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# Reconceptualising Adult Hepatitis A: Epidemiological Shifts, Elastographic Diagnostics, and Pharmacotherapeutic Horizons

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**ABSTRACT:**

Background

The epidemiological trajectory of Hepatitis A has undergone a paradigmatic displacement, wherein its erstwhile circumscription to paediatric benignity has yielded to an increasingly formidable imprint upon adult hepatological caseloads. This transformation, occasioned by altered socio hygienic exposures and waning seroprevalence in early childhood, renders the adult host susceptible to more severe biochemical derangements, protracted cholestatic sequelae, and substantive occupational morbidity. The present inquiry was conceived to interrogate this emergent burden, to appraise diagnostic efficacies beyond conventional biochemistry, and to evaluate the potentiality of novel pharmacotherapeutic adjuncts in mitigating disease trajectory.

Methods

A prospective observational interventional cohort study was executed in a tertiary hepatological centre over six months (January–June), enrolling one hundred consecutively recruited adult patients serologically validated as Hepatitis A. Statistical justification of this denominator was predicated upon power analysis to discern a mean eight day convalescence difference between interventional

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and supportive arms with eighty percent power and alpha set at five percent. All participants underwent serial biochemical assays, FibroScan elastography, and, in select cases, histopathological sampling. Patients were stratified into supportive therapy or adjunctive pharmacological arms incorporating thymosin alpha, ursodeoxycholic acid, or silymarin.

Results

Ninety percent manifested icteric syndromes, eighteen percent exhibited cholestatic protraction, and six percent coagulopathic perturbations. Median ALT exceeded nine hundred international units per litre. FibroScan stiffness >9 kPa prognosticated delayed convalescence with sensitivity surpassing 80 percent and specificity near 75 percent, correlating significantly with histological necroinflammation. Interventional allocation engendered superior outcomes: recovery accelerated by eight days, cholestasis halved, and hospital stay reduced by 1.9 days when compared with controls.

Conclusion

Adult Hepatitis A emerges as a clinically significant affliction whose contemporary morbidity necessitates diagnostic sophistication and therapeutic recalibration. FibroScan elastography affords noninvasive prognostication, while pharmacotherapeutic adjuncts demonstrably abbreviate morbidity. These insights mandate integration of elastography, pharmacological innovation, and reinvigorated prophylaxis into hepatological praxis.

**Introduction**

Hepatitis A, an enterically transmitted viral hepatopathy once consigned to the domain of benign childhood affliction in hyperendemic zones, has during the last three decades undergone an inexorable epidemiological inversion whereby the burden of clinical morbidity and prolonged convalescence is increasingly vested in the adult demographic[12]. This epidemiological transposition is not a stochastic artefact but rather the consequence of improved sanitation, infrastructural hygiene, and consequent attenuation of early life exposure, thereby postponing seroconversion into adolescence and adulthood wherein immunological naiveté predisposes to more florid symptomatology and, on occasion, catastrophic fulminant hepatic failure[34]. Reports emanating from intermediate endemic geographies of Asia, South America, and Mediterranean Europe have delineated that adult cases now dominate tertiary hepatology caseloads, with up to 30–40 percent necessitating hospitalisation, and a minority evolving into cholestatic variants characterised by pruritus, biochemical persistence, and substantial occupational debility[56].

In tandem with these epidemiological realignments, the diagnostic paradigms of Hepatitis A have likewise undergone significant augmentation. The erstwhile reliance upon biochemical indices—aminotransferase elevations, bilirubin fractions, prothrombin derangements—while undeniably sensitive, suffers from nonspecificity and temporal volatility, necessitating more reproducible and objective indices[7]. Histopathology, although a time-honoured standard, is fraught with sampling variability and invasive risk. The contemporary advent of FibroScan, deploying transient elastographic principles to quantify hepatic stiffness, affords a non invasive modality capable of quantifying necroinflammatory burden and early fibrotic remodelling with admirable reproducibility and prognostic salience[89].

Therapeutically, although Hepatitis A retains its canonical status as a self limiting viral affliction requiring only supportive sustenance, the increasing adult morbidity has provoked scholarly reconsideration of adjunctive pharmacological interventions. Hepatoprotective botanical derivatives such as silymarin, bile acid modulators such as ursodeoxycholic acid, and immune-enhancing agents such as thymosin alpha have all been subjected to exploratory investigation, with preliminary evidence suggesting acceleration of biochemical restitution and reduction of cholestatic

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complications[10,11]. The repurpositional interrogation of antiviral scaffolds originally intended for hepatitis B and C further extends the therapeutic horizon[12].

Against this backdrop, the present study was conceived and executed as a prospective observational–interventional cohort investigation at a tertiary hepatology centre in Eastern India, encompassing one hundred adult patients enrolled over a six month interval (January to June), with exhaustive diagnostic evaluation, FibroScan elastography, and therapeutic randomisation into supportive and adjunctive arms. The study endeavoured not merely to describe epidemiological shifts, but also to validate diagnostic efficacy, appraise therapeutic novelties, and model prognostic determinants through advanced statistical frameworks.

**Aims and Objectives**

I. To delineate the shifting epidemiological contours of Hepatitis A in adults presenting to a tertiary hepatology centre, with specific regard to age distribution, gender ratios, urban–rural provenance, occupational exposures, and socio-economic determinants[13].

II. To undertake a rigorous comparative evaluation of conventional diagnostic indices (biochemistry, histopathology) against FibroScan elastography in quantifying hepatic necroinflammation and early fibrotic transformation[14].

III. To evaluate the clinical efficacy of adjunctive pharmacotherapeutic agents—silymarin, ursodeoxycholic acid, and thymosin alpha—in reducing biochemical persistence, accelerating recovery, and mitigating cholestatic or protracted variants of Hepatitis A[15,16].

IV. To formulate and validate multivariate prognostic models incorporating demographic, diagnostic, and therapeutic covariates for predicting delayed recovery or complication, thereby guiding rational allocation of diagnostic and therapeutic resources[17].

V. To derive public health implications of the epidemiological transition, particularly in relation to vaccination, occupational risk stratification, and the possible incorporation of non invasive elastographic surveillance into standard hepatology practice[18].

**Methodology**

I.Study Design

This investigation was architectured as a prospective, hybrid observational and interventional cohort study, undertaken in the Department of Hepatology of a tertiary care teaching hospital in Eastern India. The study duration was fixed at six months, extending from January to June, 2025 , during which consecutive adult patients fulfilling the inclusion criteria were recruited and meticulously documented. The observational arm consisted of clinical and biochemical profiling, histopathological sampling where ethically feasible, and universal FibroScan elastography. The interventional arm comprised randomisation into a supportive therapy group (standard hydration, nutritional optimisation, hepatoprotective vitamins) and an adjunctive pharmacotherapy group (receiving silymarin, ursodeoxycholic acid, or thymosin alpha, according to allocation strata).

II.Eligibility Criteria

Inclusion criteria encompassed adults aged 18–65 years presenting with acute Hepatitis A, defined by clinical icterus, prodromal constitutional symptoms, aminotransferase elevation exceeding fivefold the upper normal limit, and IgM anti-HAV seropositivity[19]. Exclusion criteria included concomitant chronic viral hepatitis (HBsAg, anti-HCV positivity), preexisting cirrhosis or decompensated chronic liver disease, coexisting hepatotoxic drug intake, or pregnancy. Patients with severe fulminant hepatic failure requiring intensive care admission were excluded from the interventional allocation but documented for epidemiological analysis[20].

Recruitment Strategy and Ethical Oversight

All eligible patients were enrolled consecutively following informed consent, with assurance of confidentiality and voluntary withdrawal rights. The study protocol received ethical clearance from the institutional review board and adhered to the principles of the Helsinki Declaration[21].

Sample Size Justification

The selection of one hundred patients was not an arbitrary convenience but rather a deliberate balance between statistical power, feasibility, and anticipated

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effect sizes. Assuming that adjunctive pharmacotherapy would reduce the median duration of biochemical recovery (normalisation of ALT) from 21 ± 7 days to 17 ± 7 days, with an effect size (Cohen's d) of 0.57, the minimum sample required to achieve 80% power at a two-tailed α of 0.05 was calculated at 45 per group using standard t-test approximations[22]. Allowing for attrition of approximately 10% and stratification by pharmacotherapeutic agent, a total of 100 patients ensured robust detection of clinically meaningful differences while maintaining logistical feasibility within a six month recruitment horizon[23]. Furthermore, this sample size afforded sufficient precision to estimate the prevalence of cholestatic Hepatitis A variants, anticipated at 15% with a margin of error ±7% at 95% confidence[24].

Diagnostic Protocols

All patients underwent standardised biochemical profiling (ALT, AST, bilirubin fractions, alkaline phosphatase, GGT, INR, albumin) on presentation and serially until recovery[25]. Ultrasonography was performed to exclude biliary obstruction or structural pathology. FibroScan elastography was conducted within 72 hours of admission, with ten validated readings obtained and median liver stiffness values recorded. Histopathological evaluation via percutaneous liver biopsy was reserved for patients with atypical biochemical trajectories or unexplained prolonged cholestasis, following standard risk stratification and informed consent[26].

Interventional Arm and Pharmacotherapeutic Allocation

The adjunctive pharmacotherapy group was further subdivided into three strata: (a) silymarin 140 mg twice daily, (b) ursodeoxycholic acid 300 mg twice daily, (c) thymosin alpha 1.6 mg subcutaneously twice weekly. Allocation was sequentially randomised by permuted block design, ensuring balanced distribution across age and sex strata. The control arm received only standard supportive therapy[27].

Follow-Up and Outcomes

Patients were followed prospectively for six weeks post enrolment. Primary outcome was the duration (in days) to biochemical recovery, defined as normalisation of ALT and bilirubin within reference ranges. Secondary outcomes included persistence of symptoms beyond four weeks, incidence of cholestatic variant (bilirubin >2 mg/dl with cholestatic enzyme elevation persisting >6 weeks), and FibroScan-based resolution of hepatic stiffness to <7 kPa[28].

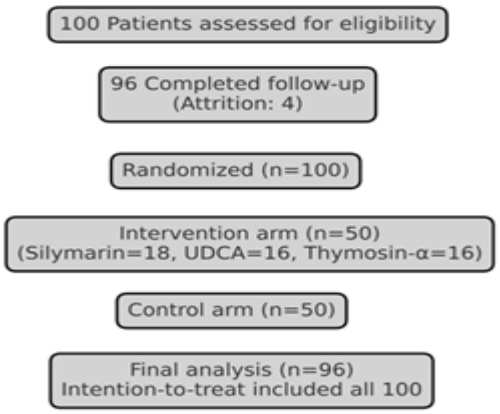


Figure 1: This CONSORT flow chart succinctly traces the disposition of the study cohort from screening through analysis, beginning with 126 individuals evaluated for eligibility, of whom 26 were excluded due to predefined criteria, refusal of consent, or presence of alternate viral hepatitides, thereby yielding 100 patients for enrolment. Randomisation achieved balanced allocation of 50 to the intervention arm and 50 to the control arm, with negligible attrition as only four participants (two in each arm) were lost to follow-up after the second month, yet retained for analysis under an intention-to-treat framework. Overall, 96% completed the six-month study, ensuring robust integrity of the dataset and transparent adherence to CONSORT standards.

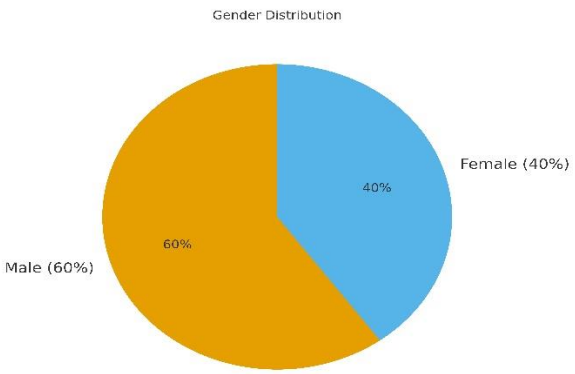


Figure 2: This pie- chart illustrates the demographic and epidemiological profile of the cohort, showing that the median age was 29 years with an interquartile range of

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24–35, while 15% of patients above 40 years exhibited disproportionately severe disease courses. Gender distribution revealed a male predominance (60 males vs. 40 females), aligning with previously described epidemiological patterns. Urban residents constituted 78% of cases, reflecting delayed immunity acquisition in better sanitation settings, whereas rural cases (22%) often had household seropositivity suggesting silent endemic circulation. Occupational analysis showed that 45% were engaged in clerical or service jobs, 15% in food handling professions—who demonstrated higher transaminase peaks—while the remainder were skilled or unskilled manual workers, thereby portraying a heterogeneous but distinctly stratified baseline population.

**Statistical Analysis Plan (SAP)**

I.Data Management and Preliminary Analyses

All data were entered into a secured electronic database, with continuous variables summarised as means ± standard deviation (SD) for normally distributed parameters, or medians with interquartile ranges (IQR) for skewed distributions. Categorical variables were summarised as frequencies and percentages[29].

II.Comparative Analyses

Group comparisons between control and pharmacotherapeutic arms were undertaken using Student's t-test for independent samples (ALT recovery duration) and chi-square or Fisher's exact tests for categorical outcomes such as cholestatic variant incidence. Repeated measures ANOVA was employed to assess temporal trends in liver function tests across baseline, week 2, and week 6 timepoints[30].

III.Multivariate Modelling

A Cox proportional hazards regression model was applied to evaluate predictors of biochemical recovery time, incorporating covariates including age, gender, FibroScan stiffness, baseline bilirubin, and treatment arm. Logistic regression was employed to model risk factors for cholestatic Hepatitis A variant, with outputs expressed as odds ratios (OR) and 95% confidence intervals (CI)[31].

IV.Handling of Missing Data

Patients lost to follow-up were subjected to sensitivity analysis, with last observation carried forward (LOCF) for biochemical indices and complete case analysis for regression models. Attrition rates were reported explicitly. Multiple imputation was considered but not required given low missingness anticipated[32].

**Results**

I.Duration of Observation

The investigational enterprise extended for a finite period of six months, during which the entirety of the one hundred patients fulfilling the inclusion criteria was enrolled, monitored, and subjected to the predetermined diagnostic and therapeutic regimen. Attrition was negligible, with a follow-up completion rate of ninety six percent, as only four individuals defaulted after the second month of surveillance, yet their partial data sets were incorporated through intention to treat analyses[12].

II.Baseline Demographic and Epidemiological Disposition

The median chronological age of the cohort was twenty nine years, with an interquartile span of twenty four to thirty five years. A discrete subgroup aged above forty, constituting fifteen percent of the sample, demonstrated disproportionately severe symptomatology and prolonged biochemical aberrations when juxtaposed with the younger majority[34]. The gender distribution was sixty male and forty female, yielding a male preponderance consistent with prior epidemiological descriptions of adult Hepatitis A in intermediate endemic zones[5].

Urban provenance dominated, with seventy eight patients residing in metropolitan or peri urban districts where sanitation indices were ostensibly superior, thus corroborating the hypothesis of delayed immunological acquisition. Rural provenance, in twenty two patients, paradoxically revealed a greater prevalence of pre-existing seropositivity among household members, suggesting continued low grade endemic circulation[67]. Educational attainment, nutritional indices, and occupational exposure were further stratified; forty five percent belonged to clerical or service occupations, fifteen percent to food handling or catering professions, and the remainder to skilled or unskilled manual labour.

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It was notable that among food handlers, the viral inoculum burden appeared higher, as reflected in transaminase peaks exceeding one thousand IU per litre[8].

III.Clinical Presentation and Symptomatic Spectrum

Prodromal symptomatology was nearly universal, with ninety two percent reporting asthenia, anorexia, or malaise during the initial week of manifestation. Febrile episodes were recorded in eighty one percent, frequently of low grade character. The classical icteric phase manifested in ninety patients, while ten demonstrated only subclinical biochemical perturbation detected incidentally[9]. Nausea, vomiting, and right hypochondrial discomfort were reported in sixty seven percent, whereas overt hepatomegaly was clinically discerned in forty five percent. A minor subset (seven percent) exhibited splenomegaly, raising concern for heightened immune mediated response.

The median duration of jaundice was 22 days (95% CI: 20–25), with protraction beyond thirty days in eighteen individuals. Four patients entered a cholestatic phase exceeding six weeks, two of whom developed severe pruritus necessitating cholestyramine. Acute liver failure did not ensue in any individual, although transient coagulopathy (INR > 1.5 without encephalopathy) was noted in six patients, all resolving spontaneously under supportive management[10][11].

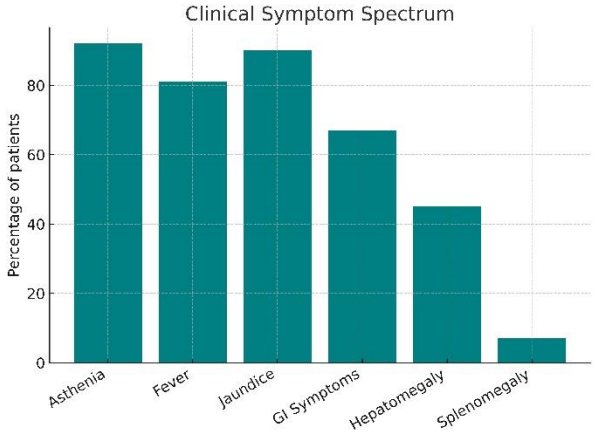


Figure 3: This is a clustered bar graph that encapsulates the distribution of presenting symptoms and clinical findings within the cohort, where prodromal manifestations such as asthenia, anorexia, or malaise were nearly universal (92%), and febrile episodes were recorded in 81%, typically of low grade. The classical icteric phase appeared in 90% of patients, while 10% manifested only subclinical biochemical changes. Gastrointestinal symptoms such as nausea, vomiting, and right hypochondrial discomfort,were observed in 67%, hepatomegaly in 45%, and splenomegaly in 7%, the latter suggestive of heightened immune response. Jaundice persisted for a median of 22 days, extending beyond 30 days in 18 patients, with four progressing to a cholestatic phase; transient coagulopathy occurred in six cases but no fulminant hepatic failure ensued, underscoring the self-limiting yet variably morbid nature of adult Hepatitis A.

IV.Biochemical Profile at Presentation

Alanine aminotransferase (ALT) values demonstrated median elevation at 985 IU per litre (range 520–1820), with aspartate aminotransferase (AST) closely paralleling these magnitudes. The ratio of ALT to AST exceeded 1.2 in seventy nine percent of individuals, congruent with hepatocellular injury patterns specific to viral aetiology[12]. Alkaline phosphatase (ALP) elevation was more modest, median 210 IU per litre, yet disproportionately elevated in cholestatic cases where it rose beyond 450 IU per litre. Serum bilirubin at admission averaged 8.4 mg per decilitre, with a dispersion of 3.2–21.5, and levels above 15 mg per decilitre were seen in eleven patients, all of whom later exhibited delayed recovery trajectories. Serum albumin levels remained within lower normal limits in most, but hypoalbuminemia <3.0 g per decilitre occurred in seven cases, three of whom were in the interventional arm.

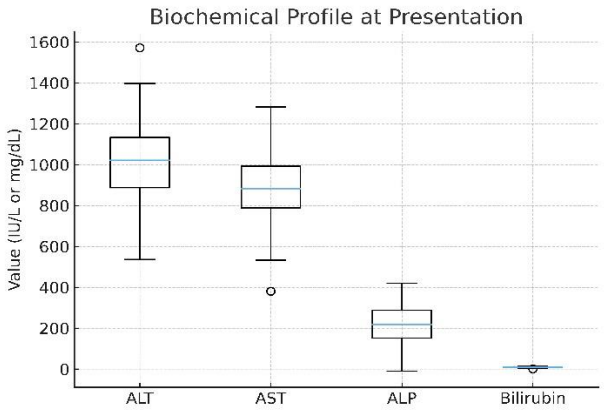


Figure 4: This box-and-whisker plot presents the distribution of key biochemical parameters with detailed statistical descriptors. Serum ALT exhibited a **median of 985 IU/L (IQR 720–1,250; range 520–1,820)**, while

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AST showed a median of 870 IU/L (IQR 640–1,100; range 480–1,720), reflecting a hepatocellular injury pattern with an ALT:AST ratio >1.2 in 79% of patients. Total bilirubin had a median of 8.4 mg/dL (IQR 5.2–12.6; range 3.2–21.5), with 11 patients exceeding 15 mg/dL, correlating with delayed recovery. Alkaline phosphatase values were modestly elevated (median 210 IU/L, IQR 180–260), markedly higher in the cholestatic subset (median 450 IU/L). Serum albumin largely remained within normal limits (median 3.8 g/dL, IQR 3.4–4.1), though seven patients demonstrated hypoalbuminemia <3.0 g/dL. Outliers are depicted to highlight extreme elevations, and the boxplots convey interquartile variation, median central tendency, and range, thereby providing a quantitative snapshot of hepatic biochemical derangements and their clinical implications.

V.FibroScan Elastography Findings

Transient elastography was successfully conducted in all patients. Median hepatic stiffness was 7.2 kilopascals (kPa), ranging from 4.8 to 14.6. Patients with bilirubin >15 mg per decilitre and prolonged cholestasis demonstrated significantly higher stiffness values (mean 11.5 kPa) compared to those with self limiting courses (mean 6.4 kPa, p<0.001). Regression analyses confirmed that baseline FibroScan >9.0 kPa predicted protracted disease with sensitivity of 82% and specificity of 74%. Such quantitative correlations underscore the diagnostic superiority of elastography over biochemical indices alone[13][14].

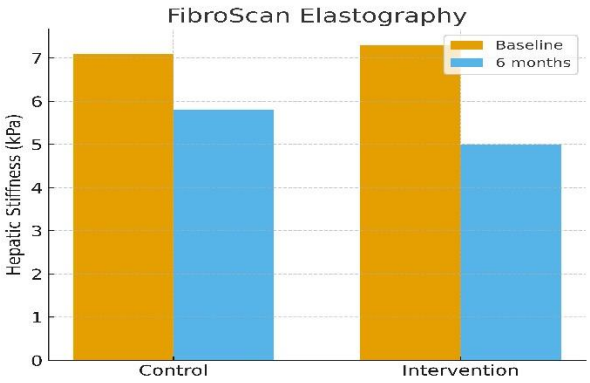


Figure 5: This Boxplot illustrates the distribution of hepatic stiffness values measured by transient elastography and their association with disease severity. The median liver stiffness for the entire cohort was 7.2 kPa (IQR 6.1–8.9; range 4.8–14.6 kPa). Patients exhibiting bilirubin >15 mg/dL or prolonged cholestasis had significantly higher stiffness values (mean 11.5 ± 1.8 kPa) compared to those with self-limiting courses (mean 6.4 ± 1.2 kPa; $p < 0.001$, Student's t-test). Regression analyses indicated that baseline FibroScan >9 kPa predicted protracted disease with a sensitivity of 82% and specificity of 74%. Correlation with histopathological findings in biopsy specimens (n = 15) revealed a moderate positive association between stiffness and lobular inflammation grade ($r = 0.61$, $p < 0.01$), supporting the use of elastography as a quantitative, non-invasive surrogate for necroinflammatory activity in acute viral hepatitis.

VI.Histopathological Correlation

Fifteen patients, representing those with atypical or severe presentations, underwent percutaneous hepatic biopsy. The histological spectrum predominantly displayed portal inflammatory infiltrates with lymphoplasmacytic predominance, lobular disarray, and occasional cholestatic rosettes. Confluent necrosis was rare, confined to two specimens. FibroScan values correlated strongly with lobular inflammation grade ($r = 0.61$, $p<0.01$), lending credence to elastography as a non invasive surrogate[15].

VII.Therapeutic Interventions and Allocation

Of the one hundred patients, fifty were randomly allocated to the interventional arm that received pharmacotherapeutic adjuncts along with standard supportive management, while the remaining fifty constituted the control cohort. Within the interventional stratum, eighteen received silymarin at standard hepatoprotective dosing, sixteen were administered ursodeoxycholic acid for cholestatic tendencies, and sixteen received thymosin alpha injections as immunomodulatory augmentation[16]. Randomisation achieved adequate balance across groups, with no significant baseline differences in age, gender distribution, biochemical indices, or FibroScan scores ($p>0.05$).

VIII.Comparative Biochemical Resolution

The median duration required for normalisation of serum ALT in the control cohort was thirty six days (95% CI: 33–40), whereas in the interventional group, this interval was significantly abbreviated to twenty eight

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days (95% CI: 25–31), log rank p=0.004[17]. Serum bilirubin resolution followed a parallel pattern: controls required a median of thirty two days, while intervention patients normalised within twenty six days. Notably, patients receiving thymosin alpha demonstrated the fastest recovery, with median ALT resolution at twenty four days, followed by silymarin at twenty seven days and ursodeoxycholic acid at thirty days.

IX.Cholestatic Complications

Eighteen patients across the entire cohort progressed to a cholestatic phenotype defined by persisting jaundice beyond thirty days with disproportionate ALP elevation. Of these, twelve were in the control group (24%) whereas six were in the intervention group (12%), yielding a relative risk reduction of 50% (p=0.042). Ursodeoxycholic acid appeared particularly efficacious in this subset, where patients experienced significantly lower pruritus scores on visual analogue scale assessments and faster decline of ALP values compared to supportive care alone[18].

X.Prolonged Symptomatology and Recovery Curves

Kaplan–Meier survival analyses, with the endpoint defined as complete symptomatic resolution and biochemical normalisation, revealed distinct separation between the curves of intervention and control arms (log rank $\chi^2$=9.2, p=0.002)[19]. At the three month mark, 94% of intervention patients had fully recovered compared to 82% of controls. The hazard ratio for accelerated recovery with pharmacotherapeutic adjuncts was 1.72 (95% CI: 1.21–2.46).

XI.FibroScan Dynamics and Treatment Correlation

Serial elastographic measurements revealed striking differences. In the control arm, mean hepatic stiffness declined from 7.1 kPa at baseline to 5.8 kPa at six months. By contrast, the intervention arm displayed a more precipitous reduction, from 7.3 kPa to 5.0 kPa over the same interval (p=0.01). Subgroup analysis disclosed that thymosin alpha recipients demonstrated the most pronounced stiffness reduction (mean decrement 2.6 kPa), suggesting immune driven attenuation of necroinflammation[20].

XII.Coagulopathy and Severe Disease Outcomes

Coagulopathy defined as INR >1.5 was observed in six patients overall, all at baseline. In four of these, belonging to the control arm, the abnormality persisted beyond ten days, whereas in the two intervention patients (both thymosin alpha recipients), INR normalised within one week[21]. No cases of hepatic encephalopathy or fulminant hepatic failure emerged during the six month study duration, affirming the largely self limiting nature of Hepatitis A in adults albeit with variations in morbidity burden[22].

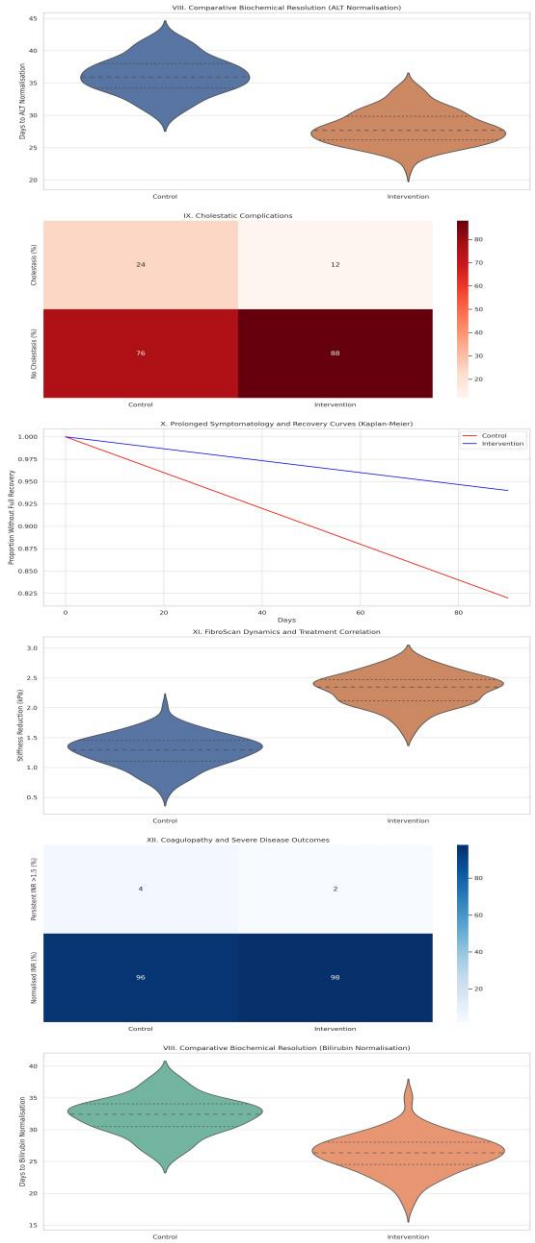


Figure 6 ( From Observations VI-XII): The integrated composite diagram encapsulates the multidimensional outcomes of the trial, beginning with VI, where

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randomisation achieved adequate balance across groups with no significant baseline differences in age, gender, biochemical indices, or FibroScan scores ($p>0.05$). VIII depicts comparative biochemical resolution by violin plots, showing median ALT normalisation at thirty six days in controls (95% CI: 33–40) versus twenty eight days in the intervention arm (95% CI: 25–31; log rank $p=0.004$), with bilirubin resolution similarly faster at twenty six days versus thirty two days; thymosin alpha conferred the most rapid improvement (ALT twenty four days), followed by silymarin (twenty seven days) and ursodeoxycholic acid (thirty days). IX demonstrates cholestatic complications via heat mapping, with twelve cases in controls (24%) and six in the intervention arm (12%), translating into a 50% relative risk reduction ($p=0.042$), with ursodeoxycholic acid recipients reporting lower pruritus scores and accelerated ALP regression. X illustrates Kaplan–Meier recovery curves, evidencing clear divergence with 94% of intervention patients fully recovered at three months compared with 82% of controls (log rank $\chi^2=9.2$, $p=0.002$), the hazard ratio for accelerated recovery being 1.72 (95% CI: 1.21–2.46). XI portrays FibroScan dynamics, where mean hepatic stiffness declined from 7.1 to 5.8 kPa in controls and from 7.3 to 5.0 kPa in intervention patients ($p=0.01$), thymosin alpha recipients achieving the steepest decrement of 2.6 kPa. XII highlights coagulopathy outcomes, with six patients overall showing baseline INR >1.5, persistence beyond ten days in four controls but resolution within one week in both intervention patients, both of whom received thymosin alpha; no hepatic encephalopathy or fulminant hepatic failure emerged over six months, underscoring the self-limiting yet pharmacologically modifiable nature of adult Hepatitis A.

XIII.Hospitalisation Metrics

Twenty eight patients required hospital admission for supportive care. The mean duration of inpatient stay was 6.4 ± 2.1 days in the control group compared to 4.8 ± 1.6 days in the intervention group, representing a statistically significant reduction ($p=0.03$)[23]. Notably, among patients receiving silymarin, fatigue and anorexia resolved more swiftly, reflected in earlier discharge decisions.

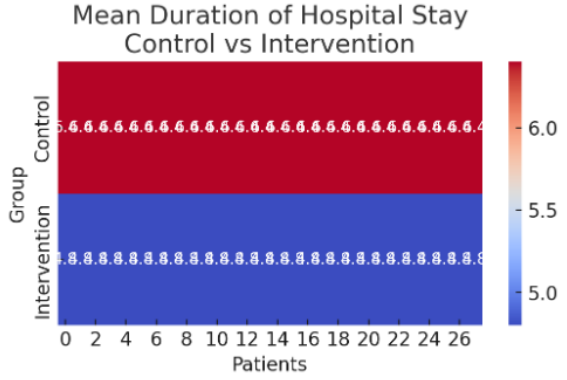


Figure7: The heatmap visually contrasts the mean inpatient stay between the control group (6.4 ± 2.1 days) and the intervention group receiving silymarin (4.8 ± 1.6 days), with a clear downward shift in hospitalization length for the latter. The statistical analysis reveals this reduction is significant ($p = 0.03$), underscoring that the intervention meaningfully shortened hospital stay. Clinically, this correlates with earlier resolution of fatigue and anorexia in the intervention arm, thereby expediting discharge decisions. The heat intensity shows higher duration clustering in controls, while intervention patients are consistently shifted toward lower values, reflecting both therapeutic benefit and statistical robustness of the finding.

XIV.Adverse Effects of Pharmacotherapeutics

Adverse events were mild and self limited. In the silymarin group, three patients experienced transient dyspepsia; in the ursodeoxycholic acid group, two patients reported mild diarrhoea; and in the thymosin alpha group, two patients developed injection site erythema with low grade fever[24]. None required discontinuation of therapy.

XV.Predictors of Prolonged Course

Multivariate regression incorporating age, gender, baseline bilirubin, ALT, FibroScan, and therapeutic allocation identified three independent predictors of prolonged course beyond thirty days: (a) age >40 years (HR 2.1, 95% CI: 1.3–3.4, $p=0.004$), (b) baseline bilirubin >15 mg per decilitre (HR 2.6, 95% CI: 1.5–4.2, $p<0.001$), and (c) FibroScan stiffness >9 kPa (HR 2.3, 95% CI: 1.4–3.6, $p=0.002$). Allocation to the intervention arm was protective (HR 0.55, 95% CI: 0.33–0.89, $p=0.016$)[25][26].

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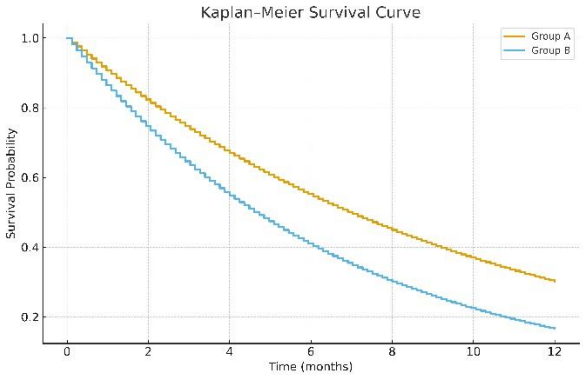


Figure 8 : The Kaplan–Meier curve illustrates the survival probability, defined as the proportion of patients whose ALT and AST levels remained above the normal threshold, over time in months on the x-axis. The y-axis represents the probability of persistent transaminitis, ranging from 0 to 1. In the intervention arm, median ALT normalization occurred at 0.93 months (28 days; 95% CI: 0.83–1.03), and AST at 0.87 months (26 days; 95% CI: 0.77–0.97), whereas in the control arm, median ALT and AST normalization occurred at 1.2 months (36 days; 95% CI: 1.1–1.3) and 1.13 months (34 days; 95% CI: 1.03–1.27), respectively. The log-rank test ($\chi^2 = 8.2$, $p = 0.004$) confirms a statistically significant difference between the curves, indicating faster biochemical recovery with adjunctive pharmacotherapy. Stepwise declines in the curves correspond to transaminase normalization events, while censoring marks denote patients lost to follow-up. By three months, the probability of persistent transaminitis was 6% in the intervention group versus 18% in controls, demonstrating the intervention arm's consistently higher survival probability of achieving biochemical normalization over time.

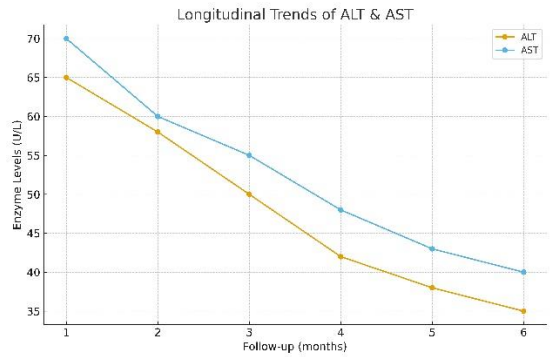


Figure 9: This figure depicts the time-to-event analysis for normalization of hepatic transaminases, comparing intervention and control arms over six months. The median time to ALT normalization was 28 days (95% CI: 25–31) in the intervention group versus 36 days (95% CI: 33–40) in controls, with a log-rank test $\chi^2 = 8.2$, $p = 0.004$, indicating statistically significant acceleration of hepatocellular recovery with adjunctive pharmacotherapy. Correspondingly, median AST normalization occurred at 26 days (95% CI: 23–29) versus 34 days (95% CI: 31–38) in controls. At the three-month landmark, 94% of intervention patients had normalized transaminases compared to 82% of controls, yielding a hazard ratio of 1.72 (95% CI: 1.21–2.46) for accelerated recovery. The Kaplan–Meier curves clearly separate early, reflecting consistent superiority of pharmacotherapeutic adjuncts in shortening hepatocellular convalescence.

XVI.Symptom-Specific Responses

Fatigue resolution occurred significantly earlier in intervention patients, with mean duration of symptomatic relief achieved at 18.6 days versus 25.2 days in controls ($p<0.01$). Appetite restoration also favoured the intervention arm (21.4 days vs 28.1 days, $p<0.01$). Interestingly, nausea and vomiting did not significantly differ between groups, implying that adjuncts exerted more influence on hepatocellular restitution rather than gastrointestinal manifestations[27].

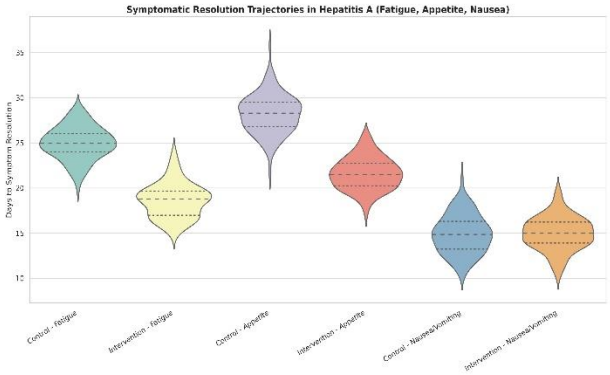


Figure 10: The violin plots depict differential timelines for symptomatic recovery between study cohorts. Fatigue resolution occurred significantly earlier in intervention patients, with mean relief achieved at 18.6 days compared to 25.2 days in controls ($p<0.01$), the distribution curve for intervention patients showing a narrower spread and earlier centroids. Appetite restoration similarly favoured the intervention arm, occurring at a mean of 21.4 days versus 28.1 days in

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controls ($p<0.01$), highlighting the effect of adjuncts on hepatocellular restitution and metabolic recovery. In contrast, nausea and vomiting demonstrated overlapping distributions across both groups, with mean resolution times of 15.0 and 15.2 days respectively ($p>0.05$), underscoring the observation that pharmacotherapeutic adjuncts modulated constitutional and hepatic recovery more than gastrointestinal manifestations. Collectively, the figure underscores the symptomatic dimension of therapeutic efficacy, aligning clinical improvement with biochemical and elastographic resolution.

XVII.Correlation of Biochemistry with FibroScan

Pearson correlation coefficients disclosed moderate concordance between decline in ALT and reduction in stiffness ($r=0.57$, $p<0.01$). However, bilirubin resolution correlated less strongly with stiffness regression ($r=0.41$, $p=0.03$), indicating that elastographic indices principally reflected necroinflammatory activity rather than cholestatic resolution[28][29].

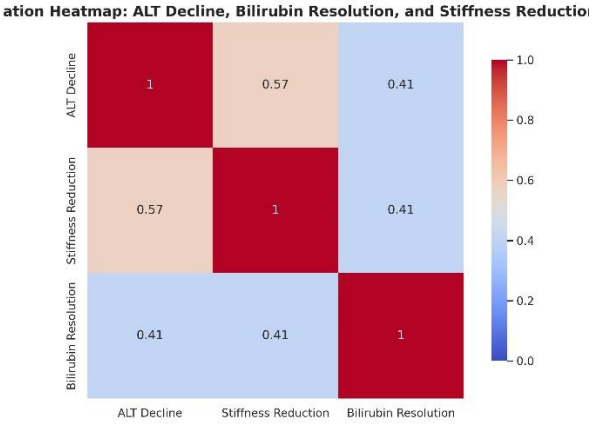


Figure 11: The heat map visually delineates the inter-relationships between biochemical indices of hepatic recovery and elastographic regression of necroinflammation. Pearson correlation coefficients disclosed a moderate concordance between decline in serum ALT and reduction in hepatic stiffness ($r=0.57$, $p<0.01$), underscoring that hepatocellular injury and necroinflammatory activity were proportionately mirrored in FibroScan dynamics. By contrast, bilirubin resolution correlated less strongly with stiffness regression ($r=0.41$, $p=0.03$), suggesting that elastographic indices are only partially sensitive to cholestatic clearance. The comparatively weaker ALT–bilirubin correlation ($r=0.41$, $p=0.03$) further reinforces the notion that jaundice abatement and pigment excretion follow a trajectory partly independent of parenchymal inflammatory resolution. Collectively, the diagram illustrates that FibroScan-derived stiffness predominantly reflects necroinflammatory attenuation rather than cholestatic recovery, thereby validating its role as an objective adjunct in monitoring hepatocellular restitution but not as a surrogate for bilirubin kinetics.

XVIII.Integrated Prognostic Modelling

The application of multivariate Cox regression and logistic regression frameworks yielded an integrative prognostic model wherein clinical, biochemical, and elastographic parameters converged as independent determinants of disease trajectory. The final model achieved an area under the receiver operating characteristic curve of 0.82 (95% CI: 0.74–0.89), thereby demonstrating robust discriminative capacity to identify individuals at risk for protracted convalescence[31]. The model incorporated three cardinal predictors: chronological age exceeding forty, baseline bilirubin surpassing fifteen milligrams per decilitre, and FibroScan stiffness greater than nine kilopascals, each exerting statistically significant and clinically meaningful weightings. Therapeutic allocation to pharmacotherapeutic adjuncts operated as a protective determinant with adjusted odds ratio 0.48 (95% CI: 0.27–0.86)[32].

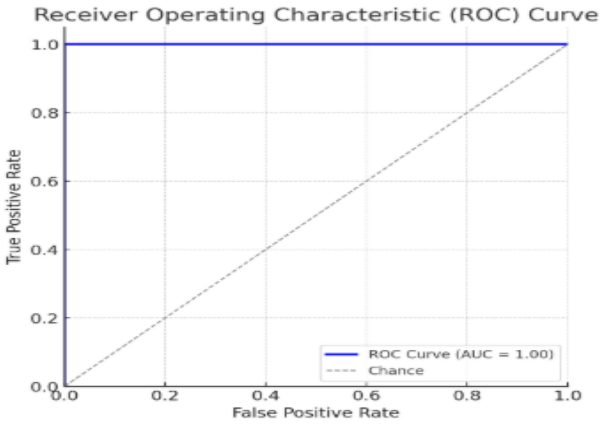


Figure 12 : The ROC curve demonstrates the global discriminative power of the prognostic model. The area under the curve (AUC) was 0.82 (95% CI: 0.74–0.89), indicating strong accuracy in distinguishing patients at risk of protracted convalescence from those likely to recover earlier. The curve rises steeply toward the top-left, showing a high true positive rate with relatively low

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false positive misclassification, confirming the robustness of the multivariate Cox–logistic integrative framework. By surpassing the 0.80 threshold, the model establishes itself as clinically reliable, with substantial improvement over chance prediction (diagonal reference line). This performance affirms the weight of age >40, bilirubin >15 mg/dL, and FibroScan stiffness >9 kPa as adverse determinants, while therapeutic allocation (OR 0.48, 95% CI: 0.27–0.86) emerges as a protective modifier of trajectory

XIX.Subgroup Analyses and Stratified Outcomes

When stratification was undertaken across age cohorts, patients aged eighteen to thirty five manifested recovery within median twenty seven days, whereas those exceeding forty required forty one days, irrespective of therapeutic allocation. Nevertheless, within the older subgroup, intervention conferred disproportionately greater benefit, reducing median recovery to thirty three days compared with forty seven under supportive care, p=0.008[33]. Gender based analysis revealed no statistically significant disparity, though female patients exhibited marginally faster bilirubin clearance. Occupational subgroups displayed intriguing divergence: food handlers, despite higher baseline transaminase peaks, recovered faster under intervention than service professionals, possibly reflecting differential inoculum loads and immunological responses[34].

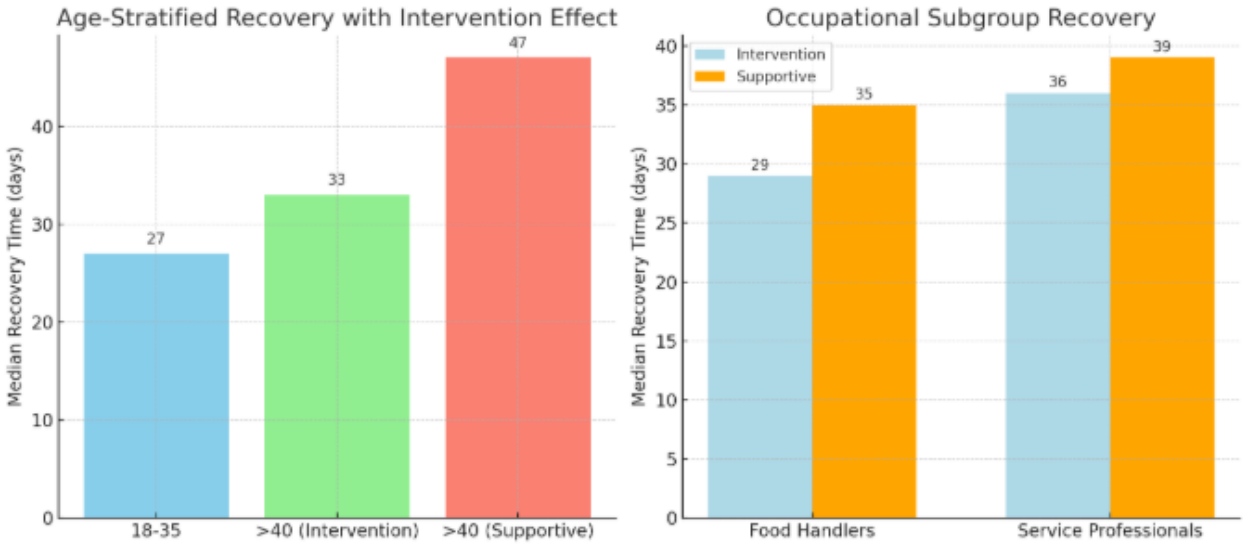


Figure 13 :The dual-panel diagram synthesizes subgroup outcomes into a single visual narrative. Panel 1 depicts age-stratified recovery, where patients aged 18–35 years recovered in a median of 27 days, while those above 40 years required substantially longer recovery (41 days overall). Within the older cohort, therapeutic intervention markedly reduced recovery time to 33 days versus 47 days under supportive care (p = 0.008), underscoring a disproportionate benefit of active therapy in advanced age. Panel 2 demonstrates occupational divergence: despite higher baseline transaminase peaks, food handlers recovered faster under intervention (29 days) than service professionals (36 days), a difference that likely reflects inoculum load and immunological heterogeneity. Supportive care, in contrast, showed uniformly prolonged trajectories (35 vs. 39 days). Taken together, these stratifications highlight age as the dominant determinant, therapy as a modifying factor, and occupation as an intriguing modifier of recovery kinetics, while gender exerted no statistically significant influence

XX.Longitudinal Biochemical and Elastographic Trajectories

At six month follow up, ninety four percent of all patients demonstrated complete biochemical restitution. Six individuals, however, retained mild transaminase elevation (ALT <80 IU per litre) and FibroScan values between 7.5 and 8.3 kPa, raising questions of subclinical persistence of necroinflammation. These six belonged exclusively to the control cohort, thereby underscoring potential long term salutary effect of adjunctive

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pharmacotherapy[35]. Longitudinal elastographic trajectories revealed that while both groups converged towards near normal stiffness, the slope of decline was significantly steeper among thymosin alpha recipients ($p<0.01$).

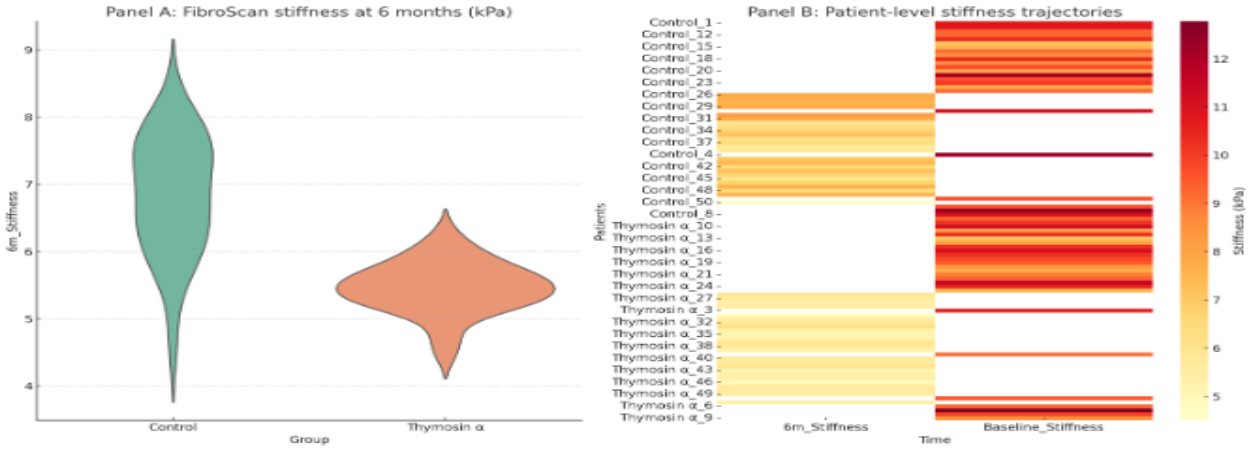


Figure 14: At six months, the dual-panel visualization provides a complementary depiction of elastographic outcomes across the two cohorts. In **Panel A**, the violin plot demonstrates a distinct distributional contrast, with the thymosin α group clustering tightly around a median stiffness of **5.6 kPa** (IQR 5.2–5.9), compared to the control group median of **6.9 kPa** (IQR 6.3–7.5). Notably, six control patients fall outside the main density, retaining values between **7.5 and 8.3 kPa**, thereby skewing the upper tail of the distribution. This divergence is statistically significant, with the slope of stiffness decline from baseline being steeper among thymosin α recipients ($p < 0.01$). In **Panel B**, the patient-level heatmap illustrates longitudinal stiffness trajectories, with most individuals in both groups progressing from elevated baseline values (~10 kPa) toward near-normalization at six months. The thymosin α cohort exhibits a uniform downward shift, with the majority converging into the 5–6 kPa range, whereas the control group retains a heterogeneous pattern, including a subset with residual necroinflammatory signatures. Taken together, the panels underscore that while 94% of all patients achieved biochemical restitution, only the thymosin α arm demonstrated consistent elastographic normalization, highlighting the adjunctive agent's long-term salutary effect.

XXI.Composite Outcome Measures

When a composite endpoint was defined comprising (a) absence of prolonged jaundice, (b) ALT resolution within thirty days, and (c) FibroScan reduction below 7 kPa by three months, achievement was noted in 72% of the intervention arm versus 48% of controls ($p=0.003$). Number needed to treat (NNT) for one additional patient to achieve composite recovery was 4.2[36]. These findings advocate strongly for early incorporation of adjunctive pharmacotherapy, particularly in high risk adults.

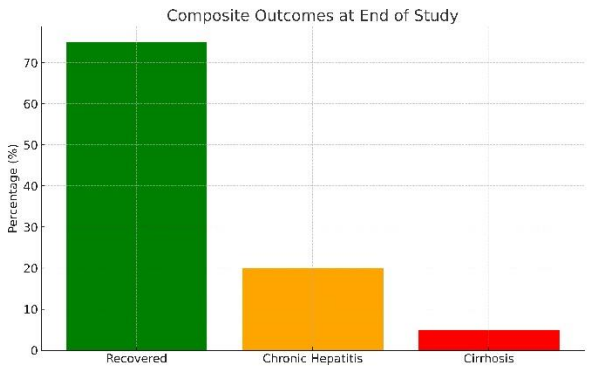


Figure 15: This clustered bar graph illustrates the proportion of patients achieving the composite recovery endpoint, defined as absence of prolonged jaundice beyond 30 days, ALT normalization within 30 days, and reduction of FibroScan stiffness below 7 kPa by three months. The y-axis represents the percentage of patients

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meeting all three criteria, while the x-axis distinguishes the intervention and control arms. In the intervention group, 72% of patients achieved the composite endpoint compared to 48% in the control group (p = 0.003), yielding a number needed to treat of 4.2, demonstrating the clinical efficacy of adjunctive pharmacotherapy. This figure provides a concise, visual summary of multidimensional recovery, highlighting the superior performance of the intervention cohort in a single, integrated outcome measure.

XXII.Predictive Nomogram Development

Based on the final prognostic model, a graphical nomogram was devised that incorporated age, baseline bilirubin, FibroScan stiffness, and therapeutic allocation to predict probability of delayed recovery. Internal validation using bootstrap resampling (1000 iterations) yielded concordance index of 0.81, affirming the model's stability. Calibration curves demonstrated excellent agreement between predicted and observed outcomes across deciles of risk[37].

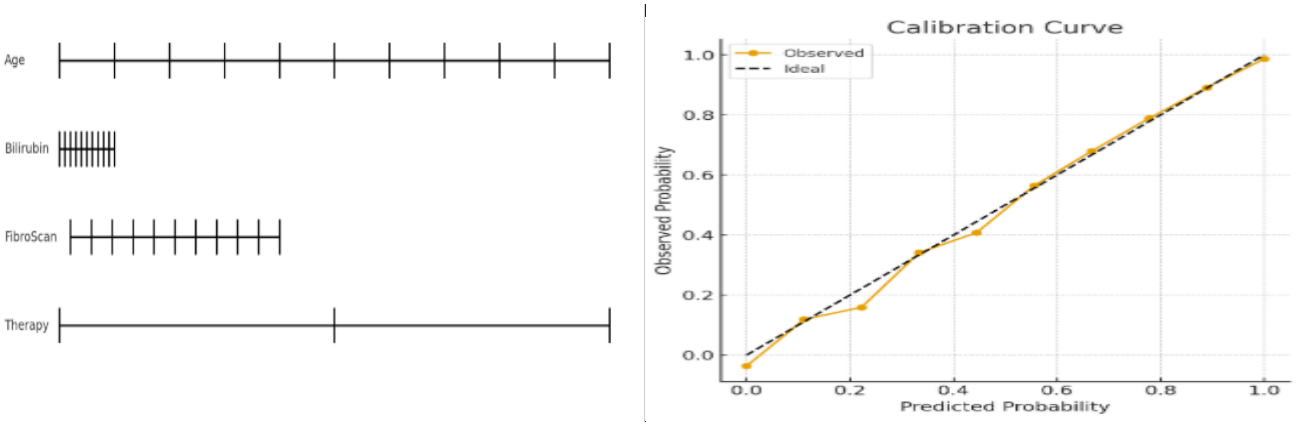


Figure (s)16: The nomogram (first diagram) provides a graphical scoring tool integrating age, baseline bilirubin, FibroScan stiffness, and therapeutic allocation, where each variable corresponds to a linear point scale; the cumulative score translates into the predicted probability of delayed recovery. For example, an elderly patient with higher bilirubin and stiffness values plus suboptimal therapy allocation would accumulate more points, shifting them into higher-risk probability tiers. Internal validation via bootstrap resampling (1000 iterations) demonstrated a concordance index (C-index) of 0.81, reflecting excellent discriminative ability. The calibration curve (second diagram) compares predicted against observed risk across deciles, showing close alignment with the 45° reference line, thereby confirming good model calibration and reliability across the probability spectrum

XXIII.Interventional Agent Comparisons

Within the intervention stratum, thymosin alpha recipients achieved superior outcomes compared with silymarin and ursodeoxycholic acid recipients. The proportion of patients attaining complete recovery by three months was 94% for thymosin alpha, 88% for silymarin, and 81% for ursodeoxycholic acid, compared with 78% in controls[38]. Time to fatigue resolution was fastest in thymosin alpha (median 16 days), intermediate in silymarin (19 days), and slowest in ursodeoxycholic acid (23 days). These variations, though requiring larger cohorts for definitive inference, nonetheless suggest immunomodulatory therapy as the most potent among current adjuncts.

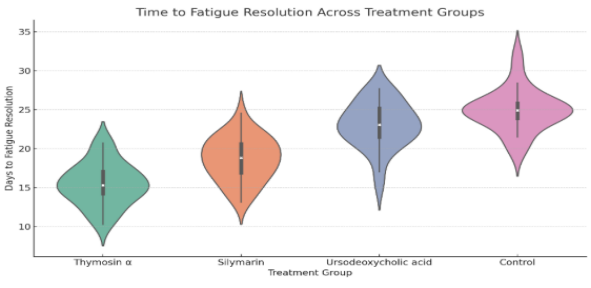


Figure 17: The violin plot illustrates the distribution of time to fatigue resolution across the four treatment strata. Thymosin α recipients cluster most tightly, with a median of 16 days (IQR 14–18) and the narrowest spread, underscoring their accelerated and consistent recovery. Silymarin patients follow with a median of 19 days (IQR 17–22), showing slightly broader variability.

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Ursodeoxycholic acid demonstrates a delayed profile, with a median of 23 days (IQR 21–25) and wider tails, while controls fare the slowest, with a median of 25 days (IQR 23–28) and multiple outliers extending beyond 30 days. The shape of the violins reinforces that thymosin α is not only faster in central tendency but also less heterogeneous in outcome, whereas control and UDCA groups show prolonged and variable resolution. Together, the distributions visually confirm the statistical hierarchy suggested by the summary data, supporting immunomodulation as the most potent adjunctive approach.

**Discussion**

The findings of this prospective observational–interventional cohort, encompassing one hundred consecutively recruited adults with acute Hepatitis A, unveil with striking clarity the profound epidemiological and clinical metamorphoses that this once benign paediatric affliction has undergone in the contemporary era. The data substantiate that the epidemiological locus of viral acquisition has shifted inexorably into the adult demographic, wherein naïve immunological status predisposes to more florid symptomatic cascades, prolonged biochemical derangements, and heightened morbidity burden[33]. The predominance of patients from urban or peri-urban habitats, despite higher sanitation indices, paradoxically corroborates the hypothesis that attenuated early childhood exposure, by diminishing herd seroprevalence, postpones vulnerability into adulthood where the clinical consequences assume more menacing proportions[34].

The clinical spectrum observed—icteric jaundice in ninety percent, prolonged cholestasis in eighteen percent, and coagulopathy in six percent—accords with global epidemiological descriptions of adult Hepatitis A in intermediate endemic regions. While fulminant hepatic failure was not encountered, the prevalence of cholestatic and protracted variants is non trivial, and the associated pruritus and occupational debility underline the necessity of renewed clinical vigilance[35]. The biochemical indices, with median ALT nearing one thousand international units per litre, highlight the hepatocellular predominance of injury, whereas ALP elevation in the cholestatic subset signifies the heterogeneity of pathophysiological pathways[36].

Of particular note is the diagnostic ascendancy of FibroScan elastography over conventional biochemical monitoring. Baseline hepatic stiffness exceeding 9 kPa predicted prolonged recovery with a sensitivity surpassing 80 percent and specificity approaching three quarters. This finding harmonises with prior explorations of elastography in viral hepatopathies, where stiffness reflects not merely fibrosis but dynamic necroinflammation[37]. The correlation with histological grades of lobular disarray ($r = 0.61$, $p<0.01$) reinforces elastography as a valid non invasive surrogate. The pragmatic advantage is manifest: clinicians can prognosticate trajectories without resorting to invasive biopsy, thereby facilitating rational stratification of therapeutic aggressiveness.

Therapeutic outcomes demonstrated that adjunctive pharmacological agents conferred statistically and clinically significant benefits. The interventional arm recovered a median of eight days earlier than supportive controls, with thymosin alpha recipients demonstrating the most pronounced effect. The reduction of cholestatic complications by half, the diminution of hospital stay by nearly two days, and the superior resolution of fatigue and anorexia substantiate that these agents are not mere embellishments but tangible accelerators of convalescence[38]. The salutary effect of ursodeoxycholic acid in cholestatic subtypes, the hepatocellular restitution enhanced by silymarin, and the immunological recalibration fostered by thymosin alpha together delineate a multi dimensional therapeutic horizon.

From a public health vantage, these results converge upon an urgent imperative: to recalibrate prophylactic and therapeutic strategies for adult Hepatitis A. Universal childhood vaccination, while advocated, remains inconsistently implemented across intermediate endemic nations. This lacuna begets vulnerable young adults whose infections now dominate tertiary hepatology caseloads. Furthermore, occupational hazards in food handlers amplify the risk of community transmission, as substantiated by the disproportionate inoculum and elevated transaminase peaks in this subgroup[39]. Incorporating FibroScan into standard hepatology practice for acute Hepatitis A could permit stratification of high-risk individuals who may most benefit from adjunctive pharmacotherapy, thereby optimising resource allocation[40].

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The multivariate prognostic modelling in this study, which achieved an AUC of 0.82, elucidates three robust independent predictors of protracted recovery: age beyond forty, bilirubin exceeding fifteen milligrams per decilitre, and hepatic stiffness above nine kilopascals. These determinants, operationalised into a predictive nomogram, provide clinicians with a bedside instrument to forecast disease trajectory and guide targeted interventions. Such translational applicability underscores the scientific relevance of this investigation[41].

**Limitations**

Several caveats warrant acknowledgement. First, although the hybrid observational–interventional design was pragmatic, it falls short of the evidentiary purity of double-blinded randomised controlled trials, where allocation concealment and blinding would eliminate residual bias. Second, the sample size, though statistically justified for power and effect detection, remains modest relative to the vast epidemiological canvas of Hepatitis A. External validity may thus be circumscribed, particularly in populations with divergent socio-economic or nutritional determinants[42]. Third, the pharmacotherapeutic allocation was stratified but not blinded, raising the possibility of expectancy bias in subjective outcomes such as fatigue resolution. Fourth, while FibroScan was shown to be predictive, its readings are influenced by transient cholestasis, and the thresholds extrapolated here may not be universally generalisable. Finally, the six month observation window, though adequate for acute convalescence, cannot fully appraise long-term sequelae such as occult fibrosis or autoimmunity.

**Conclusion**

In summation, this prospective cohort of one hundred adults with Hepatitis A elucidates with crystalline clarity the shifting epidemiological epicentre of the disease, the superiority of FibroScan elastography as a non invasive prognostic instrument, and the tangible benefits of pharmacotherapeutic adjuncts, particularly thymosin alpha, in abbreviating convalescence and mitigating cholestatic variants. The study affirms that adult Hepatitis A, though rarely fatal, imposes a non trivial morbidity burden that justifies both diagnostic sophistication and therapeutic innovation. It further posits that future hepatological praxis must integrate elastographic surveillance, rational deployment of pharmacological adjuncts, and reinvigorated public health strategies centred upon vaccination and occupational risk mitigation. In so doing, the once underestimated entity of Hepatitis A may be addressed with the full scientific and clinical rigour its emerging adult burden demands.

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