Diagnosis of liver fibrosis using digital analysis

Diagnostyka zwłóknienia wątroby z wykorzystaniem digitalizacji i analizy cyfrowej

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Abstract

Liver fibrosis is a pathological process in which excessive deposition of connective tissue occurs in the liver. It is a response to chronic liver damage caused by viral agents, alcohol abuse, drug abuse, or autoimmune diseases. Diagnosis and assessment of liver fibrosis are important in staging the disease, prognosticating its progression, and making treatment decisions. The diagnosis of liver fibrosis involves clinical interview, laboratory tests, imaging, and – the "gold diagnostic standard" – histopathological examination. Biopsying the liver allows for precise assessment of fibrosis and potential identification of other liver diseases; however, it is an invasive procedure and may carry some risk of complications. In addition, pathomorphological interpretation is often subjective. In order to minimize errors and improve the accuracy of diagnosis, digital image analysis and artificial intelligence technologies are being developed for histopathological examinations. In recent years, AI-based methods have been designed to support the assessment of liver fibrosis through analysis of imaging and clinical data. AI can help automatically recognize patterns characteristic of liver fibrosis, which could contribute to faster and more precise diagnosis. However, the final decision on the diagnosis and treatment of liver fibrosis should still be made by a qualified specialist.

Keywords: AI, diagnosis, digital analysis, liver fibrosis

Streszczenie

Zwłóknienie wątroby jest procesem patologicznym, w którym dochodzi do nadmiernego odkładania się tkanki łącznej w narządzie. Zwłóknienie jest najczęściej następstwem przewlekłego uszkadzania wątroby wywołanego wirusami hepatotropowymi, nadużywaniem alkoholu i leków, a także chorobami autoimmunologicznymi. Rozpoznanie i prawidłowa klasyfikacja zwłóknienia wątroby są istotne dla oceny stopnia zaawansowania choroby, prognozowania jej progresji i ustalenia decyzji terapeutycznych. W diagnostyce włóknienia wątroby wykorzystuje się: wywiad kliniczny, badania laboratoryjne, obrazowe oraz – co jest „złotym standardem diagnostycznym" – badanie histopatologiczne. Biopsja wątroby pozwala na precyzyjną ocenę włóknienia i identyfikację innych chorób wątroby, jest jednak

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zabiegiem inwazyjnym i może wiązać się z pewnym ryzykiem powikłań. Ponadto ocena patomorfologiczna jest często subiektywna. W celu minimalizacji błędów i poprawy trafności diagnozy rozwijane są technologie cyfrowej analizy obrazu oraz sztucznej inteligencji (AI) w badaniach histopatologicznych. W ostatnich latach opracowano metody oparte na AI, które wspierają ocenę zwłóknienia wątroby poprzez analizę danych obrazowych i klinicznych. Sztuczna inteligencja może pomóc w automatycznym rozpoznawaniu wzorców charakterystycznych dla zwłóknienia wątroby, co może przyczynić się do szybszej i dokładniejszej diagnozy. Jednak ostateczną decyzję dotyczącą rozpoznania i leczenia włóknienia wątroby powinien nadal podejmować wykwalifikowany specjalista.

Słowa kluczowe: analiza cyfrowa, diagnostyka, sztuczna inteligencja, włóknienie wątroby

DEFINITION AND PATHOMECHANISM OF LIVER FIBROSIS

Liver fibrosis is an increasingly common disease in developing countries. It is estimated that over 2 million people worldwide die every year due to complications related to fibrosis [1]. Liver fibrosis develops as a result of chronic, long-term damage to the liver and, if left untreated, can lead to cirrhosis and liver failure. There are many etiological factors of this process: alcohol abuse, viral infections (HCV or HBV), fatty liver, autoimmune diseases, drug poisoning, parasites, metabolic diseases (hemochromatosis or Wilson's disease), and diseases of the bile ducts [2].

The rate and intensity of fibrosis in the liver depends on a combination of factors damaging the liver and regenerative processes. In a normal liver, there is a perisinusoidal space of Disse between the vascular poles of the hepatocytes and the cells of the vascular endothelium. The components of the extracellular matrix contained in it (mainly type I, III, and IV collagen fibers) support the liver cells and mediate metabolic changes and protein secretion. In addition to connective tissue components, the space of Disse contains stellate cells, also called Ito cells. These are a type of specialized myofibroblasts that store lipids and vitamin A and regulate blood flow through the sinuses. Browicz-Kupffer cells also have an important function in the liver: they are hepatic macrophages that phagocytize bacteria, damaged cells, and old erythrocytes and produce cytokines affecting the function of hepatocytes [3, 4].

In a healthy liver, the connective tissue stroma constitutes up to 3% of the organ weight. Normally, there is a balance between the production and degradation of the extracellular matrix surrounding the hepatocytes. When the liver is damaged (e.g., by a virus or alcohol), this balance is disturbed due to excessive production of matrix collagen fibers by stellate cells transformed into myofibroblasts. Vascular endothelial cells, Browicz-Kupffer cells, and platelets, which secrete transforming growth factor (TGF-β1) upon activation, also participate in the progressive development of fibrosis. TGF-β1 intensifies the apoptosis of hepatocytes, activates inflammatory cells, and recruits myofibroblasts from the circulatory system [5, 6]. In addition, this factor has been shown to directly stimulate the production of substances that make up the extracellular matrix (e.g., collagen).

The pattern of fibrosis is identical regardless of the damaging factor. The connective tissue growing around the lobules compresses the liver parenchyma, leading to hepatocyte failure and impaired metabolic activity of the liver. The end-stage of fibrotic liver diseases is characterized by the presence of three features in the histopathological picture: the presence of fibrous bridges forming septa (replacing adjacent lobules), nodules in the liver parenchyma (macronodular cirrhosis is most often a consequence of viral hepatitis, while micronodular cirrhosis is usually the result of alcohol abuse or long-term consumption of other toxic substances), and a disorder of the normal architecture of the liver [7, 8].

DIAGNOSIS OF LIVER FIBROSIS

The diagnosis of liver fibrosis is based on the confirmation of the pathological deposition of connective tissue of such severity that it replaces the normal liver parenchyma and, in consequence, alters the lobular structure of the organ. Various point scales are used to assess the degree of fibrosis by determining the amount of connective tissue in the organ. The METAVIR scale has been adopted in clinical practice. It ranges from 0 to 4, where 0 means no fibrosis; 1 means mild fibrosis; 2 means moderate fibrosis; 3 means severe fibrosis; and 4 means remodeling of cirrhosis. Advanced liver fibrosis is defined as F3–F4, while minimal fibrosis is defined as F0–F1. Patients with F2 moderate fibrosis, who are in the so-called "grey zone", require repeated testing at least every 12 months to monitor the progress of fibrosis, as well as to assess the effectiveness of the treatment and lifestyle changes [1, 9, 10].

The main purpose of hepatological diagnostics is to identify the cause of the disease and to determine its severity. The symptomatology of liver diseases is very poor. Due to anatomical conditions, the liver has no pain receptors, with the exception of the hepatic capsule. This is why most liver diseases develop for many years without any symptoms [11].

LABORATORY DIAGNOSTICS

Performing a wide panel of laboratory tests is usually the first step in diagnosing liver disease. Once the patient's clinical data

is collected, a series of biochemical tests are performed that can help assess the quality of liver function. The basic laboratory test ordered in patients with suspected liver disease is a full blood count, in which attention is paid to mild anemia, leukopenia, and thrombocytopenia. Blood coagulation parameters (activated partial thromboplastin time [APTT], prothrombin time [PT], and international normalized ratio [INR]) may also be abnormal. An increase in the activity of aminotransferases (alanine aminotransferase [ALAT] and aspartate aminotransferase [ASPAT]) is observed in patients with liver disease; however, in end-stage fibrosis, the activity of these enzymes may be only slightly elevated or even within normal limits. Other markers of fibrosis include the lipid metabolism profile (cholesterol, LDL, and HDL fractions), the balance of fibrogenesis and fibrinolysis processes (e.g. 2-macroglobulin and apolipoprotein A1), and bilirubin concentration, the value of which indicates how effectively the liver is clearing bile [12, 13].

Laboratory tests are also helpful in diagnosing the causes of liver fibrosis. The gamma-glutamyl transpeptidase test (GGTP) can confirm/exclude an alcohol- or drug-induced etiology of the disease. Clinical evaluation of iron or transferrin levels is essential for the diagnosis of hemochromatosis. In turn, a decrease in copper levels and ceruloplasmin activity can indicate the presence of Wilson's disease. Viral etiology of liver disease is tested with extensive serological and molecular tests for antigens, antibodies, and the genetic material of hepatotropic viruses. However, all these tests have low specificity in diagnosing liver fibrosis. Deviations from reference values may result from many systemic diseases, primarily unrelated to the liver. In addition, in some patients, the results of laboratory tests remain within the normal range, despite the ongoing process of fibrosis [12, 14, 15].

Literature data also suggest the possibility of using "proteomic profiles" in the diagnosis of liver fibrosis. It has been shown that the concentrations of apoproteins A1 and A4, α-1-antitrypsin, transthyretin, and topoisomerase II correlate with the degree of liver fibrosis [16]. Moreover, it has been proven that the combined analysis of multiple laboratory parameters and clinical data may increase the sensitivity and specificity of the diagnosis of fibrosis. By analyzing patient's age, gender, and body mass index and by doing routine laboratory tests, a number of panels have been developed to establish the diagnosis, disease severity, and prognosis, including the AspAT-to-platelet ratio index (APRI), prothrombine time-gammaglutamyltranspeptidase-GGT (PGA), the fibrotest (analysis of 6 parameters: α2-macroglobulin, α2-globulin, γ-globulins, A1 apoproteins, γ-glutamyltransferases, and total bilirubin), and the actitest (additional ALT activity) [17-21].

IMAGING DIAGNOSTICS

Modern imaging methods allow for minimally invasive, quick, and accurate diagnosis of liver diseases. The use of ultrasonography, computed tomography, magnetic resonance imaging, and positron emission tomography has increased the sensitivity and specificity of the diagnosis of liver fibrosis. Detection of increased liver echogenicity, irregularities on the surface of the liver, as well as visualization of narrowed blood vessels and thickened interlobular spaces can aid in making the diagnosis. Another promising imaging technique is elastography, a test with many advantages, which helps to assess the degree of liver fibrosis by measuring the stiffness of the liver tissue [22]. In a study conducted on a group of patients with liver fibrosis, the accuracy of FibroScan in diagnosing advanced fibrosis was approximately 85-90% [23, 24].

The repeatability, safety, and increasing availability of non-invasive liver fibrosis diagnostics are the advantages of new methods of liver fibrosis imaging, which can be successfully used in everyday practice. However, diagnostic imaging has its limitations: it is used only in patients with overt clinical symptoms or abnormalities in laboratory tests or to facilitate the diagnosis of ambiguous cases. Imaging studies are often limited by the cost, the availability of specialized equipment and trained specialists, and the subjectivity of their assessment [25-27].

HISTOPATHOLOGICAL DIAGNOSIS

Cytological and/or pathomorphological methods are also used in the diagnosis of liver disease. Despite major advances in the laboratory assessment of liver function and improvements in imaging techniques, liver biopsy is still the "gold standard" for the diagnosis of chronic and, in justified cases, acute liver disease. Liver biopsy is performed for various reasons; however, it is most often done to assess the degree of fibrosis and the inflammatory-necrotic process, and less often to assess hepatocyte steatosis or to diagnose neoplastic lesions. Biopsy is used to assess abnormalities in liver architecture resulting from the proliferation of the connective tissue matrix [28, 29].

Liver biopsy is the only morphological examination of the liver that provides comprehensive information on the morphology (and also activity) of hepatocytes, liver stromal cells, and cells of the immune system. Biopsy can be done without the aid of imaging devices, namely, a non-targeted biopsy in which a section of the liver is obtained by inserting a needle into the abdomen at the 9th or 10th intercostal space at the right mid-axillary line. However, a targeted biopsy, guided by ultrasound or tomography, is performed more often. Targeted biopsy is divided into fine needle aspiration biopsy (FNAB) and core needle biopsy (CNB).

In FNAB, a very thin needle (usually a 22–25-gauge needle) is used to aspirate a small amount of cellular material (single cells for cytological analysis). CNB, in turn, involves using a larger biopsy needle (usually a 14–18-gauge needle) to obtain a small core or cylinder of tissue from the liver. This tissue includes cells as well as some of the surrounding tissue, which can provide more information about the tissue's structure and any abnormalities present. Differences in the type of material tested

may affect diagnostic accuracy. FNAB may be less accurate than CNB, particularly in distinguishing between benign and malignant tumors and assessing the degree of liver fibrosis. In practice, FNAB is used only to diagnose liver masses, and not to assess inflammatory activity or degree of fibrosis. It is worth noting, however, that FNAB is usually a quicker procedure that is associated with a lower risk of complications. It is less likely to cause bleeding or other adverse events. CNB carries a slightly higher risk of bleeding or other complications, but this risk is generally low and manageable. CNB may take slightly longer because it requires more precise positioning and sampling [30, 31].

The choice between FNA and CNB depends on the specific clinical situation and the information needed for diagnosis. In many cases, CNB is preferred because of its ability to provide more comprehensive information about liver tissue, but FNA may be used when a smaller cellular sample is sufficient for diagnosis or when minimizing procedure-related risks is a priority. The decision should be made in consultation with a healthcare provider based on the patient's clinical condition and the specific diagnostic goals.

However, the sensitivity of biopsy is low (50-65%), which is most often associated with errors in material collection. Despite the use of imaging techniques, punctures outside the area of fibrosis or collection of material unrepresentative of the disease occur (the histopathological image is blurred by blood or foci of necrosis). To establish the diagnosis of liver fibrosis, a 1.5-cm-long tissue section containing at least 6 portal spaces is necessary [32, 33]. It should also be emphasized that biopsy is an invasive test, which is associated with pain and a small risk of bleeding or bowel perforation, and very rarely with death. The invasive nature of biopsy precludes its widespread use in screening and monitoring the treatment outcomes of patients with chronic liver diseases.

In addition, it is very time-consuming and expensive to process the collected tissue, and the microscopic assessment can be difficult. It is often necessary to perform additional staining. Therefore, invasive diagnostics of liver disease is most often carried out by reference centers [34, 35].

Histochemical studies are valuable tools in diagnosing liver fibrosis. One of the most commonly used dyeing methods is trichrome staining, such as Masson's trichrome or Sirius Red. This staining technique is useful for detecting collagen deposition, a hallmark of fibrosis. Collagen fibers are colored blue or red when exposed to these stains, which makes it possible to visualize the fibrotic tissue and assess its distribution and severity. Elastic fiber stains, like Orcein or Verhoeff's stain, can also be used to evaluate changes in elastic fibers within the liver. These stains can be helpful in assessing liver fibrosis in alcoholic liver disease [36]. Periodic acid-Schiff staining (PAS) demonstrates glycogen and basement membranes. Gomori's silver impregnation, in turn, can help visualize reticulin fibers and assess changes in the liver's reticular framework, which can become altered in fibrosis. Oil red staining can detect the presence of fat droplets within liver tissue and steatosis, or the accumulation of fat in liver cells, which often accompanies fibrosis [37, 38].

Immunohistochemical methods are also complementary to histopathological examinations. Immunohistochemistry and immunocytochemistry are laboratory techniques that show specific antigens in cells and tissues by inducing an antigen--antibody reaction and visualizing this reaction in microscopic preparations. The markers that are most commonly used in the diagnosis of liver fibrosis are collagen type I, alpha-smooth muscle actin (α-SMA) – a marker of activated myofibroblasts – and matrix metalloproteinases (MMP), which is involved in the degradation and remodulation of the extracellular matrix. In addition, immunohistochemical tests may stain receptors of cells that are involved in fibrosis and/or modulate the course of inflammation in the liver [39, 40]. Regulation of liver remodeling may include natural killer cells, which, when activated by stellate cells, have anti-fibrotic effects as they inhibit or directly destroy fiber-producing cells. A specific subtype of CD56+CXCR3+ cells was found among the NK phenotypes, which showed increased activity directed against stellate cells, thus inhibiting the fibrosis process [39, 41].

DIGITIZATION OF MICROSCOPIC IMAGES AND DIAGNOSTIC ALGORITHMS

Due to the lack of simple and universal diagnostic algorithms, rare or atypical changes in the liver may be a source of misdiagnoses or diagnostic delays. Statistics show that histopathological assessment is subject to bias related to its subjective interpretation. Differences in the assessment of fibrosis severity in NAFLD by the same pathologist in subsequent tests occurred with a frequency of 68-85%, while inconsistency of assessment between different pathologists occurred with a frequency of 84% [42]. In scientific research, in order to minimize these differences, histopathological evaluation is performed by at least two specialists [3]. In order to avoid ordering many tests for a single patient, increasing diagnostic costs and exposing the patient to stress-inducing variability of diagnoses, clinical researchers are conducting studies on the feasibility of using computer digitization methods and artificial intelligence to standardize the results of liver diagnostic tests.

The introduction of digital, calibrated equipment – from staining devices, through microscopes, to scanners that map the entire surface of preparations – has opened the way to automated pathomorphological diagnostics supported by artificial intelligence. Most often, it is preparations routinely stained with hematoxylin and eosin that are digitized and analyzed using artificial intelligence algorithms, but it is also possible to evaluate sections stained with AZAN (visualization of collagen fibers) or subjected to immunohistochemical examination.

Computer-aided digital image analysis (DIA) is an evolving method for quantifying liver fibrosis. DIA is based on segmenting

the microscopic image and counting the pixels whose resolution corresponds to the areas of fibrosis. The digitized slides are calibrated with distinction to pixel size, which makes it possible to determine the surface area of irregular surface markings, which is impossible with light microscopy labelling. The digital image also allows for quantitative and qualitative analysis, which accurately determines the number of areas with a given color and color intensity. It is possible to exclude areas of a certain shape and size from the analysis. With DIA of histopathological preparations, a pathologist can sharpen the image, remove distortions, set contrasts, and apply color filters to the image of the stained tissue. In addition, the resulting image can be segmented, freely outlined, and evaluated in terms of surface regularity and dye-catching intensity. The scanned images do not lose their diagnostic value over time: the pathologist can always return to the analyses, check them and modify them [43, 44].

In liver fibrosis diagnostics, the areas to be analyzed are usually outlined manually by the software user. The area of interest (AOI) is marked by outlining each portal space along the contours of the endplate, taking into account the including foci of necrosis and areas with inflammatory infiltration. Because the marking process can be viewed directly, hepatocytes adjacent to the portal spaces of the venous lumen are excluded from the imaging area. The very edge of the section, where dye or antibodies may build up in immunohistochemistry, and around which the connective tissue capsule of the liver may be present, is also excluded.

The image of the scanned tissues is converted into many pixels that represent the entire spectrum of colors and intensities of the original image. Similarly labelled pixels from different images are counted together and classified as normal parenchyma or area of fibrosis. Artefacts can be removed manually if necessary. Although fully automatic algorithms for evaluating the image of lesions already exist in histopathological practice, in the diagnosis of liver fibrosis, these systems show average efficiency due to the small contrast difference between the area affected by connective tissue and the normal stroma of the liver. The liver has a complex histological structure, with a number of influx cells visible in microscopy, and the variability of the hepatocyte image makes it difficult to unify the images. Therefore, the manual intervention of an expert pathologist is still required in DIA techniques [45, 46].

An example of gating liver biopsies with marked AOI and of inflammatory cell staining is shown in fig. 1A-E. These are the results of our study on the association between NK cells and the severity of fibrosis in patients with chronic hepatitis C. Numerical analysis was carried out using the analytical software QuantCenter by 3D Histech and the HistoQuant and NuclearQuant modules.

By analyzing the entire liver parenchyma from digital histological images and calculating the area of the organ occupied by connective tissue, clinicians can precisely assess the degree of fibrosis. This computerized technology provides quantitative and objective results that enable monitoring of even minor changes in fibrosis and liver regeneration or progression. Data from the literature suggest that DIA may redefine the classification of fibrosis and may lead to differentiation between subclasses of diseases with liver parenchymal remodeling. In addition, the increased interest in computer analysis of pathomorphological images results from its potential to track clinically significant dynamics of fibrosis progression and to predict clinical outcomes with various therapies. Perhaps computer systems will allow the differentiation of fibrosis images depending on its cause or the detection of the relationship between the presence and activity of various cells of the immune system and the course of the disease [47].

Although tissue digitization technologies have advanced significantly over the last decade and have become more and more available and useful in diagnostics, e.g., of liver disease, they have not been widely adopted in clinical practice. This may be primarily due to the relatively high cost of equipment for scanning sections and the price of software. There is also still a lack of universal standardization of the method and translation of the results obtained by the DIA method into diagnostic and schedule of treatment. To partially address these limitations, databases of histopathological image analysis algorithms for the quantitative assessment of fibrosis and steatosis are being actively developed. The shared data will allow clinicians and researchers to use the algorithms from a web browser, without the need for specialist knowledge in image analysis or access to computing infrastructure [48].

ARTIFICIAL INTELLIGENCE IN PATHOMORPHOLOGICAL DIAGNOSIS

Artificial intelligence (AI) has the potential to revolutionize pathomorphological diagnostics by standardizing image evaluation, increasing the sensitivity and specificity of assays, and significantly shortening the wait time for the results. AI algorithms can analyze digital images of tissues, identify them, and classify patterns associated with specific diseases, thus helping pathologists to make more accurate diagnoses [49, 50]. AI can also help detect subtle differences in the morphology of cells that are invisible to the human eye. By analyzing the data of large groups of patients (so far, mainly cancer patients), AI algorithms can learn to recognize specific features of the tissue affected by the illness and can classify them into different types of lesions or stages of disease. This can help clinicians not only make more accurate diagnoses, but also determine appropriate treatment options, predict patient prognosis, disease progression scenarios, risk of relapse, and response to therapy. Integrating the results of multiple patients with literature data may also be useful in interpreting complex cases or identifying rare diseases [51].

Software programs based on AI learn to independently solve problems and make decisions based on large amounts of

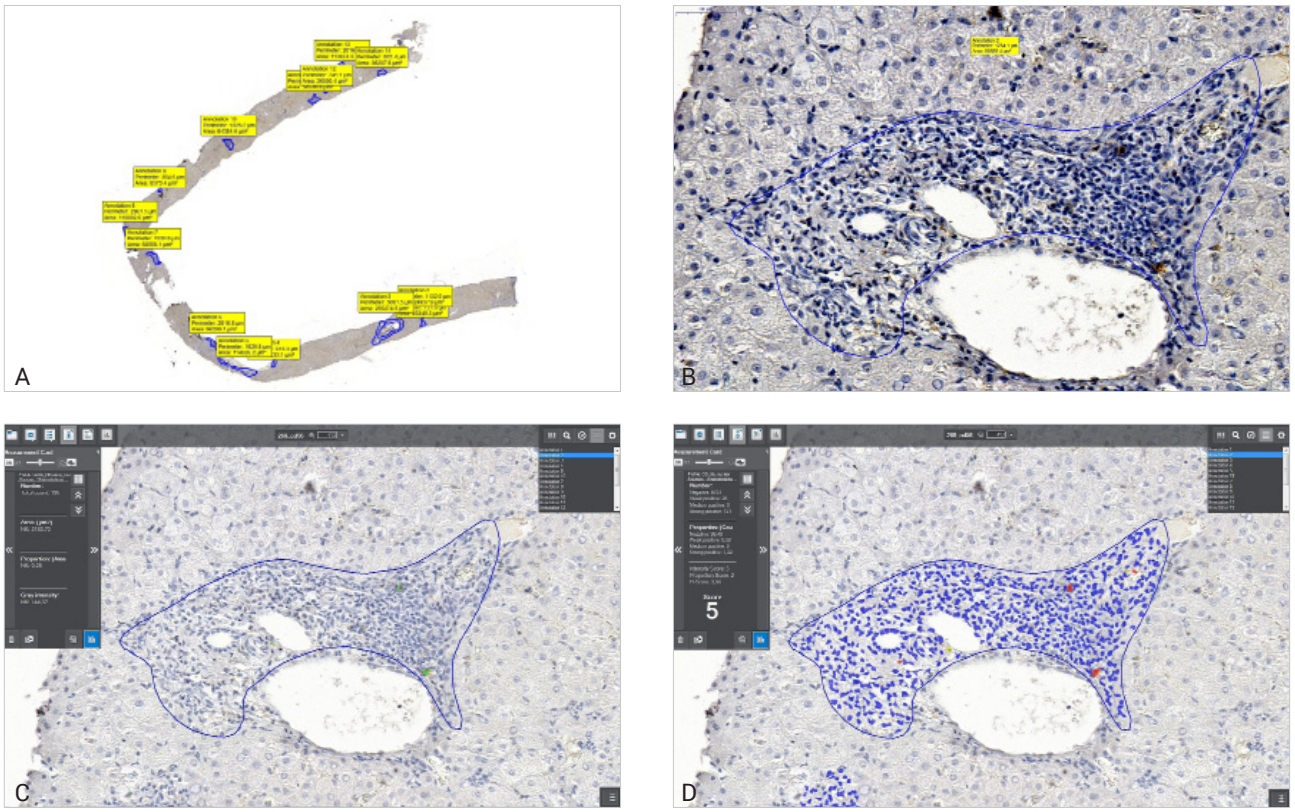

Figure 1. (A) Liver biopsy with marked AOI (approx. 80x magnification); (B) AOI with the venous lumen turned off (approx. 460x magnification); (C) Output of the HistoQuant module; CD56+ cells are marked in green (approx. 420x magnification); (D) Analysis of the NuclearQuant module; blue indicates inflammatory cells, while red and yellow indicate CD56+ cells (approx. 420x magnification); (E) Combination of the results of both counting modules; blue indicates inflammatory cells; yellow, red, and green indicates CD56+ cells (approx. 500x magnification).

information that are too large and too difficult for traditional systems to process. AI is equipped with the ability to capture, store, manage, and analyze vast amounts of often seemingly unrelated data [52].

Despite the rapid development of AI, we must be aware of its many limitations. Although it has great potential in imaging diagnostics, there is still a lack of training data that has been carefully gathered and prepared by experts. In addition, the AI network has limited ability to create new patterns. Although AI can be effective in recognizing certain patterns, it has difficulties in identifying new, previously unseen cases or rare anomalies [53]. Technological limitations are also worth mentioning. AI in imaging diagnostics relies on the analysis of vast data sets and requires powerful computational resources. In some cases, calculations can be time-consuming and AI results may require a large amount of memory or processing power. The availability and performance of appropriate computer infrastructures may affect the effectiveness of AI in diagnostic imaging [54]. In addition, ethical and regulatory issues related to the use of neural networks in medicine are also drawing attention. There are questions about how patient data is collected, stored, and used. Discussions are underway on how to maintain high standards of privacy and data protection. It remains controversial to determine what the consequences will be regarding liability in the event of incorrect diagnoses. Appropriate ethical and legal frameworks must be put in place to guarantee the safe and responsible use of AI in diagnostic imaging [55, 56].

SUMMARY

Despite the undeniable progress in medicine, the diagnosis of liver fibrosis still requires refinement. Simultaneous analysis of the results of laboratory tests and imaging and pathomorphological diagnostic findings allows us to determine the causes of the disease, the degree of fibrosis, and further progression of the lesions. Still, the assessment of the patient's condition is subjective and depends on the experience of the clinician. Image digitization and artificial intelligence tools have great potential in imaging diagnostics and collective analysis of clinical data, while further progress in technology

and research is expected to improve diagnostic effectiveness and precision. However, it should be emphasized that tools for computer data analysis are a valuable supplement to medicine rather than an independent tool for accurate diagnosis and effective treatment planning. Pathologists continue to play a key role in confirming and interpreting the results generated by AI algorithms. The final diagnosis, and patients' health and lives, depend on them.

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