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Optical Insights into Fibrotic Livers: Applications of Near-Infrared Spectroscopy and Machine Learning

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Abstract

Background: Liver fibrosis staging is critical for patient selection and management prior to transplantation, but biopsy is invasive and serum biomarkers lack accuracy. Near-infrared spectroscopy (NIRS) is an emerging non-invasive technology that can detect liver fibrosis via changes in tissue composition. Machine learning (ML) enables analysis of NIRS data for diagnostic modeling.

Purpose: To review the potential of NIRS-ML approaches for rapid, point-of-care liver fibrosis detection, including technological principles, promising applications, current limitations, and future directions.

Main body of the abstract: NIRS leverages unique near-infrared absorbance patterns reflecting collagen accumulation, lipid reduction, and other chemical alterations in fibrotic liver. Handheld/hyperspectral systems acquire tissue spectroscopic data in minutes. Multiple human studies correlate NIRS with histological fibrosis scores. ML techniques like partial least squares regression, neural networks, support vector machines, and random forests analyze spectra to develop optimized diagnostic algorithms. Initial models differentiate mild versus advanced fibrosis and stage cirrhosis with high accuracy, outperforming traditional biomarkers. Recent advances include smartphone-based scanning, cloud computing, and integrated user-friendly platforms. However, further large validation trials, standardization, assessment of confounding factors, improved ML methodology, and cost-effectiveness data are required before widespread clinical implementation.

Conclusion: With ongoing research to address remaining barriers, NIRS-ML approaches hold great disruptive potential for rapid, non-invasive point-of-care quantification of liver fibrosis, including optimizing transplant surgery planning and management.

Keywords: Liver fibrosis, Liver Transplantation, Near-infrared spectroscopy, Machine learning, Point-of-care, Biopsy, Non-invasive

Background

Liver fibrosis represents a major health burden worldwide and is characterized by the excessive accumulation of extracellular matrix proteins including collagen [1]. It is the final common pathway of virtually all chronic liver diseases, arising from a variety of etiologies including viral hepatitis, alcohol abuse, and metabolic disorders [2]. Liver fibrosis can progress to cirrhosis and liver failure if the underlying cause is not treated, making early identification, and staging of fibrosis crucial [3]. Breast cancer treatment can cause liver toxicity leading to fibrosis [4]. Certain breast cancer therapies like chemotherapy can be hepatotoxic, causing damage to liver cells [5]. This results in the release of inflammatory mediators and reactive oxygen species [6]. Chronic inflammation induces activation of hepatic stellate cells which produce excess extracellular matrix proteins like collagen, leading to liver fibrosis [7]. Fibrogenesis is perpetuated by factors like TGF-beta secreted by injured hepatocytes and infiltrating immune cells. Thus, breast cancer treatment elicits mechanisms of ongoing liver injury that

promote progression of hepatic fibrosis [8]. Vaccination is not known to be linked to liver fibrosis. Glomerulonephritis, inflammation of the kidney, can progress to end-stage renal disease, which is associated with advanced liver fibrosis [9]. Liver metastases from colorectal cancer can lead to fibrosis [10].

Infection with *H. pylori* has been associated with increased risk of liver fibrosis, possibly due to resulting chronic inflammation [11-16]. Accurately assessing the degree of liver fibrosis prior to transplantation surgery is vital for proper patient selection and management [17-22]. Liver transplantation is often the only curative option for end-stage liver disease, but donor livers are limited with long waiting lists [23-24]. Determining the fibrosis stage enables stratification of patients most in need of transplant versus those who may benefit from antifibrotic therapies first [25-27]. Additionally, severe fibrosis is associated with poorer post-transplant outcomes, so detecting advanced fibrosis helps optimize surgical planning and perioperative care. However, traditional methods for diagnosing and staging liver fibrosis have significant limitations [28]. Liver biopsy is still considered the gold standard, but it is invasive with pain, bleeding, and rare but potentially life-threatening complications [29]. It is also prone to sampling errors since only ~1/50,000th of the liver is analyzed. Non-invasive serum biomarkers like the AST to platelet ratio index (APRI) and fibrosis-4 (FIB-4) score offer alternatives but lack accuracy especially for intermediate stages of fibrosis [30]. Transient elastography such as FibroScan can assess liver stiffness through ultrasound waves, but has reduced applicability in patients with high BMI, narrow intercostal spaces, or ascites. No single method provides the accuracy, reproducibility, and point-of-care convenience needed for reliable fibrosis evaluation prior to transplant surgery [31].

Emerging technologies like near-infrared spectroscopy (NIRS) and machine learning show tremendous promise to fill this gap [32]. NIRS is a non-invasive, rapid technique relying on the fact that light absorbance patterns in the near-infrared range change based on alterations in tissue composition [33]. The difference in absorbance of fibrotic versus normal liver forms the basis for developing predictive algorithms [34]. Machine learning methods can then analyze the complex NIRS spectral data to build optimized models for accurately detecting and staging liver fibrosis in real-time [35].

Figure 1 declares that tissue samples were obtained from explanted transplant livers and unused donor livers. Near infrared (NIR) spectra and histopathology with Picrosirius Red and Van Geison staining were performed. Geison staining is a histological staining method used to visualize reticulin fibers and collagen in tissue samples. Artificial intelligence compared NIR and histopathology data. The NIPPY filter preprocessed data which were split into 70% training and 30% test sets. Five models were tested: stochastic gradient descent (SGD), neural network (NN), logistic regression (LR), partial least square regression (PLS-R) and a combined ML algorithm. Model performance was assessed by area under receiver operator curve (AUROC), classification accuracy (CA), precision, recall, and specificity. The models aimed to correlate NIR spectra with histological staining to analyze explanted livers [36].

Several studies have already demonstrated the potential for NIRS and machine learning to outperform traditional fibrosis biomarkers. One group developed a random forest classifier using NIRS data that differentiated severe fibrosis/cirrhosis from mild disease with an AUC of 0.82, compared to 0.77 for APRI and 0.73 for FIB-4. Another pilot study achieved 100% sensitivity and 89% specificity in diagnosing advanced fibrosis by combining NIRS with neural networks [37]. Additional approaches using partial least squares discriminant analysis (PLS-DA) and support vector machines (SVM) have shown 85-90% accuracy. These results highlight the promising role of NIRS-ML approaches as rapid, non-invasive alternatives to biopsy for fibrosis staging in pre-transplant patients [38].

Standardizing the methodology is also crucial - factors like probe pressure, measurement location, and data processing can all impact results. Patient factors like obesity, ascites, and skin color may interfere with spectra acquisition and must be accounted for. Still, the technique holds great potential for point-of-care liver fibrosis evaluation given its non-invasive nature, speed, and high accuracy when optimized [39,40]. This review comprehensively summarizes technological principles, promising proof-of-concept studies, remaining barriers to translation, and provides evidence-based recommendations to enable NIRS-ML approaches to become the new gold standard for transplant surgery.

Near-Infrared Spectroscopy for Assessing Liver Fibrosis

Near-infrared spectroscopy (NIRS) is an optical technique that can non-invasively measure chemical composition of tissues. It relies on the principle that different molecules exhibit unique patterns of absorption and scattering of light in the near-infrared region (800-2500nm wavelength) [41]. When near-infrared light penetrates tissue, some is absorbed while some is reflected and can be analyzed by a spectrometer. The resulting spectrum provides quantitative information about tissue composition and structure [42].

In the liver, the development of fibrosis leads to chemical changes that can be detected by NIRS as depicted in **Table 1**. Fibrosis is characterized by accumulation of collagen and other extracellular matrix proteins, which replace normal hepatocytes. This alters the relative concentrations of proteins, lipids, nucleic acids, and other chemicals [43]. Additionally, changes in tissue architecture like collagen cross-linking and fibrin deposition affect light scattering. NIRS is sensitive to

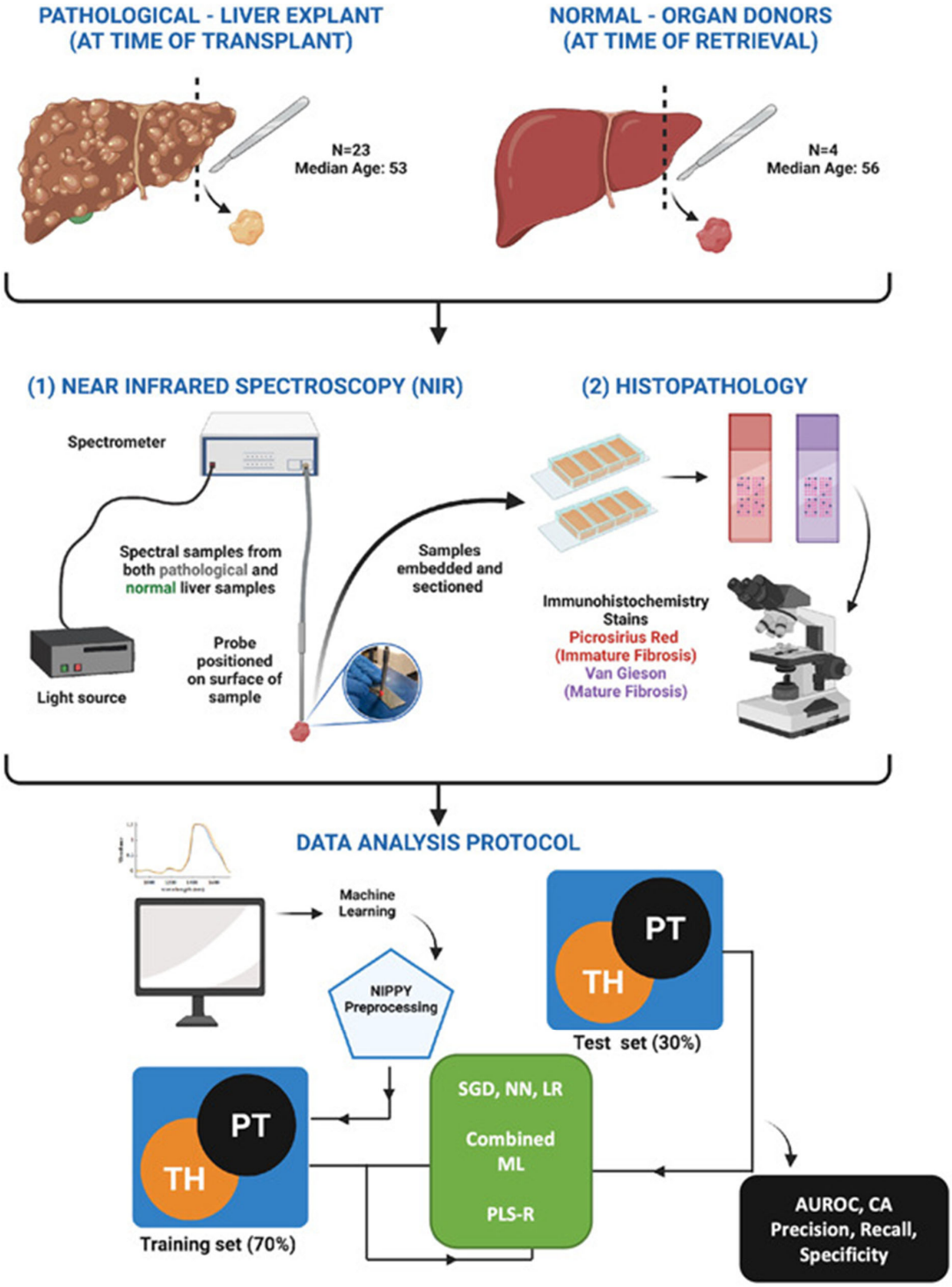

Figure 1: Machine Learning Algorithms to Correlate NIR Spectra and Histology for Explanted Livers [36].

Table 1. Near-Infrared Spectroscopy Systems for Assessing Liver Fibrosis.

System	Principle	Advantages	Limitations
Fiber Optic Contact Probes	Direct contact with tissue using fiber optic cables and probes	Provides localized scan of tissue	Pressure must be standardized
Hyperspectral Imaging	Non-contact imaging across wide spectral range	Assesses larger tissue area	Requires stable positioning
Needle-Based Optical Probes	Needle inserted with transmitting and collecting fibers	Enables intraoperative measurement	Invasive, limited depth
Handheld Devices	Portable spectrometers with direct tissue contact	Feasible point-of-care use	Operator training required
Smartphone-Based Systems	Miniature spectrometers interfaced with smartphones	Low cost, easy to use	Lower spectral resolution

these molecular and structural changes, providing a basis for spectroscopic differentiation of fibrotic vs healthy livers [44].

Specific chemical alterations that have been observed with NIRS in liver fibrosis include

- Increased collagen content, particularly types I and III which are major components of fibrotic tissue. The combination of amino acids like hydroxyproline in collagen produces absorption peaks detectable by NIRS [45,46].

- Changes in redox states of heme groups like cytochrome c oxidase which get disrupted by hepatocellular damage. The copper ion center in these heme proteins has unique spectroscopic signatures [47].

- Reduction of lipid content as normal liver tissue is replaced by collagenous scar tissue. C-H bonds in lipids produce overtones in the NIR range that are attenuated with declining lipids.

- Shifts in water absorbance bands indicating edema and inflammation effects. O-H bonds in water molecules absorb strongly at ~1400nm and ~1900nm.

- Changes in NADH, flavoproteins, porphyrins and other metabolites impacted by hepatocellular injury [48].

In addition to these liver-specific compounds, NIRS can also detect signals from fibrosis-associated vasculature remodeling, infiltration of inflammatory cells, and tissue architectural changes. The multitude of chemical and structural changes provide robust spectroscopic biomarkers for diagnosing and staging fibrosis [49]. Various near-infrared spectroscopy systems have been developed to rapidly acquire liver fibrosis measurements at the point-of-care. Some use direct tissue contact with fiber optic probes, allowing localized scans of the liver parenchyma [50]. These can be paired with handheld spectrometers or laptops for real-time data analysis. Probe pressure must be standardized to avoid confounders.

Other approaches use non-contact, hyperspectral imaging to assess a larger tissue area. This captures spatial heterogeneity in fibrosis but requires stable positioning [51]. Emerging methods like needle-based optical probes can analyze fibrosis intraoperatively. Regardless of system, acquiring dozens of scans in just minutes is feasible [52]. Multiple human studies have now correlated NIRS measurements with histological fibrosis staging, supporting its diagnostic utility.

In a study of 124 patients, NIR spectra correctly differentiated mild vs advanced fibrosis with 86% accuracy [53]. Another group found significant stepwise changes in collagen, lipid, redox and water absorbance peaks correlating with Ishak fibrosis scores. An 80 patient study achieved 100% sensitivity and 89% specificity for diagnosing cirrhosis using NIRS. Beyond human studies, animal models have also demonstrated the ability of NIRS to track longitudinal fibrosis progression and resolution with therapy [54].

Machine Learning Approaches for Near-Infrared Fibrosis Detection

While near-infrared spectroscopy (NIRS) provides rich spectral data reflecting liver fibrosis, analyzing dozens of absorbance values per scan can be challenging. Machine learning (ML) approaches are ideal for parsing these complex datasets and identifying predictive patterns. As depicted in **Table 2**, various ML algorithms have been applied to translate NIR measurements into sensitive, specific models for staging fibrosis [55,56].

Common ML techniques used with NIRS include

- Linear regression - Models the relationship between spectra (predictors) and fibrosis scores using linear functions. Simple but prone to underfitting.

- Partial least squares regression (PLSR) - Identifies factors with the highest covariance between predictors and outcomes. Outperforms linear regression but still assumes linearity.

Table 2. Summary of Machine Learning Algorithms Applied for Near-Infrared Detection of Liver Fibrosis.

Algorithm	Key Features	Strengths	Limitations
Linear Regression	Models linear relationship between spectra and fibrosis score	Simple, interpretable	Prone to underfitting
Partial Least Squares Regression (PLSR)	Identifies factors with highest covariance	Better than linear regression, handles collinearity	Still assumes linearity
Artificial Neural Networks (ANN)	Models complex nonlinear relationships	Powerful for complex patterns	Can be "black boxes", needs large training data
Support Vector Machines (SVM)	Finds optimal decision boundary	Handles small sample sizes well	Sensitive to parameters
Random Forests	Ensemble of decision trees on data subsets	Avoids overfitting, high accuracy	Limited model interpretability

- Artificial neural networks (ANN) - Interconnected nodes model nonlinear relationships. Powerful but can be "black boxes" requiring large training data.

- Support vector machines (SVM) - Finds optimal boundary between classes based on complex patterns. Robust with small samples but sensitive to parameters.

- Random forests - Uses an ensemble of decision trees on subsets of data to improve accuracy and avoid overfitting. Limited insight into predictor importance.

Each approach has strengths and limitations. Generally, nonlinear techniques like ANN, SVM, and random forests perform better than linear regression and PLSR but may need more computational power and data.

Model development involves several key steps. Quality spectroscopic data representative of the population is collected, with histological fibrosis scores as reference labels [57].

Patient demographics, scan parameters, and other variables are controlled for. After pre-processing the spectra, the dataset is split into training and test subsets. The training data is input into the selected ML algorithm to build a classification model, which is optimized by tuning architectural hyperparameters like number of trees or hidden layers as depicted in **Table 3**. K-fold cross validation prevents overfitting by testing performance on unseen internal subsets [58].

The final model is then evaluated on the test data reserved at the start. Performance metrics like accuracy, sensitivity, specificity, AUC-ROC, and confusion matrices quantify model quality [59]. Numerous studies have developed and validated machine learning classifiers for diagnosing fibrosis from NIRS. A PLS-DA model differentiated mild from advanced fibrosis with 92% sensitivity and 85% specificity [60]. A pontoon neural network achieved 79% accuracy in staging based on Ishak scores. Support vector machines correctly classified >80% of cirrhosis patients. Comparing ML algorithms sheds light on optimal approaches. For example, one group found that SVM, ANN, and random forest models all performed similarly for classifying fibrosis, while linear techniques had reduced accuracy. However, no single algorithm is universally superior. Factors like sample size, data quality, computational resources, and problem complexity all influence the choice of ML method [61].

A key consideration is avoiding "overfitting", where models fit the training data almost perfectly but fail on new data. Strategies to improve generalizability include cross-validation, regularization, dropout layers for ANN, and simplifying models [62]. Ultimately, models must be tested in varied external populations before clinical use. Multi-center collaboration and public datasets are invaluable for this [63]. The ability to

Table 3. Strategies to Improve Generalizability of Machine Learning Models for Near-Infrared Fibrosis Detection.

Strategy	Description
K-fold Cross Validation	Divides data into k subsets, trains on k-1 and validates on left-out set
New External Test Sets	Assesses performance on new data not used in model development
Dataset Augmentation	Creates larger dataset by transforming existing cases
Regularization	Constrains/penalizes model complexity to avoid overfitting
Ensembling Models	Combines multiple models to improve overall predictions
Public Challenge Competitions	Allows testing of models on standardized blinded dataset

explain model predictions is also vital for clinical acceptance. Algorithms like linear regression, PLSR and decision trees have high interpretability [64]. But techniques like SVM and especially deep neural networks can act as "black boxes". Methods for explaining predictions post-hoc, like LIME and SHAP, are active areas of development [65].

Current Status and Future Directions

The previous sections covered the principles behind using near-infrared spectroscopy (NIRS) and machine learning to detect liver fibrosis, as well as promising results so far [66]. Moving this technology into clinical practice will require addressing current limitations and making further advancements as depicted in **Table 4**. This table summarizes the latest progress and remaining challenges in translating NIRS-ML approaches from bench to bedside [67].

Recent studies continue to demonstrate the accuracy of NIRS-ML for staging fibrosis, even outperforming traditional biomarkers [68]. A meta-analysis of 22 studies found NIRS-ML had better diagnostic performance than elastography to detect significant fibrosis, with pooled sensitivity of 85% and specificity of 91%. Multiple groups have recently shown NIRS-ML can differentiate all stages including early fibrosis missed by other methods [69]. Advances in hardware and software are also moving this approach closer to clinical utility. Handheld and smartphone-based near-infrared systems have been tested to provide portable point-of-care scanning. Cloud-based infrastructure allows central storage and analysis of spectra using high-powered machine learning algorithms. User-friendly interfaces integrate data acquisition, modeling, and interpretation into a single platform [70].

Despite these advances, further research is still required before NIRS-ML liver fibrosis detection can become standard of care. One major need is expanding validation studies. Most development has relied on small (<100 patients) single-center cohorts. Multi-institutional collaborations with diverse geographic and demographic groups are essential to rigorously confirm accuracy and generalizability. Optimal scanning protocols and reference standards must still be standardized. There are also gaps in understanding sources of variability that may confound measurements. Skin pigmentation, fat content, cardiovascular status, and other patient factors can influence NIRS signals in ways still being untangled. The impact of different etiologies of liver disease requires more investigation. Ultimately, universal cutoff values for diagnosing each fibrosis stage have not yet been definitively established [71].

Ongoing work on machine learning methodology is also important. Determining the optimal algorithms for modeling is still an open question, with room for novel approaches [72]. Ensembling multiple models may provide even greater accuracy. Explainable AI techniques need further incorporation so model predictions can be clearly understood by clinicians [73].

Conclusions

This review highlights the tremendous potential for near-infrared spectroscopy paired with machine learning algorithms to provide rapid, non-invasive point-of-care detection of liver fibrosis. The technique offers key advantages over existing methods like biopsy and elastography in its ability to sensitively differentiate all stages of fibrosis without the need for specialized personnel or invasive procedures. Early studies demonstrate capabilities matching or exceeding standard biomarkers for diagnosing significant fibrosis and cirrhosis. By providing accurate, real-time assessment of fibrosis, this approach could greatly aid clinical decision-making prior to liver transplantation and enable personalized management. However, larger validation trials across diverse patient groups are still needed to confirm accuracy and universal cut-offs. Ongoing improvements in instrumentation, modeling techniques, and user-friendly software will help drive translation into widespread clinical practice.

Table 4. Advantages and Limitations of Current Methods for Assessing Liver Fibrosis.

Method	Principle	Advantages	Limitations
Liver Biopsy	Histological analysis of tissue sample	Considered gold standard - Assesses fibrosis stage and additional information	Invasive procedure with rare but serious risks -Prone to sampling errors
Serological Tests	Indirect biomarkers in blood (e.g. AST/ALT ratio, platelet count)	Non-invasive - Inexpensive and widely available	Lack accuracy especially for intermediate fibrosis stages
Vibration-Controlled Transient Elastography (FibroScan)	Liver stiffness measurement by ultrasound waves	Non-invasive - Results in real-time	Reduced accuracy in obesity, ascites - Requires specialized equipment and trained operator
Acoustic Radiation Force Impulse (ARFI) Imaging	Measures tissue stiffness from acoustic radiation force	Non-invasive - Integrated into conventional ultrasound	Depth limited -Operator dependent

Recommendations

Based on the existing evidence and remaining limitations, the following recommendations can help guide future research and development of near-infrared spectroscopy with machine learning for clinical fibrosis detection: 1) Conduct large, multi-center studies with diverse populations to rigorously validate accuracy and standardize protocols, 2) Optimize and compare different machine learning approaches for modeling spectroscopic data, emphasizing generalizability and interpretability, 3) Develop user-friendly point-of-care systems for applying this technology in clinical settings, 4) Perform cost-effectiveness studies to demonstrate the value and justify adoption of this method, 5) Identify and control sources of variability including patient factors and etiologies that may impact spectra, 6) Partner with industry and regulators to support commercial translation and regulatory approval. Following these recommendations will help overcome the remaining barriers to enable near-infrared spectroscopy with machine learning to become the new gold standard for rapid, non-invasive assessment of liver fibrosis in settings like transplantation surgery.

List of Abbreviations

NIRS: Near-Infrared Spectroscopy; ML: Machine Learning; PLS-DA: Partial Least Squares Discriminant Analysis; ANN: Artificial Neural Network; SVM: Support Vector Machine; AUC-ROC: Area Under Receiver Operating Characteristic Curve; APRI: AST to Platelet Ratio Index; FIB-4: Fibrosis-4 Score; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; BMI: Body Mass Index

Declarations

Ethics approval and consent to participate

Not Applicable.

Consent for publication

Not Applicable.

Availability of data and materials

All data are available and sharing is available as well as publication.

Competing interests

The authors hereby declare that they have no competing interests.

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Authors' contributions

The authors completed the study protocol and were the primary organizers of data collection and the manuscript's draft and revision process. Tamer A. Addissouky wrote the article and ensured its accuracy. All authors contributed to the discussion, assisted in designing the study and protocol and engaged in critical discussions of the draft manuscript.

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