

Research Article

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From Portal Tract to Central Vein: Quantifying Zonal Steatosis and Fibrotic Bridging in Human Liver H&E Histology

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ABSTRACT

Background: Conventional liver histology evaluates steatosis, inflammation, hepatocellular injury, and fibrosis, and many studies classify the former three as percentages or stages. However, few articles analyze lesions at specific sites distributed from portal to centrilobular regions in the liver lobules. The hepatic zonation is crucial for liver physiology, which can be disrupted by metabolic dysfunction-associated steatotic liver disease.

Objective: To develop an interpretable H&E-based framework for quantifying the lobular geography of steatosis and chronic remodeling in human liver histology.

Methods: GTEx Liver whole-slide images and pathology-review metadata will be used to construct pathology-review-negative reference, steatosis, fibrosis/cirrhosis, hepatitis/inflammation, and congestion challenge groups. Portal tracts and central veins will be identified according to validated morphological rules and manual quality control. Each parenchymal tile will be assigned a normalized portal-central coordinate. The primary endpoint will be the Steatosis Zonal Bias Index (SZBI), defined as pericentral minus periportal steatosis burden. Secondary endpoints will include steatosis connectivity, Portal Inflammatory Enrichment, an H&E Fibrotic Bridge Proxy, portal-central lesion-gradient entropy, and Liver Histological Distance from Normal. External biological replication will be achieved using open tissue images from the 2026 spatial atlas of the healthy human liver, which contains mild steatosis and portal fibrosis. Results: No inferential results are reported in this pre-results manuscript.

Conclusion: Spatially explicit liver histology may distinguish equal lesion burdens with different lobular geography and may provide a transparent bridge between routine H&E morphology and modern spatial liver biology.

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Abbreviations

PCC: Normalized Portal-Central Coordinate

STEAT_FRAC: Global Image-Derived Steatosis Area Fraction

SZBI: Steatosis Zonal Bias Index

STEAT_CONN_FRAC: Steatosis Connectivity Fraction

STEAT_COMP_DENS: Steatosis Component Density

PORT_INF_DENS: Periportal Inflammatory-Cell Density

LOB_INF_DENS: Lobular Inflammatory-Cell Density

PIE: Portal Inflammatory Enrichment

HFBP: H&E Fibrotic Bridge Proxy

PP_BRIDGE_FRAC: Portal–Portal Bridge-Like Component Fraction

PC_BRIDGE_FRAC: Portal–Central Bridge-Like Component Fraction

CC_BRIDGE_FRAC: Central–Central Bridge-Like Component Fraction

GRAD_ENTROPY: Portal–Central Lesion-Gradient Entropy

LHDN_MED: Median Liver Histological Distance from Normal

LHDN_P95: 95th Percentile Liver Histological Distance from Normal

LZDI: Exploratory Lobular Zonation Disruption Index

Introduction

Histological evaluation lies at the center of chronic liver disease research due to the diversity of steatosis, hepatocyte ballooning, lobular and portal inflammation, and fibrosis, which represent distinct biological processes [1-3]. Digital pathology has facilitated the standardization and consistency of quantitative assessments of these features. However, most quantitative pathology studies investigating chronic liver disease have focused on evaluating lesion burden rather than localization [4].

The liver is a highly regionalized organ both spatially and functionally; hepatocytes are subjected to a porto-central gradient of oxygen, nutrients, signaling molecules, and xenobiotics [5,6]. Consequently, different zones of the liver (periportal, midlobular, and pericentral) display unique cellular features even in a healthy/non-diseased state. In metabolic dysfunction-associated steatotic liver disease (MASLD), steatosis typically exhibits a zonal pattern that is often pericentral (zone 3), whereas progressive inflammation and fibrosis can disrupt the regular zonation pattern [7]. More generally, one can observe substantial heterogeneity in the patterns of fat accumulation, with some regions exhibiting more prominent lesions than others. For instance, a liver can display a predominantly pericentral, or lobular, or portal or periportal pattern of steatosis. It might also exhibit a mixture of different patterns, which might indicate different pathobiological mechanisms even at similar levels of total fat accumulation. In recent years, there

has been growing appreciation for the heterogeneity of lesion localization, especially in MASLD, with portal macrophage infiltration being associated with worse outcomes [8]. Thus, the extent of lesion localization is of considerable interest in liver pathology research.

A similar consideration applies to fibrosis, which can also exhibit characteristic patterns, such as portal, periportal, pericellular, perisinusoidal, central, or bridging. The latter term refers to fibrosis that involves both portal tracts and the central vein, encompassing a spectrum of fibrous septa formation and architectural distortion, ranging from mild periportal/periseptal thickening to severe cirrhosis [9,10]. Although modern digital pathology techniques enable quantification of collagen deposition and advanced fibrosis, standard hematoxylin and eosin (H&E) staining can still provide useful information about fibrosis, including the approximate location of fibrous septa, their architectural relationships, and whether they involve larger structures such as the central vein. Thus, fibrosis, similar to steatosis, exhibits considerable spatial heterogeneity that can be challenging to fully capture using global lesion quantification.

GTE_x is a unique resource for such an analysis because it contains public access to liver H&E slides, which include pathology review categories for steatosis, fibrosis, cirrhosis, hepatitis, inflammation, congestion, and other features [11-13]. Previous GTE_x image analyses have already demonstrated the utility of such data for assessing liver steatosis and congestion [14]. The current study therefore aimed to determine whether spatial heterogeneity of pathology features could be quantified in GTE_x liver sections and to what extent this heterogeneity goes beyond generic global features (e.g., total percent of steatosis). Specifically, we sought to evaluate the distribution of pathology features across the portal-central axis in the lobules.

Objectives

- First, construct a pathology-review-negative GTE_x Liver reference cohort, stratify steatosis, fibrosis/cirrhosis, hepatitis/

inflammation, and congestion challenge groups.

- Second, identify portal tracts and central veins using histologically interpretable rules and assign parenchymal tissue a normalized portal-central coordinate.
- Third, quantify zonal steatosis with the Steatosis Zonal Bias Index.
- Fourth, determine whether steatotic droplets are isolated, aggregated into local clusters, or interconnected into larger connected domains.
- Fifth, design an H&E Fibrotic Bridge Proxy that differentiates local fibrotic/interstitial expansions from portal-portal, portal-central, or central-central bridging configurations.
- Sixth, assess the contribution of lesion geography to the overall disease burden beyond the generic quantification of steatosis or fibrosis.
- Finally, evaluate the biological reproducibility of the findings using the upcoming 2026 open spatial atlas of healthy human liver and related MASLD spatial resources.

Prespecified Hypotheses

- H1:** Pathology-review-negative liver will exhibit a low lesion burden and an intact portal-central spatial organization.
- H2:** Steatosis will exhibit a detectable zonal bias, with a pericentral enrichment expected in a substantial subset of steatotic livers.
- H3:** Equal global steatosis burden can be accompanied by different SZBI and steatosis-connectivity values.
- H4:** Advanced fibrosis/cirrhosis will exhibit increased bridge-like interstitial connectivity and a decreased preservation of normal lobular architecture.
- H5:** Portal inflammatory enrichment and steatosis zonal bias will identify morphologically distinct inflammatory/metabolic patterns, even in cases of equivalent total inflammatory or steatosis burden.
- H6:** Spatially explicit features will provide additional donor-level information beyond simple percentage steatosis and global abnormal-tissue fraction (Figure 1).

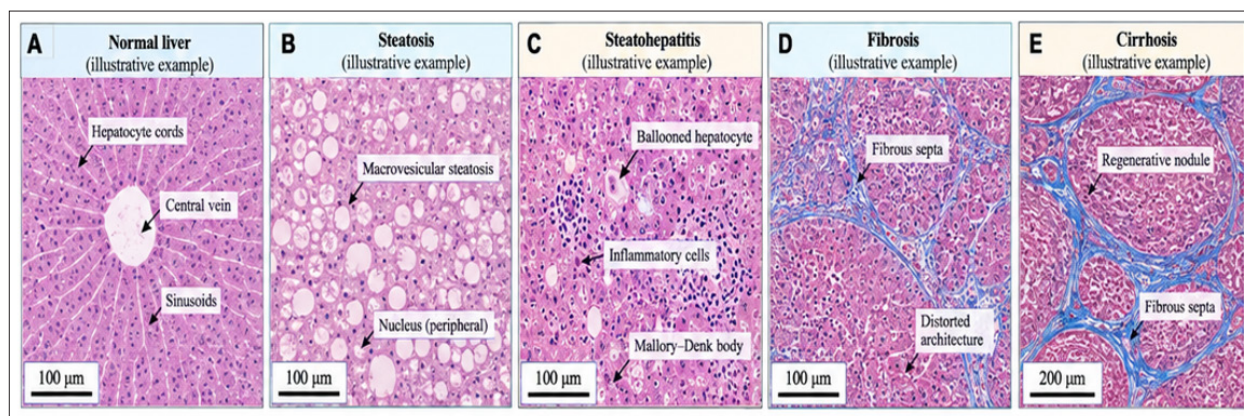


Figure 1: Illustrative Human Liver Histology Across a Pathological Spectrum. Panels Depict Preserved Liver Architecture, Macro Vesicular Steatosis, Steatohepatitis Like Injury, Fibrotic Remodeling, and Cirrhotic Nodular Architecture. These are Illustrative Manuscript Support Images and are Not Gtex Study Cases or Quantitative Results

Materials and Methods

Study Design and Public Data Sources

This paper describes a pre-results digital histology study using public, de-identified human liver tissue. GTE_x Liver H&E whole-slide images and associated pathology-review metadata will be the primary derivation and internal challenge resource. The GTE_x API and public histology viewer expose tissue identity, donor age bracket, sex, Hardy scale, pathology-note categories, and other related technical fields. One Liver specimen per donor will be used in the primary analysis if any multiple images are available. The donor is the biological unit.

Cohort Construction

The main comparison group (L0) will be created from the pathological review of negative liver with good preservation and no significant steatosis, fibrosis, cirrhosis, hepatitis, substantial inflammation, necrosis, congestion, infarction, tumor, or severe autolysis. The other comparison groups will be selected from pathology notes and direct inspection of slides: steatosis predominant liver, fibrosis/cirrhosis predominant liver, hepatitis/inflammation predominant liver, and congestion predominant liver. If pathology notes allow for ordinal categorization of severity, steatosis and fibrosis groups will be stratified prospectively; otherwise, findings of presence/absence and image-based estimation of the burden will be used instead of inventing categories.

Histological Quality Control

Slides will be subjected to blinded quality control assessment for focus, extreme staining, folds, tears, compressions, large processing defects, tissue fragmentation, autolysis-associated morphology loss, and insufficient parenchyma. Capsule, large hilar structures, very large vessels, obviously misplaced bile ducts outside representative portal tracts, necrotic debris, and artifacts will be excluded from the primary parenchymal mask during QC. Slides with borderline findings will be retained for prespecified sensitivity analyses.

Histological Compartments and Landmark Detection

Portal tracts are defined based on morphology as connective-tissue structures containing a portal venous branch with an associated bile duct and/or hepatic arterial branch, while the central veins are characterized by a relatively isolated thin-walled venous lumen devoid of the paired ductal/arterial structures characteristic of portal tracts. Candidate detection algorithms can take advantage of lumen geometry, surrounding connective-tissue texture, ductal epithelium, and local nuclear organization; however, all landmark models will undergo rigorous testing on manually annotated subsets before training across the entire cohort. Ambiguous venous structures should be excluded to avoid erroneous assignment to either the portal or central category (Figure 2 and 3).

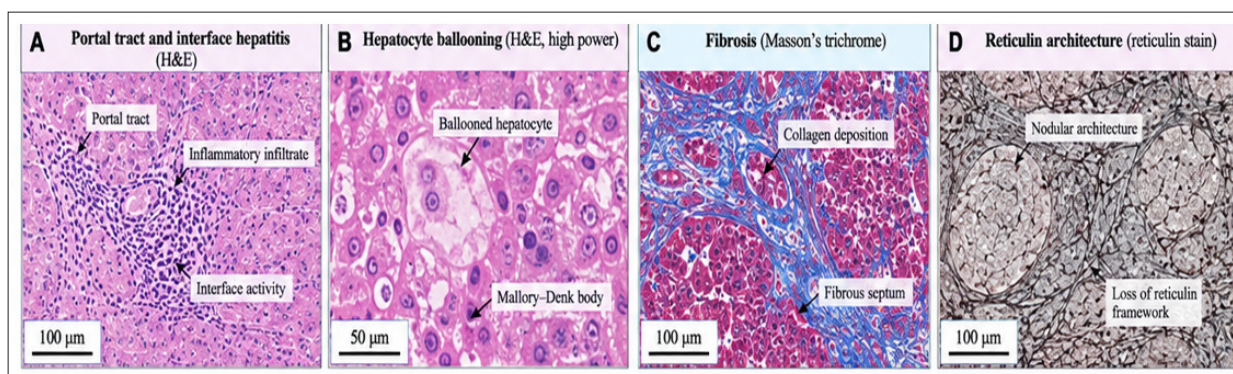


Figure 2: Additional histological features and special-stain context. The panels illustrate portal/interface inflammation, hepatocyte ballooning, collagen deposition on trichrome, and reticulin architectural change. These illustrative examples are included for pathological context; GTEx primary analysis is H&E-based, and fibrosis claims will be phrased as H&E-derived structural proxies unless validated with paired collagen-sensitive imaging

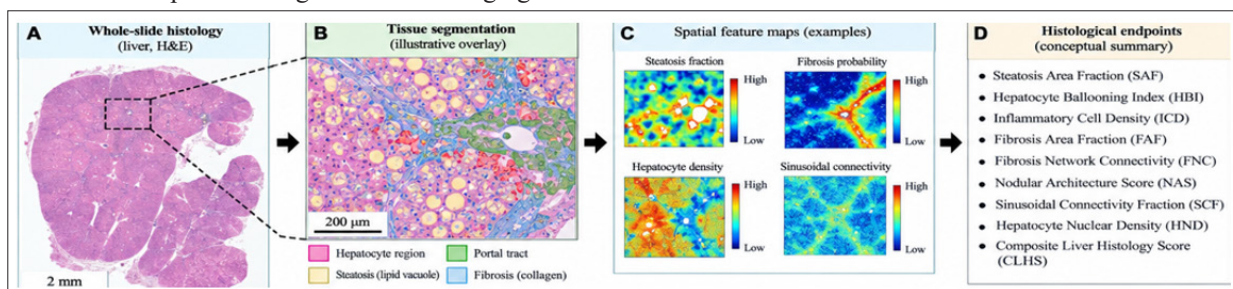


Figure 3: From liver histology to spatial analysis and morphometric endpoints. The illustrative workflow shows whole-slide tissue, conceptual segmentation, spatial feature maps, and candidate histological endpoints. It is included to connect routine morphology with interpretable quantitative outputs and does not depict measured GTEx results

Normalized Portal-Central Coordinate

For each parenchymal location, geodesic or Euclidean distance to the nearest validated portal tract and central vein will be calculated after exclusion of major obstacles. A normalized portal-central coordinate (PCC) will then be defined:

$$PCC = d(\text{portal}) / [d(\text{portal}) + d(\text{central})]$$

PCC tends to 0 near portal tracts and 1 near central veins. The main analysis will dichotomize the axis in periportal (0.00-0.33), midlobular (0.33-0.67), and pericentral (0.67-1.00) bands. The preferred sensitivity analysis will use continuous-coordinate modeling, as the distinction between discrete zones represents an approximation of a biological gradient (Figure 4).

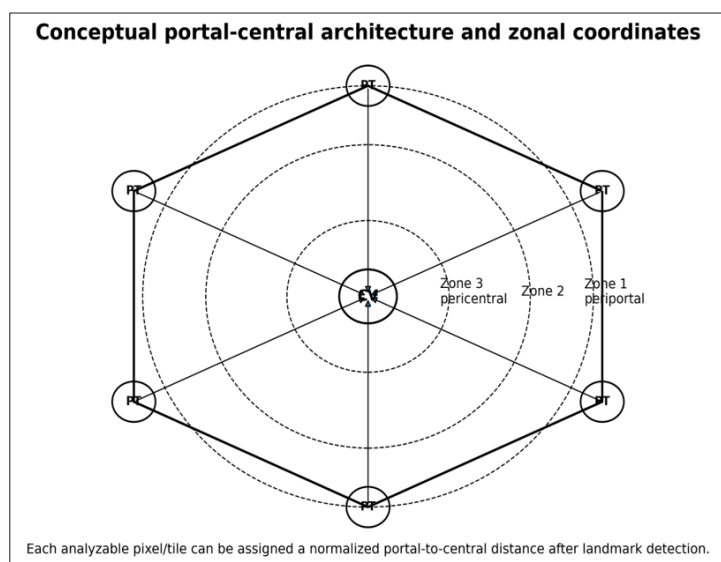


Figure 4: Conceptual portal-central architecture and zonal coordinates. Portal tracts form peripheral reference landmarks and the central vein defines the pericentral reference. Each analyzable tissue location receives a normalized portal-central coordinate. This is a schematic of the analysis geometry, not a literal claim that every 2D section contains a complete classical lobule

Steatosis Segmentation and Burden

Macrovesicular steatosis candidates will be identified as optically clear approximately rounded intracytoplasmic vacuoles within hepatocyte-rich parenchyma, excluding vascular lumina, tissue tears, fixation voids, bile ducts, and section-edge spaces. The candidate rules will be validated manually, as H&E only lipid-vacuole detection is susceptible to processing artifacts. Primary burden measures will include total steatosis area fraction, droplet-density estimates, median and 95th percentile vacuole size, and tile level heterogeneity. These measurements will be image derived, and will not be presented as an exact clinical steatosis percentage without validation against pathologist annotations.

Steatosis Zonal Bias Index

The main spatial endpoint will be the Steatosis Zonal Bias Index (SZBI):

$$\text{SZBI} = \text{Steatosis fraction(pericentral)} - \text{Steatosis fraction(periportal)}$$

Positive values would indicate relative enrichment in the pericentral zone, values not far from zero will indicate little net portal-central bias (either positive or negative), and negative values indicate relative periportal enrichment. A normalized ratio version would be considered as a sensitivity analysis but will not replace the difference-based primary metric since ratios can be unstable at low burdens (Figure 5).

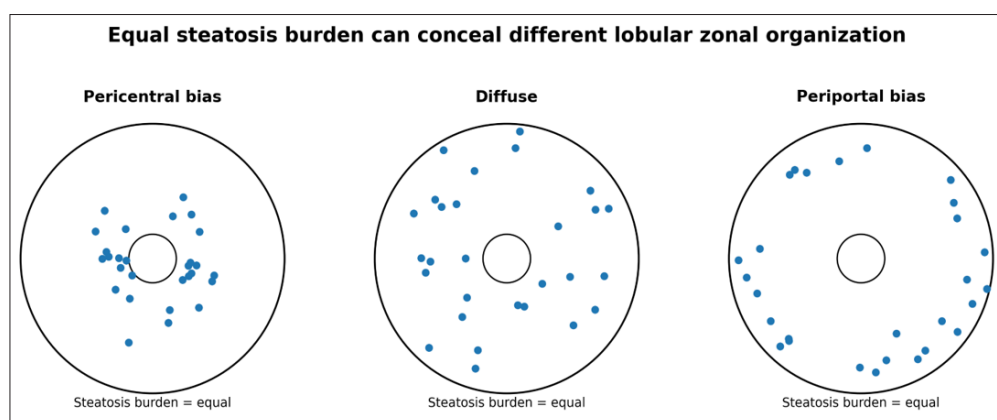


Figure 5: Equal steatosis burden can conceal different lobular zonal organization. The three schematic fields contain the same number of steatotic foci but differ in pericentral, diffuse, or periportal localization. The figure illustrates why global steatosis percentage and spatial zonation are non-equivalent descriptors

Steatosis Connectivity and Lesion Geography

In sum, steatotic regions will be characterized not only by burden, but by connected-component structure. Secondary endpoints will include Steatosis Connectivity Fraction (largest connected steatotic component divided by total steatotic area), component density, median component size, spatial autocorrelation, and nearest-neighbor clustering. These measures provide a means of differentiating between diffuse, multifocal and locally coalescent patterns of lipid accumulation.

Portal and Lobular Inflammation

The number of inflammatory-cell candidates will be determined by their nuclear density, size, chromatin texture, and clustering, with manual inspection of individual instances. Given the potential for error in H&E cell typing, the main quantitative readouts will be inflammatory-cell density rather than specific classifications. Portal inflammatory enrichment (PIE) will be calculated from periportal inflammatory-cell density divided by midlobular/pericentral density or, when the denominator was low, PIE will be calculated as the difference between the two. The inflammatory-cell clusters in lobules will be analyzed separately from the portal/interface inflammatory cells.

H&E Fibrotic Bridge Proxy

Fibrosis is best detected using collagen-specific stains. Therefore, the primary H&E analysis will not directly estimate collagen deposition, but will identify candidate expanded eosinophilic interstitial/septal tissue regions by texture, width, linearity, tract continuity, and associated architectural distortion. The H&E Fibrotic Bridge Proxy (HFBP) will be defined as the fraction of candidate fibrotic/interstitial tissue regions associated to components connecting two validated lobular landmarks (portal-portal, portal-central, or central-central). The proxy designation will be retained except when validated against paired trichrome, Sirius Red, second-harmonic generation imaging or pathologist-confirmed fibrosis maps.

Lobular Zonation Disruption Index

An exploratory Lobular Zonation Disruption Index (LZDI) will be generated encompassing standardized deviations from the L0 reference across SZBI magnitude, the portal-central lesion-gradient entropy, steatosis connectivity, PIE, HFBP, and architectural heterogeneity. The index will be retained as exploratory in the main analysis because it will not be optimized on disease-specific labels.

Liver Histological Distance from Normal

In this manuscript, we propose a multivariate Liver Histological Distance from Normal (LHDN) model that will be fit exclusively in L0 using a shrinkage covariance estimate over prespecified H&E features. Summaries at the patient level will report median, 95th percentile, and high-distance tissue fraction. The LHDN can serve as a general abnormality axis on which to compare lesion-specific zonal features.

Burden-Matched Analyses

To test the proposition that geometry provides independent information beyond lesion amount, steatotic livers will be matched or stratified by total amount of steatosis, and within burden-matched strata, SZBI, steatosis connectivity, portal-central gradient entropy and LHDN will be compared. Similarly for fibrosis analyses, cases will be matched on overall H&E interstitial/fibrotic proxy fraction and then bridge topology compared. This is a critical falsifiable test of the proposition that equal lesion burden does not imply equal lobular architecture.

External Biological Replication

A 2026 Nature spatial atlas of the healthy human liver from live donors constitutes a valuable complement to the proposed work, as it includes tissue imaging, portal-central spatial information, cases with mild steatosis, and cases with portal fibrosis; associated spatially resolved transcriptomic tissue images are openly available on Zenodo [15]. The main question for replication in this study would pertain to whether image-derived portal-central steatosis bias and regional architectural patterns match the spatial

context established in the atlas. In turn, a 2025 spatial multi-omics study on human MASLD will serve as the basis for biological contextualization and, if processed tissue images are made openly available, allow for exploratory replication [16].

Statistical Analysis

All inferential analyses will be done at the donor level. The primary steatosis model will regress SZBI on steatosis status/burden, adjusting, where appropriate, for age bracket, sex, autolysis score, Hardy scale as a sensitivity covariate, and technical batch. Continuous steatosis burden will be modeled with restricted cubic splines to test if zonal bias changes non-linearly with increasing burden. Secondary outcomes will include Steatosis Connectivity Fraction, PIE, HFBP, LHDN, and gradient entropy; false-discovery-rate control will be applied to secondary families. Models with only burden will be compared to those with burden-plus-spatial using cross-validated R^2 or deviance, AIC/BIC where appropriate, and likelihood-ratio tests. No tile should be considered an independent biological replicate.

Sensitivity Analyses

- Repeat portal-central zone definitions using continuous PCC rather than three discrete bands.
- Apply varying confidence thresholds for portal/central landmarks and exclude ambiguous landmarks.
- Repeat analysis of steatosis after more aggressive exclusion of tears and vascular lumina.
- Repeat analyses in narrower age strata.
- Exclude slides with severe congestion or autolysis that might distort lobular geometry.
- Repeat fibrosis/bridging analysis only in slides with strong pathologist evidence of fibrosis or cirrhosis.
- Compare proxies for fibrosis from H&E with external collagen sensitive images, where available.
- Assess local lesion measures in tiles/windows of size around 125, 250 and 500 micrometres.
- Use geographically distributed sampling to assess sensitivity to tissue heterogeneity.

Histological Interpretation Safeguards

The analysis makes a distinction between visible histological zonation and molecular zonation. While H&E can localize lesions relative to portal and central landmarks, it cannot measure oxygen gradients, metabolic gene-expression programs or Wnt signaling. Similarly, interstitial expansion in H&E is not the same as collagen-specific fibrosis. Any biological interpretation will be anchored to morphology, and will be referred to spatial-omics studies, rather than inferred from H&E alone (Figure 6, Table 1 and 2).

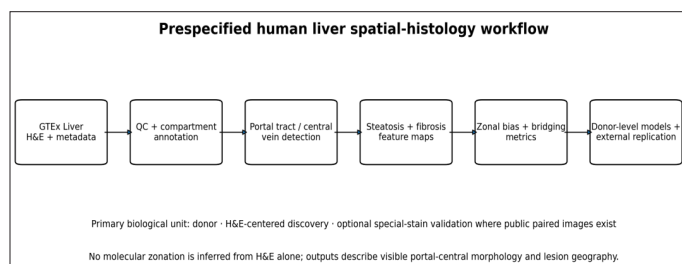


Figure 6: Prespecified human liver spatial-histology workflow. GTEx Liver H&E and metadata undergo QC, landmark detection, lesion segmentation, portal-central spatial assignment, and donor-level modeling. External replication is biological and technical; no molecular zonation is inferred directly from H&E

Table 1: Prespecified Liver Histology Endpoints

Endpoint	Definition	Primary interpretation	Role
Steatosis area fraction	Image-derived steatotic vacuole area / analyzable hepatocyte-rich parenchyma	Global steatosis burden	Baseline
SZBI	Pericentral steatosis fraction - periportal steatosis fraction	Portal-central steatosis bias	Primary
Steatosis Connectivity Fraction	Largest connected steatotic region / total steatotic area	Coalescence of steatosis	Secondary
PIE	Periportal inflammatory density relative to non-portal parenchyma	Portal inflammatory enrichment	Secondary
HFBP	Landmark-bridging candidate fibrotic/interstitial tissue / total candidate fibrotic tissue	Bridge-like remodeling proxy	Secondary
Gradient entropy	Entropy of lesion burden across portal-central coordinate	Loss of zonal localization	Secondary
LHDN_MED / P95	Multivariate distance from L0 normal reference	Overall histological abnormality	Secondary
LZDI	Composite standardized zonal-disruption summary	Exploratory multicomponent disruption	Exploratory

Table 2: Histological Phenotype Logic

Phenotype	Expected burden	Expected zonal signal	Expected connectivity	Key safeguard
L0 reference	Low	No lesion-specific bias	Preserved architecture	Not clinically disease-free
Steatosis-predominant	Variable fat burden	Often pericentral, but heterogeneous	Variable steatosis clusters	Exclude tears/vessels as pseudo-vacuoles
Hepatitis/inflammation	Variable	Portal and/or lobular enrichment	Inflammatory clustering	Do not infer immune lineage from H&E alone
Fibrosis/cirrhosis	Higher interstitial/septal proxy	Bridge-related architecture loss	Higher HFBP	H&E is not collagen-specific
Congestion	Vascular/sinusoidal change	May be centrilobular	Not a steatosis signal	Treat separately from metabolic remodeling

Discussion Framework

The main finding from our work lies in a conceptual improvement; that liver lesions reside on a zoned organ and, therefore, the evaluation of their amount (expressed as a percentage of steatosis) is quantified differently than their location (expressed as a SZBI score). The two measurements describe different qualities of the same observation and, therefore, are not mutually exclusive in their description.

This distinction is particularly relevant in MASLD, given that portal-central zonation is biologically relevant and can become disrupted as disease progresses. A strongly pericentral pattern, diffuse lobular pattern, and portal-enriched pattern may thus represent different structural states, albeit with a similar global fat burden. In addition, the recent recognition of portal-based disease features in MASLD suggests otherwise.

The fibrosis component follows the same general logic. Conventional staging remains a critical reference frame, but bridge geometry encodes additional information about the structural reorganization of the lobule implied by the pattern of scarring. Studies using digital quantification of bridging fibrosis have demonstrated that the architectural arrangement of septa within the lobule often contains useful information beyond what is captured by conventional categorical staging. This framework aims to partially encode that information in an H&E-compatible public data set, while acknowledging this as a proxy at a particular level of analysis.

The study also serves to connect traditional histology with spatial-omics liver biology. The 2026 live-donor liver atlas shows that portal-central gradients and early steatosis can be resolved in situ in human liver and that corresponding tissue images are publicly available. Although H&E cannot capture transcriptomic zonation, it provides a scalable morphological coordinate system to which visible lesions can be registered.

External replication will be critical. GTEx is a postmortem resource in which liver tissue was not collected as a standardized MASLD biopsy cohort, and a successful framework should therefore survive not only internal GTEx variation but also marked differences in procurement and clinical context; failure to transport would be informative because it would indicate which landmark or lesion definitions are too strongly biased by source-specific processing.

That said, if the prespecified hypotheses are supported, the main utility of the framework would not be as an automated disease diagnosis. But rather it would provide a transparent quantitative language for describing portal-central lesion geography, lesion connectivity, and lobular architectural disruption from routine histology.

Strengths

- Histology-first and interpretable, not black-box, classification.
- Explicit use of portal and central anatomical landmarks.
- Separates lesion burden from lesion geography and connectivity.
- Uses donor-level inference and avoids tile-level pseudoreplication.
- Leverages GTEx pathology categories already known to include liver steatosis and congestion.
- Includes a contemporary open human liver spatial atlas for external biological replication.
- Builds in safeguards for H&E limitations in fibrosis and immune-cell interpretation.

Limitations

Several limitations are expected. GTEx liver is postmortem, and thus subject to alterations like autolysis, congestion, fixation, and tissue collapse. A 2D section through a classical lobule may not always capture its entirety, complicating the topographic assignment of lobules amenable to portal-central classification. The distinction between central veins and portal venous branches is not always automated, requiring manual verification. Lipid vacuoles in H&E are prone to segmentation errors caused by processing artifacts, and H&E interstitial expansion is not a specific collagen-linked fibrosis marker. The GTEx pathology-note lexicon was not initially designed to implement standardized MASLD scoring, and thus the present study cannot be used to retroactively generate NAFLD Activity Scores or fibrosis stages. Lastly, the external live-donor atlas is smaller, more complementary than independent, and less representative of an alternative diagnostic cohort.

Conclusion

This article proposes an interpretable framework to quantify where in the liver the pathology occurs, not only how much. Interpreted on a portal-central coordinate system, the routine H&E histology can be transformed into a spatially structured tissue, instead of the isolated lesions as seen before. The Steatosis Zonal Bias Index and related connectivity metrics offer falsifiable, donor level endpoints, which can be first tested on the GTEx and subsequently benchmarked against contemporary spatial liver atlases[17-18].

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