Choice of liver failure treatment using set-theoretic models

Nikolay A. Blagosklonov and Boris A. Kobrinskii
Institute of Artificial Intelligence Problems
Federal Research Center "Computer Science and Control" of the Russian Academy of Sciences
Moscow, Russia
nblagosklonov@gmail.com, kba_05@mail.ru

***Abstract*—The article presents the set-theoretic models of liver failure, allowing the diagnosis of the disease forms and personalized selection of traditional and new methods of treatment. Separate types are presented in the form of 5 sets which correspond to the known clinical forms of the studied pathology: "chronic liver failure", "acute-on-chronic liver failure", "acute liver failure", "fulminant liver failure" and "drug-induced liver injury". The models allow to take into account the dynamics of transition from one form to another in the process of developing the disease with continued influence of negative factors. The proposed approach allows the difference in the clinical manifestations of the pathology, the fuzzies of the transitional disease states, specific and non-specific signs of etiologically and pathogenetically different forms, which are the criteria for selecting similar cases to choice the most effective therapies. Personalized treatment is based on comparing a patient with a specific subset of the multiset.**

***Keywords*—set-theoretic model, multiset, approximate sets, meta-analysis, liver failure, personalized therapy**

I. Introduction

Liver failure is receiving increasing attention in studies in different countries, despite the relatively rare morbidity due to extremely high patient mortality. Acute liver failure is a life-threatening disease in which liver fails to function normally. The sudden loss of the synthetic and detoxifying functions of the liver leads to jaundice, encephalopathy, coagulopathy, and multiorgan failure. The etiology of liver failure is extremely variable. Mortality reaches 40–50%. Primary care depends on timely recognition of the condition and early detection of etiology. Treatment includes intensive therapy, support for specific etiology treatment, if any, and early identification of candidates for liver transplantation. Liver transplantation remains the only therapeutic intervention with proven efficacy of survival in patients with irreversible liver failure. Activities aimed at combating various types of hepatitis and medicinal injuries of the liver will help reduce the incidence and mortality from liver failure [1].

However, there are no universal methods for treating this pathology [2]. This is largely determined by the relevance of this study, involving the search for adequate methods of personal therapy, based on taking into account the specific characteristics of disease progression in individuals.

There are numerous forms of the disease: acute, fulminant, chronic, acute-on-chronic and a condition preceding liver failure – drug-induced liver injury. All of them have similar symptoms, the main difference lies in the timing of the development of hepatic encephalopathy regarding the first manifestations of jaundice, excluding drug-induced liver injury [3]. It is possible to transfer from one form of liver failure to another in the process of developing the disease and the continuing impact of adverse factors. Thus, physicians deal with fuzzy manifestations of the disease, which creates serious difficulties for the diagnostic plan.

Clinical trials of new approaches to the treatment of this disease are constantly being conducted. Knowledge of modern methods of treatment by the attending physician can increase the survival of patients with liver failure. The number of new publications is so huge that knowing with them seems impossible for a practitioner. This problem can be solved by developing a system that will find similar cases in the literature and select the method of treatment that most effectively showed itself on a sample of similar patients.

To implement such a system, two models were developed, combining different variants of the course of the disease and methods of treatment. In the present study, a set-theoretic approach was chosen for building models, with the help of which various forms of the disease and relations defined on them are described.

In the present formulation of the problem, syndromes and symptoms were used as elements of the sets of symbolic agents, as well as associated diseases, the presence or absence of which in the patient is essential for the formation of the clinical picture of liver failure. The concept and description of sets from the standpoint of different authors is quite diverse. The sets of signs presented in this study are a prerequisite for an accurate diagnosis and choice of treatment tactics. Since the model includes various forms of the disease, which have a similar set of manifestations, the diagnostic criteria are repeated several times with minor changes. These differences must be considered in the differential diagnosis. Due to the fact that the elements will be repeated, the set-theoretic approach with the presentation of liver failure as a multiset is chosen as the basis of the model.

A multiset is a set that allows the possibility of multiple presence of elements, that is, the existence of several identical instances of the same element [4], [5]. Due to the fact that hepatic insufficiency is characterized by blurred clinical manifestations of individual forms and features of a particular patient and different etiological causes, the multi-set model includes fuzzy sets. Although any set can be represented as a continuous image of space in which all sets are closed. In this sense, all locally connected continua are Jordan continua, that is, continuous images of a segment of a straight line [6]. In a certain sense, one can also speak of the connectedness of the sets under consideration. According to William Weiss [7], set theory is a true study of infinity.

II. Clinical and formal problems of fuzziness of pathological manifestations

In approximate sets, the boundary region allows to simulate inaccuracy, and improving accuracy means reducing the boundary region. The theory of approximate sets [8] provides formal means for working with incomplete or inaccurate information in terms of three-valued logic [9].

Medical information has a certain degree of fuzziness, determined by the possibility of an atypical course of the disease. The specific characteristics of individuals create a situation of fuzziness in the manifestation of diseases. Based on the diverse knowledge of pathological manifestations, a model of the disease is formed, which includes various forms and variants of development. In other words, a model is a set that includes the interpretation of some symbols of relations and constants, which may or may not be present in specific cases. The course of the disease can be characterized by the emergence of new signs, which does not exclude the transition of individual elements (objects that characterize the condition of patients) from one subset to another.

In computer science, the characteristic function of a fuzzy set is considered in the range from 0 to 1 [10]. Thus, using the concept of fuzziness in medical knowledge, it becomes possible to ensure that subsequent features take into account the clinical characteristics of individual patients.

Consider also the concept of granulation as the ability to operate with data and knowledge at various levels of detail as interval mathematics. It should be remembered about the general principle of granulation L. Zadeh [11]: to work effectively with inaccurate information should choose the largest granules in accordance with the permissible level of inaccuracy. This will help to reflect the level of generalization-detail when considering specific processes. One of the main components of the theory of granulation [12] are formal models of granules. These are subsets, clusters, neighborhoods, multisets, approximate sets, fuzzy sets, etc.

The process of designing granules can be downward or upward. In the descending process, a universal set is taken as a basis, which is divided into a family of subsets. In the upstream process, the original subset of objects is grouped into a granule, and then the smaller granules are combined into larger ones. This is similar to disease subclasses and classes. An important characteristic of fuzzy logic is that any theory can be fuzzified and, therefore, generalized by replacing the notion of a clear set with the notion of a fuzzy set. The win from the fuzzification is the greater generality and the best fit of the model to reality [13]. In the same article, attention was drawn to the fact that fuzzy logic underlies the methods of working with inaccuracy, granular structure (granulation) of information, approximate reasoning, and computing with words.

III. Set-theoretic models of patient and treatment of liver failure

A formal presentation of the problem of liver failure treatment, including various clinical forms, and approaches to the choice of appropriate treatment tactics, it seems expedient to consider from the standpoint of set theory.

Accordingly, in the present study, two mathematical models were developed: a diagnostic "Model of a patient with liver failure" and a model for selecting options for targeted therapy, called the "Liver failure treatment model". Both models are based on the concept of a multiset and include fuzzy sets and subsets, which are different forms of liver failure. Their fuzzies determines the difficulty of deciding on the choice of the most effective therapy.

As a result, 5 sets were formed that characterize various clinical forms of liver failure: "chronic liver failure", "acute-on-chronic liver failure", "acute liver failure", "fulminant liver failure" and "drug-induced liver injury". When establishing relations between the five initially distinguished sets, it was considered expedient to group them into two contiguous, though not intersecting sets: “Form of chronic liver failure” and "Form of acute liver failure". Inside each of the newly formed united sets, there are subsets that are closest in composition to the elements, which were initially considered as separate sets. This is explained by the fact that the subset "acute-on-chronic liver failure" has a similar clinical picture and etiopathogenetic mechanism of development with the subset "chronic liver failure", the difference is that the exacerbation was caused by the appearance of a provoking factor in a patient with chronic liver disease, which caused a similar disease dynamic. The second formed set "Form of acute liver failure" included a subset of "acute liver failure" and "fulminant liver failure", the latter of which is characterized by the absence of chronic liver disease in the patient, but develops with

lightning speed. The third subset of "drug-induced liver injury" only partially overlaps with the set "Form of acute liver failure", as it has a similar clinical picture and timing of complications, but the syndrome of hepatic encephalopathy does not develop in this event. However, in the absence of timely treatment, hepatic encephalopathy syndrome is manifested and the disease turns into an acute form of liver failure. Both sets represent the "Liver failure" multiset.

The "Model of a patient with liver failure" contains groups of criteria that ensure the exclusion of cases of liver failure that were not considered in this study, since they require the interaction of specialists from different areas of medicine. One of the groups were presented signs (elements of subsets), the presence of which is necessary for the diagnosis of the liver failure form, named as inclusion criteria. The other group consisted of non-specific criteria, the presence or absence of which in a patient is considered necessary to clarify the clinical picture of the liver failure form and to establish the etiological features of occurrence of the disease in a particular patient.

During operation, the model checks the signs from which groups are present in a particular case and allow to confirm the hypothesis about the diagnosis. On this basis, in the future, a sample was selected from the literature for the selection of an adequate method of treatment.

The "Liver failure treatment model" is based on a diagnostic model, taking into account various classes of treatment involving traditional and new approaches to therapy. This made it possible to form patterns that ensure the selection of analogues according to clinical manifestations and answers to the applied methods and resources of treatment. Currently, this is especially important with the development of high-tech treatment methods. Although applied and well-proven drugs in certain situations. Thus, the main methods of treating patients with hepatic insufficiency are: drug therapy, liver transplantation, extracorporeal liver support systems, and cellular technologies. The choice of treatment tactics may be affected by various symptoms, such as a history of chronic liver disease, hepatitis, viral diseases, sepsis, etc. When analyzing the Russian and world literature, it was found that the principles of treatment for various forms of liver failure do not differ in regions of the world. Basically, there are similar points of view regarding the therapeutic approach to the treatment of patients with liver failure, the use of extracorporeal technology and transplantation, the use of stem cells.

For the formalized presentation of knowledge obtained from literary sources, linguistic scales for signs of liver failure were developed. With their help, the forms of the disease, described in various publications, are written in the form of equations, which further allows us to carry out comparison operations with them in subsequent analysis. The basic designations of the disease sets:

- **LF** – "liver failure" multiset.
- FCLF – "form of chronic liver failure" set.
- FALF – "form of acute liver failure" set.
- *CLF* – "chronic liver failure" subset.
- *ACLF* – "acute-on-chronic liver failure" subset.
- *ALF* – "acute liver failure" subset.
- *FLF* – "fulminant liver failure" subset.
- *DILI* – "drug-induced liver injury" subset.

The multiset, sets, and subsets consist of elements. Designations of the main elements:

- j – jaundice,
- b – total bilirubin,
- c – coagulopathy,
- i – international normalized ratio (INR),
- p – prothrombin activity,
- e – hepatic encephalopathy,
- a – ascites,
- d – liver disease history,
- t_s – time of development of complications of liver failure (hepatic encephalopathy and/or ascites) since the first manifestations of liver damage (jaundice).

The elements jaundice, total bilirubin, coagulopathy, INR, prothrombin activity, hepatic encephalopathy, ascites, and a history of liver disease in the model are encoded in a binary type [0, 1], where 0 indicates either the absence of manifestation of this trait, or, in the case of laboratory indicators, the norm. For the time of symptom development, a scale consisting of 5 values [0, 1, 2, 3, 4] was introduced, where 0 is up to 7 days (1 week), 1 is up to 14 days (2 weeks), 2 is up to 28 days (4 weeks), 3 – up to 56 days (8 weeks), 4 – more than 56 days (8 weeks). There is a connection between some elements. For example, jaundice syndrome is diagnosed by elevated bilirubin levels, that is:

$$j_{0,\ b-normal}^{1,\ b-evelated} \tag{1}$$

This statement is also true for coagulopathy syndrome and prothrombin activity and INR:

$$c_{0,\ i<1.5,\ \ p>40\%}^{1,\ i\geq 1.5,\ \ p\leq 40\%} \tag{2}$$

Using this designation of elements, the subset of "acute-on-chronic liver failure", which corresponds to the definition: "jaundice (serum bilirubin $\geq$ 5 mg / dL) and coagulopathy (INR $\geq$ 1.5 or prothrombin activity $<$ 40%), with complications in the form of ascites and/or encephalopathy for 4 weeks in patients with previously diagnosed or undiagnosed chronic liver disease" [14] can be written in the following form:

$$\begin{cases} ACLF = j^1, c^1, a^1, e^1, t_s^2, d^1 \\ ACLF = j^1, c^1, a^1, e^0, t_s^2, d^1 \\ ACLF = j^1, c^1, a^0, e^1, t_s^2, d^1 \\ ACLF = j^1, c^1, a^1, e^1, t_s^2, d^0 \\ ACLF = j^1, c^1, a^1, e^0, t_s^2, d^0 \\ ACLF = j^1, c^1, a^0, e^1, t_s^2, d^0 \end{cases} \tag{3}$$

that will correspond to all variants of the course of the disease, which the authors considered in their article. Similar scales are used to record treatment methods and their results. Subsequently, with equations, operations are performed using special algorithms to identify the most effective methods of treating patients with the same forms of the disease.

IV. Personalized approach to the choice of treatment

Approaches to the selection directed (targeted) [15] treatment are determined by the necessity of a personalized approach to treatment with targeted areas of action for certain cells. This is achieved by assigning the individual to one of the subsets of the "Model of a patient with liver failure", which are defined by the fuzzy boundaries of the various forms of this disease.

Proper selection of targeted therapy due to the need to consider the characteristics of the disease in a given individual. In fact, personalized treatment is selected by assigning the patient to one of the subsets of the multiset.

Clinical variants of liver failure in the form of subsets, implemented in the models described above, were used to search for similar cases in various studies available in the PubMed database for describing clinical cases with parameters similar to those observed in a particular patient.

Queries to the international publication databases reflect the manifestations of various forms of liver failure (including exclusion terms, the combination of which with the underlying disease should not be contained in the collection of publications given to the doctor), treatment methods and research designs. It should be noted that in terms of evidence-based medicine, meta-analysis and randomized studies have the greatest degree of evidence (validity). In this study, a meta-analysis was applied to various types of studies [16]. The formation of a database of treatment methods was carried out by marking up the corpus of articles, including inclusion criteria, exclusions and non-specific criteria in a model of a patient with hepatic insufficiency.

Selection of treatment is carried out on the basis of similar clinical cases, published in Russian and foreign literary sources in relation to various ethnic groups, that is, on cases-analogs and precedents.

V. Conclusion

The problem of selecting an adequate treatment for liver failure is still relevant and causes considerable difficulties. At the same time, adequate therapies have appeared that provide a good effect. However, the search for a method of treatment appropriate to a particular case of disease presents a serious problem for the physician. Features of the clinical picture of liver failure largely determine the tactics of patient management. A large volume of databases of literary sources does not allow timely detection of similar cases with an effective result of treatment.

Methods of mathematical modeling, in particular the set-theoretic approach, considering fuzzy sets and subsets of forms of liver failure and suggest the selection of targeted therapy in each case using the method of meta-analysis of large specialized databases.

References

[1] Ch. Panackel, R. Thomas, B. Sebastian, S.K. Mathai. Recent advances in management of acute liver failure. Indian J Crit Care Med, 2015, vol. 19, no 1, pp.27–33.

[2] S. Yasui, K. Fujiwara, Y. Haga, M. Nakamura, R. Mikata, M. Arai, T. Kanda, S. Oda, O. Yokosuka. Infectious complications, steroid use and timing for emergency liver transplantation in acute liver failure: analysis in a Japanese center. J Hepatobiliary Pancreat Sci, 2016, pp.1–3.

[3] C.–T. Liu, T.–H. Chen, C.–Y. Cheng. Successful Treatment of Drug-Induced Acute Liver Failure with High-Volume Plasma Exchange. Journal of Clinical Apheresis, 2013, no 28, pp.430–434.

[4] A.B. Petrovsky. Group Multiple Criteria Decision Making: Multiset Approach. Recent Developments and New Directions in Soft Computing. Studies in Fuzziness and Soft Computing, 2014, vol. 317, pp.19–33.

[5] A. Syropoulos. Mathematics of multisets. Multiset Processing, 2001, vol. 2235, pp.347–358.

[6] F. Hausdorff. Set Theory. New York, AMS Chelsea Publishing, 2005, 352 p.

[7] W.A.R. Weiss. An Introduction to Set Theory. CreateSpace Independent Publishing Platform, eBook, 2014, 119 p.

[8] Z. Pawlak. Rough Sets. International Journal of Computer and Information Sciences, 1982, vol. 11, pp.341–356.

[9] V.B. Tarasov. Granuljacija informacii [Granulation information]. *Podhody k modelirovaniju myshlenija* [*Approach to modeling thinking*]. V.G. Redko Eds. 2016, pp. 219–261.

[10] L.A. Zadeh. Fuzzy sets as a basis for a theory of possibility. Fuzzy Sets Systems, 1978, vol. 1, no 1, pp.3–28.

[11] L.A. Zadeh. Toward a theory of fuzzy information granulation and its centrality in human reasoning and fuzzy logic. Fuzzy sets and systems, 1997, vol. 90, pp.111–127.

[12] A. Bargiela, W. Pedrycz. Granular computing: an introduction. Dordrecht: Kluwer Academic Publishers, 2003.

[13] L.A. Zadeh. Rol' mjagkih vychislenij i nechetkoj logiki v ponimanii, konstruirovanii i razvitii informacionnyh / intellektual'nyh sistem [The role of soft computing and fuzzy logic in the understanding, design and development of information / intelligent systems]. *Iskusstvennyj intellekt* [*Artificial Intelligence*], 2001, no 2–3, pp.7–11.

[14] X.–Z. Duan, F.–F. Liu, J.–J. Tong., H.–Z. Yang, J. Chen, X.–Y. Liu, Y.–L. Mao, S.–J. Xin, J.–H. Hu. Granulocyte-colony stimulating factor therapy improves survival in patients with hepatitis B virus–associated acute-on-chronic liver failure. World Journal of Gastroenterology, 2013, vol. 19, no 7. pp.1104–1110.

[15] H.J. Kim, N. Hawke, A.S. Baldwin. NF–kappaB and IKK as therapeutic targets in cancer. Cell Death Differ, 2006, vol.13, no 5, pp.738–747.

[16] B.A. Kobrinsky, A.I. Molodchenkov, N.A. Blagosklonov, A.V. Lukin. Primenenie metodov metaanaliza v diagnostike i lechenii pacientov s pechenochnoj nedostatochnost'ju [Applying meta-analysis methods in liver failure diagnosis and treatment]. *Programmnye produkty i sistemy* [*Software & Systems*], 2017, vol. 30, no 4, pp.745–753.

ВЫБОР АНАЛОГИЧНЫХ МЕТОДОВ ЛЕЧЕНИЯ ПЕЧЕНОЧНОЙ НЕДОСТАТОЧНОСТИ ПРИ ИСПОЛЬЗОВАНИИ ТЕОРЕТИКО-МНОЖЕСТВЕННЫХ МОДЕЛЕЙ

Благосклонов Н.А., Кобринский Б.А.

В статье представлены теоретико-множественные модели печеночной недостаточности, позволяющие осуществлять диагностику форм заболевания и персонифицированный подбор традиционных и новых методов лечения. Отдельные типы представлены в виде 5 множеств, которые соответствуют известным клиническим формам исследуемой патологии: «хроническая печеночная недостаточность», «обострение хронической печеночной недостаточности», «острая печеночная недостаточность», «фульминантная печеночная недостаточность» и «лекарственно-индуцированное поражение печени». Модель позволяет учесть динамику перехода от одной формы к другой в процессе развития заболевания при продолжающемся воздействии негативных факторов. Предложенный подход учитывает различие клинических проявлений патологии, нечеткость переходных состояний болезни, специфические и неспецифические признаки этиологически и патогенетически различных форм, являющихся критериями отбора аналогичных случаев для выбора наиболее эффективных методов терапии. Персонализированное лечение основано на сопоставлении пациента с определенным подмножеством мультимножества.

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