnose liver diseases as soon as possible to prevent chronic, and often fatal, degeneration of hepatocellular structures. However, medical diagnosis is a highly demanding task, requiring expert physicians to analyze and judge various examination frameworks (i.e. symptoms/signs), as well as laboratory and radiological findings. Acquiring sufficient

experience and developing substantial expertise may take several years for a physician. Moreover, experience and expertise alone do not guarantee accurate diagnosis. Heavy clinical workload raises the risk and uncertainty of the medical diagnosis. For this, the need of auxiliary systems for diagnosis has become increasingly crucial.

Since few decades the rapid developments of information technology helped physicians to avoid transcribing patient medical histories. Using computer data processing systems, medical histories and other related information could be efficiently stored, in great amount, in databases for quick retrieval and analysis. This late possibility opened new sceneries, starting with statistical analysis of groups of patients or using different computer aided strategies. One of these last, whose potentialities are not yet fully explored, is provided by the so-called artificial neural networks (ANNs). ANNs, originally from neurobiological models, are systems composed of highly interconnected and interacting simple signal-processing units. Just like human brain, an ANN can learn by example and dynamically modify itself to fit and understand the input data. An ANN should be an innovative tool for clinical decision-making and have been applied in several medical research areas, including thyroid function, myocardial infarction, and cancer diagnosis[3-12]. Several authors have also used ANNs to analyze different aspects of liver disease diagnosis. Particularly, Kim et al.[13] used ANNs to analyze liver disease risk factors, Nakano et al.[14] to discriminate mild and severe chronic active hepatitis, Piscaglia et al.[15] to classify significant fibrosis, cirrhosis, and other liver diseases, and, finally, Maiellaro et al.[16] to predict therapy response of patients with chronic hepatitis C.

The main goal of this study was to investigate if an ANN is able to identify the kind of (liver or hepatobiliary) disease in a cohort of selected patients, affected with several, already diagnosed, hepatobiliary diseases, using only few clinical and laboratory findings, in order to provide an useful tool for physicians for differential diagnosis of their patients in the real-life clinical context. Stated in different words, we were interested to build up an efficient and 'economic' network, i.e. a network which may suggest an high-probability diagnosis to the doctors without expensive laboratory and radiologic tests, guiding them to consider and perform further diagnostic examinations, i.e. more expensive laboratory, radiologic and invasive tests.

Patients and methods

Clinical data

This study was carried out using a database accounting data from the medical records of a sample of 270 patients mean age 52 (18-83) years, 109 females, mean age 51 (19-81) years, and 161 males, mean age 52 (21-80) affected with several hepatobiliary diseases, admitted to our Department, during the period 2002-2010, as outpatients or inpatients. Diagnosis of hepatobiliary disease was achieved assessing clinical history, registering symptoms, physical examination, laboratory and radiologic findings, and, in some case 34 patients, (12.6% of total), by liver biopsy and pathology examination.

Data set

Using the medical records of the patients, we identified 289 relevant variables, corresponding to symptoms, signs, and abnormalities from biomedical tests. These variables, with the corresponding reference ranges used in the laboratory of our Institution, are listed in Tables 1-3. Some of the considered variables were structured data (e.g. check boxes in the medical records, which were crossed out depending on normality or abnormality of clinical finding, and laboratory results). Others, on the contrary, were unstructured (e.g. text elements found in the medical records, especially for symptoms and signs). We adopted, for each variable introducing an intrinsic degree of arbitrariness for unstructured data, a value on a scale 0-10, (corresponding to the presence and to the intensity 0 pointing out absence, 1 to 10 for mild to severe) of every symptom, sign, and biomedical test abnormality of each single patient. The patients were divided in three groups, named G_{train}, G_{test} and G_{val}, the first being used to *train* the network; the second, with clinical and laboratory data not very different from G_{train}, to *test* the trained ANN, and the third to further *validate* the procedure. However, before training the network, a set of 40 input variables, S, was extracted from the complete set of 289 inputs, and only these variables were used to train the (ANN Table 4).

To uniquely determine which kind of liver disease affects the patient it would have been natural, in principle, to consider all the original 289 symptoms, signs and laboratory abnormalities, and, using their values, to deduce the corresponding disease. However, this is not necessarily the best procedure, since, for instance, two different sets of these 289

inputs may correspond to the same disease. In other words, there is not a one-to-one correspondence between diseases and these complete 289 input data. The main criterium adopted in choosing *S* was to focalize on few symptoms/signs/laboratory tests, in our view, more predictive of liver disease. A second criterium was to avoid, as much as possible, expensive laboratory tests, in order to economize patient's first evaluation. Other symptoms/signs, as well as expensive tests, would have been considered at a second stage of the analysis, especially if the network's outcome were not enough persuasive. Thirdly, if a disease can be found only by performing a certain laboratory test, then this must be included in *S*, otherwise, not surprisingly, the network will not be able to recognize this particular disease i.e. Hepatitis D Virus antigen demonstration). Finally, two different diseases must correspond to two different input vectors (see below). This is to prevent the network to confuse the two. For this reason, *S* cannot be taken too small.

ANN analysis and construction

Neural networks have been applied along the years, in several fields[17,18]. An ANN consists of simple signal-processing units, the so-called "neurons". Each neuron can have multiple inputs, but it only has a single output. The input-output relationship is controlled by a transfer function. The inputs of a neuron are first multiplied by a weighting factor that determines the extent to which each input influences the output, then the weighted inputs are summed to form a pre-neuron sum. This is finally plugged through the transfer function resulting in the neuronal output. An artificial network is built up organizing individual neurons into a series of layers. In a so-called feed-forward fully-connected network, each neuron gets an input from neurons located in the preceding layer, generating a single output result, becoming itself new input variable for each neuron in the successive layer. The layers between the first input variables and the final output layer are called "hidden" layers. Assuming to have fixed the transfer function and the layers topology, the desired behaviour of an ANN can be driven by adjusting the neuronal connections. This is called *training the network*, and is carried out by using a data set for which the correct output of the corresponding input variables is known. This is the phase during which G_{train} is used. A good network is obtained when the training process is able to reduce the output errors for the training set to negligible values. When this is achieved, then the ANN has properly *learned*. In other words, after the learning process, if you give to the network a particular input data vector, which was already used to train the network, you should get the same (correct) result. This is a natural requirement, which, however, is not automatically satisfied, because of the very large freedom degrees intrinsic in the definition of any ANN. The trained ANN can then be *used* to estimate the output values for new input data, e.g. for patients which were not used during the training procedure, for instance for those in G_{test}. This is the phase called *testing the network*, which is essential to check the stability of the ANN under minor modifications of the inputs. If the performance of the network is not good, i.e. if the outputs corresponding to G_{test} differ significantly from the correct known ones, the network should be remodelled, changing the number of neurons, the layers, fixing a different value of the acceptable error, and so on. This new network should now be trained again, using G_{train}, and then tested, using G_{test}. Adding neurons or hidden layers to a network doesn't mean, necessarily, improving its efficiency, due to the intrinsic complexity of an ANN, and a more complex ANN architecture could disperse the results. Hence, finding the correct number of neurons and of hidden layers to get an efficient ANN is already a difficult task. The last phase has been called here *validating the network*: the patients in G_{val} were used to check the concrete ability of the network to recognize the known diseases. The main difference with the testing and the training phases was in the choice of G_{val}, which included only those patients of our data set whose related vectors were significantly different from those in $G_{train}$and G_{test}. After the training, the testing and the validating phases, if we give to the network a new vector of data for which the output in unknown, the network should determine an output value, which should be interpreted as the disease described by this vector. This procedure permits to hint a diagnosis for new data set, i.e. for other patients with suspected liver diseases.

Building G_{train}, G_{test} and G_{val}

As stated above, patients were divided in three groups of 30, 90 and 150 ones, respectively. The first group, G_{train}, whose patients were chosen because of their "paradigmatic" characteristics, according to the international literature, was used to

train the network. The 90 patients in G_{test}, chosen because of their similarities with those of G_{train}, were used to test the trained network. The set G_{val}, consisting of patients significantly different from those of the above sets, was finally used to further validate the diagnostic capabilities of our ANN. The idea underlying this particular partition of the patients can be easily understood: once the ANN is trained, we wanted to check if the network is stable under minor modifications (i.e. changing a little bit the inputs does not change much the outputs). This is important to avoid problems arising from the uncertainty intrinsic, for instance, in the "text-to-number" procedure used for unstructured data, generating the input vectors. Another source of uncertainty is determined by the probability that different input variables values could correspond to the same disease. For instance, the numerical value of a given sign can be different from a patient to the other, even if they suffer with the same disease. Furthermore, two different physicians may attribute two slightly different values to the same sign of a certain patient. After checking this stability, we were interested in considering the ANN's reaction to major modifications (i.e. to major changes in the input vectors).

Using the above-described criteria, we extracted N_{sym} symptoms out of the ones listed in Table 1, N_{signs} signs out of the ones listed in Table 2, and N_{lab} laboratory results out of the ones listed in Table 3. Hence, S is made of $N_{sym} + N_{signs} + N_{lab} = NS$ (quantities =40). Each patient Pj in the training set $G_{train} = \{ P_j, j = 1, 2, \ldots, M_{train} = 30 \}$ does therefore correspond to an NS-dimensional vector X_j, where the N_S components of X_j are the values of the corresponding symptoms, signs and laboratory results, as listed in Table 4. The (known) output, corresponding to X_j, is a 30-dimensional vector (one dimension for each disease) Y_j, with all zero entries, except in the j - *th* position, in which the vector takes the value one: $(Y_j)_k = \delta_{j,k}$. For testing purpose, a second group of 90 patients, $G_{test} = \{ P_j, j = 1, 2, \ldots, M_{test} = 90 \}$, has been considered. Our testing phase consists in checking whether the trained network recognize these diseases. In other words, each P_j belonging to G_{test} was described, again, by a 40-dimensional vector X_j, while the disease affecting P_j is known, but, in this testing procedure, should be confirmed by the network. Our analysis was concluded by a validating phase, involving a third group of 150 patients, $G_{val} = \{ P_j, j = 1, 2, \ldots, M_{val} = 150 \}$. Our validating phase consists in checking whether the network recognize the (again, known) disease affecting these other patients, whose vectors were significantly different from those describing the ones in the two other groups.

1	Abdominal pain	43	Itch
2	Abdominal pain radiate to the back	44	Joint pain
3	Abdominal pain radiate to the right shoulder	45	Leg pain
4	Abnormal gait	46	Lethargy
5	Alteration of consciousness	47	Localized colicky abdominal pain
6	Amenorrhea	48	Loss of libido
7	Anorexia	49	Loss of sexual inhibitions
8	Arthralgias	50	Lower abdominal pain
9	Asthenia	51	Memory impairments
10	Back pain	52	Meteorism
11	Bile-stained vomiting	53	Muscle pain
12	Bone pain	54	Nausea
13	Chills	55	Numbness
14	Chronic alcoholism	56	Oligomenorrhea
15	Coetaneous hyperpigmentation	57	Pain in left hypochondrium
16	Colicky pain in the epigastrium and right hypochondriac	58	Pain in right hypochondrium
17	Coma	59	Pericardial pain
18	Confusion	60	Pleuritic pain
19	Constipation	61	Polydipsia
20	Depression	62	Polyphagia
21	Diarrhea	63	Polyuria
22	Diarrhea with blood and/or mucus	64	Precordial pain
23	Diffuse abdominal pain	65	Productive cough
24	Dry cough	66	Psychomotor agitation
25	Dyspepsia	67	Right cost vertebral angle pain
26	Dysphoria	68	Right hemithorax pain
27	Dyspnea	69	Right hemithorax sense of weight
28	Dysuria	70	Right hypochondrium sense of weight
29	Early gastric sense of filling	71	Seizures
30	Early satiety	72	Sore throat
31	Easy fatigue	73	Speech disorders
32	Epigastric pain	74	Spontaneous miscarriages
33	Euphoria	75	Spread colicky abdominal pain
34	Flatulence	76	Steatorrhea
35	Food vomiting	77	Stupor
36	General malaise	78	Tremor
37	Headache	79	Urinary retention
38	Heartburn	80	Urticaria
39	Hyperactivity	81	Vomit
40	Irritability	82	Weight loss
41	Inappetence	83	Xerophthalmia
42	Incoordination		

Table 1: Symptoms of liver disease (in alphabetic order).

The Software

Several possible software to build up efficiently ANNs are available. In this study we have used a software which has turned out to be very powerful and convenient for our analysis, EasyNN-plus©, that can be obtained from the web site www.justnn.com. This software allows to fix several aspects of the

1	Abdominal distention	47	Hepatomegaly	93	Scratching injuries
2	Abdominal pain	48	Hippocratic facies	94	Shock
3	Acholia of the stool	49	Hippocratic fingers	95	Side abdominal circles
4	Altered state of consciousness	50	Hyperchromic urine	96	Sign of the ice
5	Amenorrhea	51	Hyperpigmented skin	97	Sign of the surge
6	Anuria	52	Hypertension	98	Skin rash
7	Arrhythmias	53	Hypocholia of the stools	99	Small and medium-sized bubbling rales
8	Arthritis	54	Hypotension	100	Smooth and solid swelling of the right upper quadrant
9	Ascites	55	Incoordination	101	Snappy liver margin
10	Ataxia	56	Intractable abdomen	102	Spider angioma
11	Baseline pulmonary rustling	57	Irregular liver margin	103	Spider naevi
12	Basilar dullness on percussion	58	Jaundice	104	Splenomegaly
13	Batrachians abdomen	59	Jugular swelling	105	Steatorrhea
14	Blumberg sign	60	Kayser-Fleischer corneal ring	106	Sunflower cataract
15	Body Mass Index >30	61	Keratoconjunctivitis	107	Swelling, which moves in consensus with diaphragm
16	Bone fractures	62	Laterocervical lymphadenopathy	108	Systolic tricuspid murmur
17	Bulbar syndromes	63	Lichen planus	109	Tachyarrhythmias
18	Cardiac area dilation	64	Loss of hair	110	Tachycardia
19	Cardiomegaly	65	Malnutrition	111	Tactile vocal fremitus reduction
20	Central obesity	66	Melanodermia	112	Tender hepatomegaly
21	Chamfer liver margin	67	Melena	113	Testicular atrophy
22	Convex liver surface	68	Mooren corneal ulcer	114	Third hearth sound
23	Cool skin	69	Motor neuropathy	115	Tremor
24	Coordination deficits	70	Murphy's sign	116	Tympanic abdomen
25	Courvoisier-Terrer's sign	71	Nephrolithiasis	117	Urinary bladder overdistension
26	Cranial nerves neuropathy	72	Obstipation in feces and gases	118	Urticarial rash
27	Dehydration	73	Oliguria	119	Vesicular murmur reduction
28	Descent to transversal umbilical line of liver lower margin	74	Orthostatic dyspnea	120	Voluntary guarding
29	Diastolic pulmonary murmur	75	Orthostatic hypotension	121	Vomica
30	Diffusely tender abdomen	76	Osteoarthritis	122	Weight loss
31	Doubling pulmonic second heart sound	77	Painful purpuric skin lesions	123	Xanthelasma
32	Dupuytren's sign	78	Palmar erythema	124	Xanthomas
33	Dyspnea	79	Paralytic ileus	125	Zygomatic hypertrichosis
34	Dystonia	80	Pericardial friction		
35	Ecchymosis	81	Peripheral polyneuropathy		
36	Edema of lower extremities	82	Petechiae		
37	Epigastric mass	83	Pleural rub		
38	Erythema nodosum	84	Profuse sweating		
39	Excoriation	85	Purulent vomica		
40	Fever	86	Recurrent epistaxis		
41	Flapping tremor	87	Reduced expansibility of the chest with breathing		
42	Flushing	88	Reduced expiratory diaphragm excursion		
43	Foamy urine	89	Reduction of sensory		
44	Gynecomastia	90	Right hemidiaphragm elevation		
45	Hematemesis	91	Right upper quadrant mass		
46	Hepatojugular reflux	92	Rigidity		

Table 2: Signs of liver disease (in alphabetic order).

ANN to construct. In particular, it could fix the number of layers, the number of neurons for each layer, the learning rate and the error threshold used to stop the training procedure. The network we used consisted in one hidden layer made by 40 neurons. We fixed the learning rate value, and the value 10^{-5} for the error. The network was trained with a back propagation algorithm, and the threshold error was achieved after 2012 epochs, which corresponds, working with an ordinary laptop, with no particular calculating power (the one used here has a 2.5MHz dual core processor, and 3Gb of RAM), to few seconds. The transfer function used in each neuron is a sigmoidal: $f(x) = 1/(1+e^{x})$.

Results

ANN results on patients in set G_{test} and G_{val} are given in Tables 5 and 6, respectively. These are organized in the following way: the first column lists the various diseases considered by the ANN; the second shows the percentage of correct diagnosis, whose corresponding number is given, together (when needed) with the uncorrected one, in the third col-

1	Anaemia (hemoglobin r.r.: male 13.0-17.0 g/dl; female 12.0-16.0 g/dl)	29	Hyperbilirubinemia (r.r.: <1.2 mg/dl)	57	Increased serum gamma-glutamyl transpeptidase (r.r.: male 8.0-61.0 U/L; female 5.0-36.0 U/L)
2	Anti-actin antibodies (positive 1:40)	30	Hypercalcemia (r.r.: 8.4-10.2 mg/dl)	58	Increased serum C Reactive Protein (r.r.: <0.5 mg/dl)
3	Anti-extractable nuclear antigens antibodies (positive 1:40)	31	Hypercholesterolemia (r.r.: <200 mg/dl)	59	Increased serum desialed transferrin (r.r.: 200-360 mg/dl)
4	Anti-HBe antibodies positivity (r.r.: negative)	32	Hypercreatininemia (r.r.: male 0.67-1.17 mg/dl; female 0.51-0.95 mg/dl)	60	Increased serum total IgA (r.r.: 70.0-400.0 mg/dl)
5	Anti-HBs antibodies positivity (r.r.: negative)	33	Hyperferritinemia (r.r.: male 30.0-400.0 ng/ml; female 15.0-150.0 ng/ml)	61	Increased serum total IgG (r.r.: 700.0-1600.0 mg/dl)
6	Anti-HBc IgM antibodies positivity (r.r.: negative)	34	Hyperglycaemia (r.r.: 82-115 mg/dl)	62	Increased serum total IgM (r.r.: 40.0-230.0 mg/dl)
7	Anti-Hepatitis C Virus (HCV) antibodies positivity (r.r.: negative)	35	Hyperlipasaemia (r.r.: 13.0-60.0 U/L)	63	Increased transferrin saturation (r.r.: male 20-50%; female 15-50%)
8	Anti- Hepatitis D Virus (HDV) antibodies positivity (r.r.: negative)	36	Hypersideremia (r.r.: male 59.0-158.0 µg/dL; female 37.0-145.0 µg/dL)	64	LDL-hypercholesterolemia (r.r.: <160 mg/dl)
9	Anti-mitochondrial antibodies (positive: 1:40)	37	Hypertransaminasemia (aspartate aminotransferase r.r.: male <41.0 U/l; female <31.0 U/l; alanine aminotransferase r.r.: male <37.0 U/l; female <31.0 U/l)	65	Leucocytosis (white blood cells count r.r.: 4.0-11.0 x 103/µl)
10	Anti-nuclear antibodies (positive: 1:40)	38	Hypertriglyceridemia (r.r.: <200 mg/dl)	66	Leukopenia (white blood cells count r.r.: 4.0-11.0 x 103/µl)
11	Anti-SLA/LP antibodies (positive 1:40)	39	Hyperuricaemia (r.r.: male 3.4-7.0 mg/dl; female 2.4-5.7 mg/dl)	67	Liver-kidney microsomes antibodies (positive: 1:40)
12	Anti-smooth muscle antibodies (positive 1:40)	40	Hypoalbuminemia (r.r.: 3.48-5.39 g/dl)	68	Low urinary sodium (r.r.: 30-300 mEq/24h)
13	Bilirubinuria (r.r.: negative)	41	Hypocalcemia (r.r.: 8.4-10.2 mg/dl)	69	Lymphocytopenia (lymphocytes count r.r.: 1.0-5.0 x 103/µl)
14	Direct hyperbilirubinemia (r.r.: <0.3 mg/dl)	42	Hypocholesterolemia (r.r.: <130 mg/dl)	70	Lymphocytosis (lymphocytes count r.r. 1.0 - 5.0 x 103/µl)
15	Echinococcus IgG antibodies (r.r.: negative)	43	Hypochromic anaemia (hemoglobin r.r.: male 13.0-17.0 g/dl; female 12.0-16.0 g/dl; mean corpuscular hemoglobin r.r.: 27.0-32.0 pg)	71	Macrocytic anaemia (hemoglobin r.r.: male 13.0-17.0 g/dl; female 12.0-16.0 g/dl; mean corpuscular volume r.r.: 78-95 fL)
16	Elongation of prothrombin time (r.r.: 24.0-36.0 sec.)	44	Hypofibrinogenemia (r.r.: 150.0-450.0 mg/dl)	72	Neutropenia (white blood cells count r.r.: 2.5-7.5 x 103/µl)
17	Eosinophilia (r.r.: <0.8 x 103/µl)	45	Hypoglycaemia (r.r.: 82-115 mg/dl)	73	Neutrophilia (white blood cells count r.r.: 2.5-7.5 x 103/µl)
18	Erythrocytosis (red blood cells count r.r.: male >5.9 x 106/µl; female >5.2 x 106/µl)	46	Hyponatremia (r.r.: 132.0-147.0 mEq/L)	74	Peri-nuclear antineutrophil cytoplasmic antibodies (positive 1:40)
19	HBeAg (r.r.: negative)	47	Hypotriglyceridemia (r.r.: <40 mg/dl)	75	Polyclonal hypergammaglobulinemia (r.r.: 0.67-1.56 g/dl)
20	HBsAg (r.r.: negative)	48	Hypovitaminosis D (r.r.: >30 ng/ml)	76	Reduction of serum folate (r.r.: 4.6-18.7 ng/ml)
21	Hepatitis B Virus (HBV)-DNA	49	IgG anti-HBc positivity (r.r.: negative)	77	Reduction of serum pseudocholinesterase (r.r.: 5320.0-12920.0 U/L)
22	HCV-RNA (r.r. negative)	50	IgM anti-Hepatitis A Virus positivity (r.r.: negative)	78	Reduction of serum Vitamin B12 (r.r.: 191-663 pg/ml)
23	HDV-Ag (r.r. negative)	51	IgM anti-HBc positivity (r.r.: negative)	79	Rheumatoid Factor positivity (r.r: negative)
24	HLA-DR3 (r.r.: positive/negative)	52	Increased serum alkaline phosphatase (r.r.: male 40.0-129.0 U/L; female 35.0-104.0 U/L)	80	Serum α-fetoprotein (r.r.: <7 ng/ml)
25	HLA-DR4 (r.r.: positive/negative)	53	Increased CA 19.9 blood levels (r.r.: <39 U/ml)	81	Thrombocytopenia (thrombocytes count r.r.: 150.0-450.0 x 103/µl)
26	Hyperammonemia (r.r.: 9.0-30.0 µmol/l)	54	Increased serum CarcinoEmbryonic Antigen (r.r.: <5.2 ng/ml; smokers <6.5 ng/ml)		
27	Hyperamylasaemia (r.r.: 28.0-100.0 U/L)	55	Increased Erythrocyte Sedimentation Rate (r.r.: male 2.0-15.0 mm/hr; female 2.0-20.0 mm/hr)		
28	Hyperazotaemia (r.r.: < 71 mg/dl)	56	Increased ethanol blood concentrations (r.r.: <10 mg/dl)		

Table 3: Laboratory findings of liver disease (in alphabetic order) and corresponding reference ranges used in the laboratory of our Institution.
r.r.: reference range

umn.

The other three columns list the outputs produced by the network in decreasing order of probability, expressed by a value deduced, looking at the numerical results of the ANN output vectors: the larger the output value, the greater the probability of the corresponding disease. We gave only the first three choices. For instance, in Table 5, in line 1,

2	Dyspepsia
3	Abdominal pain radiate to the back
4	Abdominal pain
5	Colicky pain in the epigastrium and right hypochondriac
6	Pain in right hypochondrium
7	Coetaneous hyperpigmentation
8	Itch
9	Steatorrhea
10	Bile-stained vomiting
11	Acholia of the stool
12	Altered state of consciousness
13	Ascites
14	Side abdominal circles
15	Hepatomegaly
16	Flapping tremor
17	Jaundice
18	Scratching injuries
19	Melena
20	Sign of the surge
21	Sign of the ice
22	Murphy's sign
23	Spider naevi
24	Splenomegaly
25	Elongation of prothrombin time
26	Anti-HBs antibodies positivity
27	Anti-HBc IgM antibodies positivity
28	Anti-Hepatitis C Virus (HCV) antibodies positivity
29	Increased serum alkaline phosphatase
30	Increased serum gamma-glutamyl transpeptidase
31	HBsAg
32	Hepatitis B Virus (HBV)-DNA
33	HCV-RNA
34	HDV-Ag
35	IgM anti-Hepatitis A Virus positivity
36	Hyperazotaemia
37	Hyperbilirubinemia
38	Hypertransaminasemia
39	Hypoalbuminemia
40	Thrombocytopenia

Table 4:Selected input variables (S) used to train the ANN

corresponding to “hepatocellular adenoma”, our network produced three times (i.e. in all the subjected cases), as its first choice diagnosis, the correct one. The second and third choices were “autoimmune hepatitis type I” and “liver haemangioma”, respectively. This means a 100% of correct diagnoses. On the other hand, “biliary tract cancer”, in line 30, was recognized 2 times out of 3. The uncorrected diagnosis of the network was “acute cholangitis” as first choice, even if, however, the correct diagnosis was the second choice. In some cases (i.e. line 14, “gallbladder empyema”), many disease are listed as second or third choice, given their identical or strictly similar probability values, or no third choice is listed, since all the other diseases were considered, by the ANN, equally unlikely. Table 6 is organized in the same way.

Results described in Table 5 were quite interesting: the network provided the right answer (i.e. the same disease diagnosed by a standard diagnostic approach) 96% of the times, while in the remaining 4% network outputs were only partly wrong. First of all, because the correct disease was the second (never the third) choice. Secondly, and more important, because network mistakes were not real ones: with the same kind of information, even a physician would have done exactly the same set of choices. Therefore, it seems that the network worked like a human being, or even better. This shows that our approach essentially imitates, in a certain sense, a real physician's behaviour: he doesn’t estimate errors, or compute standard deviations. He just considers what he thinks is the most probable disease. Recalling that the set G_{test} is not very different from G_{train}, the main conclusion of this first part of our analysis is that our ANN is stable under minor modifications.

Table 6 represents results on the patients in set G_{val}, which were sufficiently different (from a qualitative and, therefore, from a quantitative point of view) from the ones chosen to train and to test the network. Looking at this table, we still obtained acceptable results (i.e. stability under major modifications). In fact, out of the 150 cases proposed to the network, 120 (80%) were correctly diagnosed. It must be noticed also that the remaining (wrong) results were, again, sufficiently right, i.e. they were compatible with the information possessed by the network.

Summarizing, considering together the sets G_{test} and G_{val}, the percentage of correct diagnosis provided by the network was the 86%.

Discussion

Emerging results from this study suggested that our ANN was able to predict, with a good accuracy, in a set of patients affected with known several hepatobiliary diseases, the type of hepatobiliary disease, using only few, minimal, clinical and biochemical variables, as input data, in a efficient, economic and pre-imaging procedure.

Based on the results of this study, the proposed model can be used as a supporting system in making decisions related to hepatobiliary disease diagnosis and subsequent treatment. ANN can retrieve the most similar case from the case database in order to solve a new hepatobiliary disease problem. Reducing diagnostic errors, ANN could be an innovative way to early achieve hepatobiliary disease differential diagnosis.

	Disease	Percentage of correct diagnosis	Number of Correct/Incorrect diagnosis	First choice	Second choice	Third choice
1	Hepatocellular adenoma	100%	3	Hepatocellular adenoma	Autoimmune hepatitis type I	Liver haemangioma
2	Liver haemangioma	100%	3	Liver haemangioma	Hepatocellular adenoma	Autoimmune hepatitis type I
3	Hepatic abscess	100%	3	Hepatic abscess	Liver haemangioma	Gallbladder cancer
4	Gallstones	100%	3	Gallstones	Gallbladder cancer	Hepatic echinococcosis Hepatocellular adenoma
5	Primary biliary cirrhosis	100%	3	Primary biliary cirrhosis	Primary sclerosing cholangitis	Hepatocellular carcinoma in cirrhosis
6	Secondary biliary cirrhosis	100%	3	Secondary biliary cirrhosis	Autoimmune hepatitis type II	Primary biliary cirrhosis
7	HCV-related cirrhosis	100%	3	HCV-related cirrhosis	Hepatocellular carcinoma in cirrhosis	Chronic HCV hepatitis
8	Acute cholangitis	100%	3	Acute cholangitis	Acute cholecystitis	Gallbladder cancer Biliary tract cancer
9	Primary sclerosing cholangitis	100%	3	Primary sclerosing cholangitis	Acute HAV hepatitis	Gallbladder cancer
10	Acute cholecystitis	100%	3	Acute cholecystitis	Acute cholangitis	Gallbladder empyema
11	Common bile duct lithiasis	100%	3	Common bile duct lithiasis	Gallbladder cancer	Primary sclerosing cholangitis
12	Hepatic echinococcosis	100%	3	Hepatic echinococcosis	Gallstones	Liver haemangioma
13	Hemochromatosis	100%	3	Hemochromatosis	Liver haemangioma	Hepatocellular adenoma
14	Gallbladder empyema	100%	3	Gallbladder empyema	Acute cholangitis Common bile duct lithiasis Acute HDV hepatitis Acute cholecystitis Gallbladder cancer	-
15	Autoimmune hepatitis type I	100%	3	Autoimmune hepatitis type I	Hepatocellular adenoma	Drug-induced hepatitis
16	Autoimmune hepatitis type II	100%	3	Autoimmune hepatitis type II	Autoimmune hepatitis type I	Primary sclerosing cholangitis
17	Drug-induced hepatitis	100%	3	Drug-induced hepatitis	Autoimmune hepatitis type II	Acute HDV hepatitis
18	Acute HAV hepatitis	100%	3	Acute HAV hepatitis	Chronic HBV hepatitis	Acute HCV hepatitis Chronic HBV and HDV hepatitis Gallbladder cancer
19	Acute HBV hepatitis	100%	3	Acute HBV hepatitis	Non-alcoholic steatohepatitis	Primary sclerosing cholangitis Acute HBV hepatitis Chronic HBV and HDV hepatitis Alcoholic liver disease Chronic HCV hepatitis
20	Acute HCV hepatitis	67%	2	Acute HCV hepatitis	Acute HCV hepatitis	Acute cholecystitis
			1	Chronic HCV hepatitis	Acute HCV hepatitis	Autoimmune hepatitis type II
21	Acute HDV hepatitis	100%	3	Acute HDV hepatitis	Autoimmune hepatitis type I	Chronic HBV and HDV hepatitis
22	Chronic HBV hepatitis	100%	3	Chronic HBV hepatitis	Acute HCV hepatitis	Non-alcoholic steatohepatitis
23	Chronic HBV and HDV hepatitis	100%	3	Chronic HBV and HDV hepatitis	Hepatic echinococcosis	HCV-related cirrhosis
24	Chronic HCV hepatitis	67%	2	Chronic HCV hepatitis	Chronic HCV hepatitis	-
			1	Acute HCV hepatitis	HCV-related cirrhosis	Secondary biliary cirrhosis Hemochromatosis
25	Hepatocellular carcinoma in cirrhosis	100%	3	Hepatocellular carcinoma in cirrhosis	Hepatic abscess	Autoimmune hepatitis type II
26	Alcoholic liver disease	100%	3	Alcoholic liver disease	Biliary tract cancer	Acute cholangitis
27	Cholestatic syndrome	100%	3	Cholestatic syndrome	Liver haemangioma	Acute HDV hepatitis Chronic HBV and HDV hepatitis
28	Non-alcoholic steatohepatitis	67%	2	Non-alcoholic steatohepatitis	Non-alcoholic steatohepatitis	Hepatic echinococcosis
			1	Liver haemangioma	Common bile duct lithiasis	Primary sclerosing cholangitis
29	Gallbladder cancer	100%	3	Gallbladder cancer	Primary sclerosing cholangitis	Cholestatic syndrome Acute cholangitis
30	Biliary tract cancer	67%	2	Biliary tract cancer	Biliary tract cancer	Cholestatic syndrome
			1	Acute cholangitis		
	Total Cases with right diagnosis	**96%**	**86**			
	Total Cases		**90**			

Table 5:ANN results on the patients in set G_{test}

It should be stressed that this study did not want to suggest possible replacement of experienced clinicians by advanced computer-aided decision systems, but simply to point out that these systems should be accounted as a potential decision aid in order to better address investigations, to save costs, and to better use resources, as already described in other fields of medical settings. In

	Disease	Percentage of correct diagnosis	Number of Correct/Incorrect diagnosis	First choice	Second choice	Third choice
1	Hepatocellular adenoma	60%	3	Hepatocellular adenoma	Autoimmune hepatitis type I	Hemochromatosis
			2	Liver haemangioma	Hepatocellular adenoma	Hepatic echinococcosis
2	Liver haemangioma	60%	3	Liver haemangioma	Hepatic echinococcosis	Hemochromatosis Hepatic abscess
			2	Hepatic echinococcosis	Liver haemangioma	Chronic HBV hepatitis Hemochromatosis Non-alcoholic steatohepatitis
3	Hepatic abscess	60%	3	Hepatic abscess	Liver haemangioma	Non-alcoholic steatohepatitis
			2	Liver haemangioma	Hepatic echinococcosis	Hepatic abscess
				Hepatic echinococcosis	Liver haemangioma	Hemochromatosis
4	Gallstones	80%	4	Gallstones	Hepatocellular adenoma	Gallbladder cancer
			1	Gallbladder cancer	Gallstones	Hepatocellular adenoma
5	Primary biliary cirrhosis	100%	5	Primary biliary cirrhosis	Drug-induced hepatitis	Secondary biliary cirrhosis
6	Secondary biliary cirrhosis	100%	5	Secondary biliary cirrhosis	Hepatocellular carcinoma in cirrhosis	Hemochromatosis
7	HCV-related cirrhosis	60%	3	HCV-related cirrhosis	Hepatocellular carcinoma in cirrhosis	Non-alcoholic steatohepatitis
			2	Hepatocellular carcinoma in cirrhosis	HCV-related cirrhosis	Secondary biliary cirrhosis
				Non-alcoholic steatohepatitis	HCV-related cirrhosis	Secondary biliary cirrhosis
8	Acute cholangitis	100%	5	Acute cholangitis	Gallbladder cancer	Biliary tract cancer
9	Primary sclerosing cholangitis	100%	5	Primary sclerosing cholangitis	Drug-induced hepatitis	Gallbladder cancer
10	Acute cholecystitis	60%	3	Acute cholecystitis	Gallbladder cancer	Gallstones
			2	Gallbladder empyema	Acute cholecystitis	Gallbladder cancer
				Gallbladder empyema	Gallbladder cancer	Common bile duct lithiasis
11	Common bile duct lithiasis	80%	4	Common bile duct lithiasis	Primary sclerosing cholangitis	Biliary tract cancer
			1	Primary sclerosing cholangitis	Common bile duct lithiasis	Biliary tract cancer
12	Hepatic echinococcosis	60%	3	Hepatic echinococcosis	Hepatocellular adenoma	Chronic HCV hepatitis
			2	Liver haemangioma	Hepatic echinococcosis	Hepatocellular adenoma Hemochromatosis
13	Hemochromatosis	80%	4	Hemochromatosis	Autoimmune hepatitis type II	Secondary biliary cirrhosis
			1	Secondary biliary cirrhosis	Non-alcoholic steatohepatitis	Hemochromatosis
14	Gallbladder empyema	100%	5	Gallbladder empyema	Common bile duct lithiasis	Acute cholecystitis
15	Autoimmune hepatitis type I	100%	5	Autoimmune hepatitis type I	Common bile duct lithiasis	Autoimmune hepatitis type II
16	Autoimmune hepatitis type II	100%	5	Autoimmune hepatitis type II	Autoimmune hepatitis type I	Acute HDV hepatitis
17	Drug-induced hepatitis	60%	3	Drug-induced hepatitis	Autoimmune hepatitis type I	Primary sclerosing cholangitis
			2	Autoimmune hepatitis type I	Autoimmune hepatitis type II	Acute HAV hepatitis Common bile duct lithiasis
				Autoimmune hepatitis type II	Drug-induced hepatitis	Acute HDV hepatitis
18	Acute HAV hepatitis	100%	5	Acute HAV hepatitis	Autoimmune hepatitis type II	Primary sclerosing cholangitis
19	Acute HBV hepatitis	40%	2	Acute HBV hepatitis	Chronic HBV hepatitis	Hemochromatosis
			3	Acute HDV hepatitis	Acute HBV hepatitis	Acute HCV hepatitis
20	Acute HCV hepatitis	60%	3	Acute HCV hepatitis	Common bile duct lithiasis	Gallbladder empyema
			2	Chronic HCV hepatitis	Hepatic echinococcosis	HCV-related cirrhosis
21	Acute HDV hepatitis	60%	3	Acute HDV hepatitis	Chronic HBV and HDV hepatitis	Acute HCV hepatitis
			2	Chronic HBV and HDV hepatitis	Acute HDV hepatitis	Hepatic abscess
				Non-alcoholic steatohepatitis	Acute HDV hepatitis	Chronic HBV and HDV hepatitis
22	Chronic HBV hepatitis	100%	5	Chronic HBV hepatitis	Hepatic echinococcosis	Liver haemangioma
23	Chronic HBV and HDV hepatitis	60%	3	Chronic HBV and HDV hepatitis	Non-alcoholic steatohepatitis	Cholestatic syndrome
			2	Chronic HBV hepatitis	Chronic HBV and HDV hepatitis	Liver haemangioma
	Chronic HCV hepatitis	100%	5	Chronic HCV hepatitis	Hepatic echinococcosis	Gallstones
25	Hepatocellular carcinoma in cirrhosis	100%	5	Hepatocellular carcinoma in cirrhosis	Acute HAV hepatitis	Hemochromatosis
26	Alcoholic liver disease	100%	5	Alcoholic liver disease	Non-alcoholic steatohepatitis	Liver haemangioma
27	Cholestatic syndrome	40%	2	Cholestatic syndrome	Biliary tract cancer	Drug-induced hepatitis
			3	Biliary tract cancer	Cholestatic syndrome	Acute cholangitis
28	Non-alcoholic steatohepatitis	100%	5	Non-alcoholic steatohepatitis	Liver haemangioma	Alcoholic liver disease
29	Gallbladder cancer	80%	4	Gallbladder cancer	Gallbladder empyema	Common bile duct lithiasis
			1	Gallstones	Gallbladder cancer	Hepatocellular adenoma
30	Biliary tract cancer	100%	5	Biliary tract cancer	Primary sclerosing cholangitis	Acute cholangitis
				Acute cholangitis		
	Total Cases with right diagnosis	**80%**	**120**			
	Total Cases		**150**			

Table 6: ANN results on the patients in set G_{val}.

other words, our intention was not to build a network that fully substitutes physicians and their role. Really, our network basically provides a diagnostic orientation, a sort of hint for real-life physician, an aid for differential diagnosis of their patients, with a high probability of being true (= very close to definitive diagnosis). The ability of our network was to orient well, in absence of further laboratory and radiological investigations, or in economical restricted conditions, towards a correct diagnosis, although it is clear the need, even just for forensic reasons, to perform, for real-life patient, other diagnostic and follow-up tests[3-12].

We are aware that the current study has some limits. First of all, there was a certain freedom in our "text-to-number" procedure for unstructured data of patients' medical records, and in assigning a given number to the various symptoms/signs/laboratory tests for the various patients of the three groups. Secondly, even if we tried to motivate our choice, the set S and N_S could have been chosen differently. However, our extraction procedure was not very different from what any physician really does during the deduction of a diagnosis, keeping those information which he assumes to be the most relevant and neglecting the others. Last but not least, the results achieved by our ANN were quite satisfactory: this suggests that our choices were correct and produce an efficient network.

Moreover, we should also recall that there was a certain freedom in choosing which patients should be included in G_{train}, G_{test} and G_{val}. Motivations of such a choice were argued above, considering the different characteristics of the three phases of ANN implementation.

A final comment concerning our ANN is the following. The network has proved to be efficiently trained by using a single patient for each disease. This is an interesting feature of our ANN, which is probably due to an appropriated choice of the set S. As results showed, there was absolutely no need to train the network with more patients for each disease. Of course, this implies that the training procedure was very fast, while it would surely take more time when fixing M_{train} >30. Concerning N_S, and the explicit choice of the set S, we had a lot of freedom. After some attempts, we fixed N_S = 40, and the related set S. As a matter of fact, adopting this choice, the ANN produced satisfactory results when compared with the amount of information given to the network, and with other possible choices of N_S and S.

In conclusion, the current analysis can be described as a preliminary study. It will need further validation in a separate cohort of patients with liver diseases. Also, a prospective study that compares the ANN with physician assessment in real time will be of interest, particularly, if the ANN diagnosis changes the decision-making process at the point of care. In addition, it could be interesting to write a dedicated software to deal with medical diagnostic-related analysis, also in view of other possible application fields. In fact, it is clear that a similar ANN can be organized for different kind of diseases, so that many possibilities were opened by our analysis.

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DEDICATION

FB and PM dedicate this paper to their common roots, Giovanna, Benedetto and Serafino.

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