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YKL-40 in Virus-Associated Liver Disease: A Translational Biomarker Linking Fibrosis, Hepatocarcinogenesis, and Liver Transplantation

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Abstract

Virus-associated hepatocellular carcinoma (HCC) remains a major global health burden despite effective antiviral therapies. Chronic infection with hepatitis B (HBV), hepatitis C (HCV), and hepatitis D (HDV) promotes malignant transformation through overlapping pathways of fibrosis, immune dysregulation, and microenvironmental remodeling. YKL-40, a glycoprotein secreted by hepatic stellate cells, hepatocytes under stress, macrophages, and endothelial cells, has emerged as a marker that reflects stromal activation rather than direct hepatocyte injury. Its expression is reinforced by profibrotic and angiogenic circuits, and circulating concentrations correlate with advanced fibrosis, residual risk after viral suppression, and oncologic outcomes. This review synthesizes current evidence on YKL-40 across HBV, HCV, and HDV cohorts, with emphasis on its role in bridging molecular mechanisms to clinical applications. We examine its utility in non-invasive fibrosis assessment, longitudinal monitoring after antiviral therapy, and prognostic modeling in HCC. Particular attention is given to its potential in the liver transplant pathway, where YKL-40 may refine eligibility beyond morphology, inform bridging therapy response, and predict post-transplant recurrence or graft fibrosis. Remaining challenges include its lack of disease specificity, assay variability, and limited multicenter validation. Future integration of YKL-40 into multimarker, algorithm-based frameworks could enable risk-adaptive strategies that align surveillance and transplant decisions with the evolving biology of virus-associated liver disease.

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1. Introduction

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and accounts for a substantial proportion of global cancer mortality [1]. Many cases develop in the context of chronic viral hepatitis, particularly from persistent infection with hepatitis B virus (HBV), hepatitis C virus (HCV), or hepatitis D virus (HDV) [2,3]. Antiviral strategies such as nucleos(t)ide analogues for HBV and direct-acting antivirals (DAAs) for HCV have significantly improved therapeutic options. However, important challenges remain, with persistent disparities in diagnosis and screening, limited access to antiviral treatment in many regions, and the continuing risk of virus-associated HCC even after viral suppression or clearance [4,5].

The progression from chronic viral hepatitis to HCC arises through cumulative hepatocellular injury, with activation of hepatic stellate cells (HSCs) driving extracellular matrix (ECM) deposition and fibrosis, while chronic inflammation and dysregulated regenerative signaling promote oncogenic transformation [6,7].

Current serum biomarkers for HCC surveillance, including alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP), have limited diagnostic performance, particularly in early-stage disease or in tumors lacking typical secretory phenotypes [8]. These limitations highlight the need for biomarkers that can reflect the fibrotic and stromal changes driving malignant progression. Among such candidates is YKL-40 (chitinase-3-like protein 1, CHI3L1), a glycoprotein secreted by activated HSCs and immune cells. By participating in ECM turnover, inflammatory signaling, and hepatic remodeling, YKL-40 provides information distinct from AFP and DCP, capturing the stromal and fibrogenic processes central to virus-associated carcinogenesis [9]. Circulating levels have been shown to correlate with progressive fibrosis, aggressive tumor phenotypes, and adverse outcomes in chronic liver disease and HCC [10,11].

Despite these associations, the virus-specific contributions of YKL-40 and its translational potential in guiding liver transplantation (LT) remain incompletely understood. In this narrative review, we critically synthesize current evidence on YKL-40 in HBV-, HCV-, and HDV-associated disease, emphasizing its mechanistic basis, clinical applications, and implications for biologically adaptive decision-making across the fibrosis-carcinogenesis-transplant continuum.

2. Mechanistic and Clinical Relevance of YKL-40 in Virus-Associated Fibrosis and Hepatocarcinogenesis

2.1. HBV: Viral Persistence, Fibrogenic Signaling, and Oncogenic Remodeling

The persistence of HBV is maintained through covalently closed circular DNA (cccDNA), a stable episomal template that remains transcriptionally active despite antiviral suppression [12]. Continuous viral gene expression creates a state of chronic immune disturbance, with exhausted T cells, increased secretion of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), and expansion of regulatory immune subsets that blunt antiviral cytotoxicity [13–15]. These signals converge on HSCs, where profibrogenic mediators such as transforming growth factor-beta (TGF-β), connective tissue growth factor (CTGF), and hepatocyte-derived exosomes initiate ECM deposition and architectural remodeling [16,17].

Sustained stimulation gradually reprograms stellate cells into a fibrogenic state characterized by enhanced collagen synthesis and reduced matrix degradation, supported by contractile and proliferative changes that consolidate their myofibroblastic phenotype [18–22]. Scar tissue becomes further stabilized through collagen cross linking by lysyl oxidase-like 2 (LOXL2), which limits the potential for reversal [23]. Insights from single-cell transcriptomic studies add nuance, showing that activation is not uniform across the liver but varies by zone, with periportal and pericentral stellate subsets contributing in distinct ways to the fibrotic landscape [24,25]. This heterogeneity has clinical significance because fibrosis may progress silently despite normal alanine aminotransferase (ALT) levels [26]. In this context, circulating YKL-40 has emerged as an informative biomarker, with

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elevated levels reported in HBV cohorts with advanced fibrosis and potential utility for staging and disease monitoring [27,28].

As fibrosis advances, the altered microenvironment facilitates oncogenic transformation. Epigenetic changes such as aberrant DNA methylation and dysregulated noncoding RNAs weaken tumor-suppressive programs, while HBV DNA integration activates oncogenes including telomerase reverse transcriptase (TERT) and cyclin E1 (CCNE1), promoting clonal expansion of genetically unstable hepatocytes [29–32]. These processes destabilize genomic integrity and create conditions permissive for malignant evolution [33].

HBV also promotes cancer through direct molecular drivers. The hepatitis B virus X protein (HBx) is central to this process. It impairs DNA repair, disrupts cell-cycle checkpoints, and alters chromosomal organization [34,35]. HBx can engage chromatin remodeling machinery such as SWI/SNF and displace Polycomb repressors, opening proto-oncogenic loci to transcriptional activation [36,37]. In parallel, interferon signaling and antigen presentation are dampened, and apoptotic thresholds are shifted via mitochondrial and death-receptor pathways, weakening immune surveillance [38,39]. Although no direct studies have linked HBx activity to YKL-40 expression, the fibrogenic and inflammatory environment fostered by HBV provides a biologically coherent basis for its up-regulation, emphasizing the need for studies that clarify its virus-specific contributions and translational potential.

2.2. HCV: Immune Polarization, Fibrotic Programming, and Inflammation-Driven Transformation

Unlike HBV, which achieves persistence through cccDNA reservoirs and integration into the host genome, HCV maintains chronic infection by evading innate immune recognition while sustaining replication in the hepatocyte cytoplasm [40,41]. Viral proteins such as NS3/4A and NS5A disable mitochondrial antiviral signaling protein (MAVS) and interfere with toll like receptor (TLR) dependent interferon cascades, weakening antiviral defenses mediated by retinoic acid inducible gene I (RIG-I), interferon regulatory factor 3 (IRF3), and signal transducer and activator of transcription 1 (STAT1) [42,43]. By silencing these sensors, HCV establishes an intracellular niche where replication can proceed, while fibrogenic signaling gradually builds.

Persistent antigenic stimulation progressively reshapes adaptive immunity. Virus specific $CD8^+$ T cells show features of exhaustion, with elevated expression of programmed cell death protein 1 (PD-1) and lymphocyte activation gene 3 (LAG-3) [44]. Regulatory T cells (Tregs) expand and further dampen cytotoxic responses, while Kupffer cells and infiltrating macrophages adopt a profibrogenic, anti-inflammatory phenotype marked by IL-10, TGF-β, and arginase-1 [45]. These immune changes converge on HSCs, initiating ECM deposition and stromal remodeling. In this context, hepatocyte injury arises less from direct viral cytotoxicity and more from persistent low-grade inflammation. Mediators such as IL-1β, CXCL10, and reactive oxygen species (ROS) sustain a chronic inflammatory loop that reinforces fibrogenic activity [46,47], a milieu in which serum YKL-40 is higher in HCV with advanced fibrosis [48].

Macrophage polarization further stabilizes this fibrogenic axis. Under sustained IL-10 and TGF-β exposure, alternatively activated macrophages drive HSCs toward a myofibroblastic state characterized by increased collagen production, impaired ECM degradation, and expression of markers such as ACTA2, COL1A1, and TIMP1 [49–51]. Kupffer cells and infiltrating macrophages amplify this circuit through secretion of CCL2 and osteopontin, which recruit additional inflammatory and profibrogenic cells into perisinusoidal regions [52,53]. In this setting, YKL-40 likely mirrors both matrix turnover and the intensity of macrophage-stellate cell cross talk, though direct mechanistic evidence in HCV remains limited.

As fibrosis matures, structural cues reinforce its persistence. Increasing ECM stiffness enhances integrin mediated activation of latent TGF-β, which locks HSCs into a self-sustaining fibrogenic program [54]. This consolidation is amplified by lysyl oxidase like 2 (LOXL2), which promotes collagen cross linking [55], while downregulation of matrix metalloproteinases (MMPs) reduces turnover and secures a rigid fibrotic state [56]. Insights from single cell transcriptomics add another

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dimension, showing that HSC activation varies by hepatic zone, with central vein associated HSCs emerging as dominant collagen producers and periportal and pericentral subsets showing distinct patterns of ACTA2, remodeling enzymes, and chemokine receptors, although more detailed zone-specific data are still needed [57]. Endothelial signaling and oxygen gradients further shape these spatial responses, integrating immune, vascular, and metabolic inputs into the fibrotic architecture [58].

Whether circulating YKL-40 reflects not only the extent of fibrotic remodeling but also the immune polarization characteristic of HCV remains uncertain, yet its consistent association with advanced fibrosis across cohorts indicates potential value as a stromal biomarker [48].

2.3. HDV: Intensified Immunopathology and Fibrotic Escalation

HDV depends on the hepatitis B surface antigen (HBsAg) for assembly and propagation, making HBV co- or superinfection a prerequisite for its persistence [59]. Clinically, HBV/HDV coinfection follows a more aggressive course than HBV alone, with accelerated progression to cirrhosis, earlier decompensation, and higher risk of HCC [60].

The large hepatitis D antigen (L-HDAg) is a central driver of this pathogenic phenotype [61]. Beyond its direct viral functions, L-HDAg promotes an inflammatory and profibrogenic milieu within the liver. Kupffer cells and infiltrating monocytes adopt activated states and release cytokines such as TNF-α and IL-1β, which sustain stellate-cell activity and drive collagen I accumulation [61]. Together these mechanisms provide a foundation for the rapid fibrotic trajectory observed in HBV/HDV coinfection.

Additional studies show that L-HDAg also promotes oxidative stress through nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and activates STAT3 and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling [62]. It further disrupts endoplasmic reticulum homeostasis, triggers unfolded-protein-response pathways, and perturbs proteostasis, thereby maintaining a chronically inflamed hepatic niche reinforced by type I interferon activity [62]. These signals accelerate stellate-cell activation and matrix deposition, deepening the fibrotic response.

Clinical evidence supports these mechanistic observations, demonstrating that fibrosis progresses more rapidly in HBV/HDV coinfection compared with HBV monoinfection, in line with the heightened inflammatory burden [63]. Adaptive immunity is also reshaped. Virus-specific $CD8^+$ T cells gradually acquire features of exhaustion, regulatory pathways expand, and cytotoxic lymphocytes lose functional capacity. This imbalance limits viral control while amplifying hepatocellular injury, hastening cirrhosis and elevating oncogenic risk compared with HBV alone [64,65].

Direct evaluation of YKL-40 in HDV infection is not yet available. Even so, the profibrotic and inflammatory profile of HBV/HDV coinfection creates a biologically plausible setting for its up-regulation. Evidence from HBV and HCV cohorts, where higher YKL-40 levels correlate with advanced fibrosis and adverse outcomes, provides a strong rationale for testing whether similar associations are present in HDV. Addressing this gap will be important for determining whether YKL-40 can serve as a clinically useful biomarker in this uniquely aggressive viral context.

2.4. Cross-Etiology Synthesis: YKL-40 as a Read-Out of Stromal Activation

HBV, HCV, and HDV maintain persistence through different virological strategies, yet over time they drive the liver toward a similar endpoint in which the hepatic microenvironment becomes fibrotic and immunologically altered, creating conditions that favor malignant progression [66–68]. Within this shared landscape, YKL-40 reflects stromal activation that connects fibrosis with oncogenic risk, providing a common signal across viral contexts [69].

The principal similarities and differences between HBV- and HCV-associated mechanisms of YKL-40 induction and function are summarized in Table 1, highlighting how virus-specific pathways converge on shared stromal signatures with translational biomarker potential.

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Table 1. Comparative mechanisms of YKL-40 induction and function in HBV and HCV infection: from viral triggers to biomarker translation.

Pathogenic axis	HBV-associated mechanisms	HCV-associated mechanisms	Shared features
Viral trigger	HBx activates TGF-β/SMAD and IL-6/STAT3 signaling	Core and NS5A proteins induce ROS and NF-κB activation	Upregulation of IL-6, TGF-β, and VEGF
Fibrogenesis	cccDNA persistence sustains HSC activation, even in inactive carriers	ROS-driven HSC activation and progressive fibrotic remodeling	Collagen I and fibronectin accumulation with impaired ECM turnover
Immune modulation	Expansion of M2 macrophages and IL-10, dominant immune tolerance	T-cell exhaustion with PD-1⁺ CD8⁺ subsets	Recruitment of Tregs and MDSCs; promotion of angiogenesis
YKL-40 expression	Elevated even at low viremia, correlates with necroinflammatory activity	Persists in a subset after SVR, associated with residual fibrosis	Reflects active stromal remodeling and immunosuppressive microenvironment
Biomarker potential	Sensitive marker of fibrogenic activity in HCC-naïve patients	Identifies a high-risk phenotype post-SVR	Applicable to early HCC risk stratification and supportive in pre-transplant decision-making pathways

cccDNA: Covalently closed circular DNA; CD8+: Cluster of differentiation 8-positive; ECM: Extracellular matrix; HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HBx: Hepatitis B X protein; HCV: Hepatitis C virus; HSC: Hepatic stellate cell; IL-6: Interleukin-6; IL-10: Interleukin-10; LT: Liver transplantation; M2: M2 macrophage phenotype; MDSCs: Myeloid-derived suppressor cells; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NS5A: Non-structural protein 5A; PD-1: Programmed cell death protein 1; ROS: Reactive oxygen species; SMAD: Small mothers against decapentaplegic (SMAD family of proteins); STAT3: Signal transducer and activator of transcription 3; SVR: Sustained virologic response; TGF-β: Transforming growth factor-beta; Tregs: Regulatory T cells; VEGF: Vascular endothelial growth factor; YKL-40: Chitinase-3-like protein 1.

3. YKL-40 as a Translational Biomarker in Virus-Associated Liver Disease

3.1. Molecular Basis of YKL-40 Expression

YKL-40 stands out among candidate biomarkers because it is produced by different cell populations that act together in the chronically injured liver. This explains why it is consistently measurable in both tissue and circulation and why its signal is not limited to hepatocyte injury alone [70,71].

The strongest evidence for YKL-40 production comes from HSCs, which secrete it as they adopt a matrix-producing phenotype during fibrogenesis [72,73]. Hepatocytes also contribute when exposed to stress, particularly at the edges of fibrous septa, where staining is most pronounced in HDV, followed by HCV and HBV [72]. Macrophages add further expression during inflammatory activation [70,71], while endothelial and epithelial cells increase secretion under hypoxia or pro-angiogenic conditions [70,73]. These diverse sources position YKL-40 as a multicellular stress response that reflects how parenchymal, stromal, and vascular compartments adapt under chronic injury.

Its induction is reinforced by inflammatory and stress-responsive circuits. IL-1β and IL-6 activate STAT3 and NF-κB, embedding YKL-40 in transcriptional programs that remain active long after acute injury subsides [74]. Oxidative stress, matrix stiffening, and hypoxia further sustain

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expression, which explains why serum concentrations remain elevated in advanced fibrosis even when ALT values normalize [75].

Secreted YKL-40 then links these upstream signals to structural remodeling. Binding to interleukin-13 receptor subunit alpha-2 (IL-13Rα2) together with transmembrane protein 219 activates extracellular signal-regulated kinase (ERK), protein kinase B (AKT), and Wingless-related integration site/β-catenin (Wnt/β-catenin) signaling [76]. Interactions with syndecan-1 and integrins αvβ3 and αvβ5 amplify motility and ECM turnover in endothelial and stromal cells [77]. These overlapping receptor pathways align with the consistent observation that YKL-40 is concentrated at fibrotic and angiogenic interfaces in diseased tissue [73,78].

Functional studies illustrate the consequences of this biology. In stellate cells, YKL-40 stimulates proliferation and collagen synthesis, accelerating matrix accumulation [72,73]. In endothelial models, it enhances tube formation and vascular endothelial growth factor (VEGF) expression, supporting the angiogenic remodeling characteristic of cirrhosis [77]. Neutralization experiments demonstrate that blocking YKL-40 can reduce tumor vascularization, confirming its role at the tumor-stroma interface [77]. In immune compartments, YKL-40 promotes macrophage recruitment and polarization toward an alternatively activated (M2-like) phenotype, reshaping cytokine balance and matrix metalloproteinase activity in ways that favor tolerance and invasive growth [70,79].

Virus-specific data strengthen these mechanistic insights. In HCV infection, YKL-40 supports hepatocyte viability and profibrogenic cytokine release, and there is evidence that it may even facilitate viral replication [75]. In HBV and HCV cohorts, circulating levels rise in step with fibrosis stage and remain elevated when hepatocyte injury markers decline [71,75]. Broader reviews of HSC activation and chitinase-like proteins in cancer highlight YKL-40 as a central driver of stromal remodeling that connects fibrotic progression with oncogenic potential [73,78].

Taken together, these findings show that YKL-40 is not just a bystander of tissue damage but a multicellular stress signal sustained by cytokines and environmental inputs. Its effects on fibrogenesis, angiogenesis, and immune adaptation explain why it is stable in circulation and provide the rationale for testing its translational value across HBV, HCV, and HDV populations and along the transplant pathway.

3.2. Clinical and Translational Applications of YKL-40

Evidence now quantifies how much information YKL-40 can add to day-to-day decisions. A recent meta-analysis that pooled seventeen liver fibrosis studies reported areas under the receiver operating characteristic curve (AUC) of 0.91 for advanced fibrosis and 0.87 for severe fibrosis with corresponding sensitivities near 0.80 and specificities near 0.85 across cohorts, which places YKL-40 in a performance range suitable for clinical triage rather than exploratory use [80]. The question then becomes where such a signal changes management. Histology-driven work in chronic hepatitis B shows that a considerable share of patients who meet biochemical definitions of normal ALT still carry significant necroinflammation or stage F2 or higher. In these cohorts the proportion with significant histological disease remains near a quarter to a third even when stricter upper limits of normal are applied, which creates a clear use case for a marker that can prioritize elastography or biopsy when standard biochemistry is quiet [81]. A second study focused on HBeAg-positive hepatitis B with normal ALT reached the same practical conclusion by detailing how often clinically silent activity appears on biopsy, which again supports targeted non-invasive testing rather than routine deferral of staging [82].

A move from static to longitudinal use further clarifies how to integrate YKL-40. In chronic hepatitis B, models that incorporate repeated measurements classify cirrhosis with an AUC of 0.939 and capture change over follow up, which is the type of performance that supports interval testing in clinics that already run serial algorithms for inactive carriers and for treated patients [82]. In HBeAg-negative hepatitis B, single-timepoint YKL-40 discriminates minimal from significant fibrosis with an AUC of 0.818 and with sensitivity and specificity around eighty and seventy percent. It also aligns with fibrosis indices such as FIB-4 and the gamma-glutamyl transpeptidase to platelet ratio,

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which allows simple cross-checks during routine visits without adding imaging at every timepoint [83]. At the level of pooled evidence, a meta-analysis across viral hepatitis datasets reported overall sensitivity and specificity near seventy four and seventy six percent, which provides a benchmark for centers that are considering adoption and want to compare their own operating points against external data [84].

Therapy studies show when the marker should be rechecked. In HCV infection, YKL-40 correlates with liver stiffness at baseline and detects cirrhosis with an AUC of 0.939. After direct-acting antivirals it falls by about one fifth within months, yet levels in many patients remain above those of healthy comparators. Untreated cirrhotics trend upward over the same horizon, which maps the marker to real trajectories rather than to a single post-treatment snapshot and supports planned retesting after cure in patients who remain at risk [84]. Host factors also shape downstream outcomes. In patients who cleared hepatitis C with direct-acting antivirals, common variants in the YKL-40 locus and an intergenic site identified groups with higher HCC risk after virological cure. The risk was greatest when more than one locus carried the at-risk genotype, which points to a host component that can be considered alongside serum measurement when long-term surveillance is planned [85].

Oncologic endpoints define where YKL-40 influences decisions beyond fibrosis staging. A meta-analysis of forty one cohorts across solid tumors showed that elevated serum YKL-40 associated with poorer overall survival with a pooled hazard ratio of 1.44, which sets an external expectation for effect size when the marker is used to refine prognosis [86]. HCC specific data mirror that pattern. After curative hepatectomy, higher preoperative YKL-40 independently predicted overall survival with adjusted hazard ratios in the range of 1.4 to 1.5, and a prognostic nomogram that added YKL-40 to tumor number, tumor size, the neutrophil to lymphocyte ratio, the international normalized ratio, and alpha-fetoprotein achieved areas under the curve near 0.75 in training and validation. A practical cut-point close to 199 ng per milliliter separated survival curves, which offers a starting threshold for programs that are designing preoperative risk conferences and postoperative follow up schedules [87].

Implementation details determine how reliable the readouts will be once YKL-40 is brought into routine use. Population data indicate that circulating levels rise with age, and that up to about one quarter of interindividual variation can be explained by common genetic polymorphisms in the YKL-40 gene. Laboratory practice also matters because most measurements use immunoassay formats with different reportable ranges and different sample handling requirements. These facts argue for age aware interpretation, for attention to serial change rather than single values, and for harmonized pre-analytical routines so that trajectories reflect biology rather than processing noise [88]. Broader oncology experience reaches a similar conclusion about standardization and about context. YKL-40 is elevated across many inflammatory and neoplastic states. It is therefore most useful when applied in defined hepatology pathways that already incorporate imaging and clinical scores and when its thresholds and sampling intervals are prespecified by etiology and treatment state [89].

These clinical studies show that YKL-40 has progressed from a descriptive marker of stromal activity to a tool with operational relevance. It uncovers fibrosis that escapes detection by routine biochemistry, it remains informative after antiviral cure when residual scarring drives long-term risk, and it strengthens prognostic models in HCC, particularly in patients without conventional tumor marker elevation. At the same time, its performance is influenced by age, genetic variation, and assay practice, underlining the importance of standardized protocols for future adoption. The convergence of these findings highlights why YKL-40 is now being considered not only for staging and surveillance but also for peri-transplant assessment, where the balance between fibrotic burden, oncologic risk, and immune adaptation becomes critical.

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4. Pre- and Post-Transplant Applications of YKL-40 in HCC: From Eligibility to Risk Stratification

4.1. Informing Transplant Eligibility Beyond Morphology

Selection for LT in HCC has traditionally been determined by morphologic frameworks such as the Milan and University of California, San Francisco (UCSF) criteria, which define limits of tumor size and number [90]. These thresholds improved outcomes by restricting transplantation to patients with favorable imaging features, yet they cannot capture tumor biology or the state of the hepatic microenvironment, both of which drive recurrence risk after transplantation [91]. More recent allocation tools, including Metroticket 2.0 and AFP-based models, have added serological signals to extend predictive accuracy, but they remain limited in patients with low or discordant AFP expression [92,93].

YKL-40 provides a way to interrogate the biological state of the host rather than the morphology of the tumor [94]. In practice, this can sharpen decision-making at two critical junctures. First, in candidates who appear to meet morphologic thresholds, high YKL-40 may uncover a stromal environment already primed for recurrence, suggesting that eligibility should be reconsidered or that intensified bridging therapy is warranted before listing. Second, in patients undergoing downstaging, declining YKL-40 values can provide reassurance that the fibrotic and angiogenic drive has slowed, strengthening the case to proceed to transplantation. Data from TACE cohorts reinforce these scenarios, where serum YKL-40 predicted overall survival independently of AFP and retained value in AFP-negative phenotypes, which are precisely the cases where current allocation models are least informative [95].

4.2. Refining Pre-Transplant Risk Stratification

Once eligibility is confirmed, the next challenge is to refine biological risk before committing scarce donor organs [96,97]. Conventional stratification relies on imaging and response to bridging therapy, yet these assessments can miss the stromal activity that sustains recurrence beneath apparently stable radiology [98,99].

YKL-40 provides a complementary perspective by signaling microenvironmental activity that is otherwise invisible. Elevated levels correlate with larger tumor burden, vascular invasion, and reduced survival across HCC cohorts [101]. Trajectories of YKL-40 during bridging therapy add actionable value. Persistently high concentrations indicate that stromal activity continues and that recurrence risk is greater. Declining levels indicate that biological activity has slowed and provide stronger reassurance to proceed with transplantation.

The mechanistic basis for these associations has been described in experimental models, but their clinical implications can be summarized more directly. Table 2 illustrates how YKL-40 related pathways map onto outcomes that matter in the transplant setting, converting biological activity into markers of recurrence risk and treatment response.

Table 2. YKL-40-associated tumor mechanisms and their clinical implications in pre-liver transplant HCC risk stratification.

Tumor-promoting mechanism	YKL-40-associated effect	Clinical implication
Activation of invasive signaling	Activates PI3K/AKT and TGF-β pathways in cancer models	Indicates high-risk tumor phenotype beyond AFP/morphology
ECM remodeling	Upregulates MMP-9 expression, promoting ECM degradation	Reflects stromal remodeling undetectable by imaging
Loss of epithelial adhesion	Suppresses E-cadherin, facilitating epithelial–mesenchymal transition (EMT)	Correlates with dedifferentiation and early metastatic potential

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Angiogenesis	Induces endothelial cell migration and tube formation independently of VEGF	May predict microvascular invasion and post-LT recurrence
Resistance to bridging therapy	Persistently elevated levels despite radiologic response suggest stromal or residual tumor activity	Supports re-evaluation of treatment response and LT candidacy

AFP: Alpha-fetoprotein; AKT: Protein kinase B; ECM: Extracellular matrix; EMT: Epithelial-mesenchymal transition; E-cadherin: Epithelial cadherin; LT: Liver transplantation; MMP-9: Matrix metalloproteinase-9; PI3K: Phosphoinositide 3-kinase; TGF-β: Transforming growth factor-beta; VEGF: Vascular endothelial growth factor; YKL-40: Chitinase-3-like protein 1.

4.3. Post-Transplant Recurrence Prediction and Integration into Biomarker Panels

Even with stringent selection criteria, 10-20% of LT recipients experience HCC recurrence, which emphasizes the limits of morphology-based models [102,103]. Recent studies now provide LT-specific evidence. In a large transplant cohort, elevated peri-transplant YKL-40 was linked with shorter overall and recurrence-free survival. The association was strongest in patients with myosteatosis, a systemic frailty phenotype that is invisible to conventional tumor markers [104]. These results identify YKL-40 as a clinically meaningful signal for peri-transplant risk stratification, particularly in patients who are AFP- or DCP-negative and therefore lack reliable tumor-derived markers [87].

The value of YKL-40 is not confined to recurrence alone. It also shows potential as a biomarker of graft fibrosis. In recipients with recurrent hepatitis C, serial measurements distinguished rapid from slow fibrosis progressors and tracked with histologic progression [105]. Genetic findings reinforce this plausibility. A functional promoter polymorphism in the YKL-40 gene was associated with higher circulating levels, more severe rejection, and faster fibrosis progression after transplantation [106]. These observations support a dual role for YKL-40 in the post-transplant setting, both as a predictor of oncologic recurrence and as a non-invasive marker of graft injury.

Implementation requires careful attention to context. YKL-40 is not disease specific, and elevations can reflect infection, rejection, or systemic inflammation, all of which are common in the early post-transplant course [88]. Laboratory factors also matter, since assay platforms vary in sensitivity and reproducibility, and recent high-dynamic-range immunoassays have highlighted challenges for cross-center comparison [107]. For the marker to be integrated into practice, multicenter validation is needed to confirm whether its addition to prognostic models such as RETREAT or MoRAL provides meaningful reclassification and supports risk-adapted surveillance strategies [108].

4.4. Future Directions

The next phase for YKL-40 in transplantation will be integration into multidimensional models rather than stand-alone use. Stromal biomarkers can complement tumor-derived signals such as AFP and DCP, together with imaging features and clinical scores, to refine recurrence prediction and graft surveillance. Multicenter prospective cohorts will be needed to validate performance across diverse populations and to determine how best to align thresholds and sampling intervals with specific clinical contexts.

Advances in computational approaches may accelerate this translation. Machine-learning and artificial intelligence frameworks are particularly well suited to accommodate nonlinear interactions between stromal activity, immune adaptation, and tumor biology, creating dynamic prediction tools that move beyond static cut-offs. Embedding YKL-40 into such models could enable risk-adapted transplant pathways in which surveillance intensity, bridging therapy, and adjuvant strategies are tailored to the evolving tumor-host interplay. In this way, YKL-40 has the potential to shift from a descriptive marker of stromal activity to a functional component of precision transplantation.

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5. Conclusions

The value of YKL-40 lies less in isolated performance metrics and more in its ability to signal a transition from morphology-driven assessment toward biologically adaptive models of care in liver transplantation. While current evidence shows consistent associations with fibrosis stage, tumor behavior, and graft outcomes, its adoption in clinical pathways remains limited. Progress will depend on robust validation in multicenter cohorts, harmonization of assay platforms, and clear definition of dynamic thresholds that can be interpreted across different disease stages and treatment states. Prospective integration of YKL-40 into transplant registries and biomarker-guided surveillance trials will be essential to determine whether it adds value beyond established scores and imaging. The next step is not to test YKL-40 in isolation but to embed it into algorithmic frameworks that combine stromal, tumor, and host signals. Such multidimensional approaches can support risk-adaptive strategies and bring precision medicine in transplantation closer to practice.

Abbreviations

ACTA2	Alpha-smooth muscle actin
AFP	Alpha-fetoprotein
AKT	Protein kinase B
ALT	Alanine aminotransferase
αvβ3	Integrin alpha-V beta-3
αvβ5	Integrin alpha-V beta-5
cccDNA	Covalently closed circular DNA
CCL2	C-C motif chemokine ligand 2
CCNE1	Cyclin E1
$CD8^+$ T cells	Cluster of differentiation 8 positive T lymphocytes
COL1A1	Collagen type I alpha 1 chain
CTL	Cytotoxic T lymphocyte
CTGF	Connective tissue growth factor
CXCL10	Interferon gamma-induced protein 10
DAA	Direct-acting antiviral
DCP	Des-gamma-carboxy prothrombin
DNA	Deoxyribonucleic acid
ECM	Extracellular matrix
EMT	Epithelial-mesenchymal transition
ERK	Extracellular signal-regulated kinase
FIB-4	Fibrosis-4 Index
IFN	Interferon
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBx	Hepatitis B X protein
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HSC	Hepatic stellate cell
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IL-10	Interleukin-10
IL-13Rα2	Interleukin-13 receptor subunit alpha-2
IRF3	Interferon regulatory factor 3
LAG-3	Lymphocyte-activation gene 3
L-HDAg	Large hepatitis D antigen

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LOXL2	Lysyl oxidase-like 2
LT	Liver transplantation
M2	Type 2 macrophage polarization
MAVS	Mitochondrial antiviral signaling protein
MMP	Matrix metalloproteinase
NADPH	Nicotinamide adenine dinucleotide
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NS5A	Non-structural protein 5A
PDGFRB	Platelet-derived growth factor receptor beta
SMAD2/3	Mothers against decapentaplegic homologs 2 and 3
STAT3	Signal transducer and activator of transcription 3
SVR	Sustained virologic response
SWI/SNF	Switch/sucrose non-fermentable
PD-1	Programmed cell death protein 1
RIG-I	Retinoic acid-inducible gene I
RNA	Ribonucleic acid
TACE	Transarterial chemoembolization
TERT	Telomerase reverse transcriptase
TGF-β	Transforming growth factor-beta
TIMP1	Tissue inhibitor of metalloproteinases-1
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor-alpha
Tregs	Regulatory T cells
UCSF	University of California, San Francisco
VEGF	Vascular endothelial growth factor
Wnt/β-catenin	Wingless-related integration site/β-catenin
YKL-40	Chitinase-3-like protein 1

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