

Integration of Biochemical Biomarkers and Quantitative Ultrasound Liver Assessment for Prediction of Chemotherapy-Associated Hepatotoxicity in Patients with Solid Malignancies: A Prospective Cohort Study

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ABSTRACT

Background: Chemotherapy-associated hepatotoxicity may interrupt effective cancer treatment, while conventional liver biochemical tests often identify injury only after clinically relevant hepatic damage has developed. Quantitative ultrasound could reveal subclinical structural abnormalities and help predict risk earlier.

Objective: To determine whether integration of biochemical biomarkers with quantitative ultrasound improves prediction of chemotherapy-associated hepatotoxicity in patients with solid malignancies.

Methods: This prospective cohort study included 80 adults with histologically confirmed solid malignancies receiving systemic cytotoxic chemotherapy from January 2025 to January 2026. Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline Phosphatase (ALP), gamma-glutamyl transferase (GGT), Bilirubin, albumin, and Lactate Dehydrogenase were evaluated as baseline parameters. Hepatic attenuation coefficient (AC) and liver stiffness measurement (LSM) were obtained by quantitative ultrasound. Biochemical, ultrasound, and integrated models were compared, and biochemical or ultrasound parameters were identified as predictors by multivariable logistic regression and receiver operating characteristic analysis.

Results: Hepatotoxicity occurred in 20 patients (25.0%). Increased GGT, AC, and LSM levels were each independently associated with liver damage. The biochemical model area under the curve (0.76) was less than the quantitative ultrasound area under the curve (0.81). The integrated model had the highest discrimination with an AUC of 0.89, sensitivity of 85.0%, specificity of 81.7%, and negative predictive value of 94.2%. The model was validated using bootstrap, and the optimism-corrected AUC was 0.87, suggesting that the model was stable despite the small cohort size.

Conclusion: Combination of biochemical markers with quantitative ultrasound was helpful to better predict hepatotoxicity due to chemotherapy and may help to more safely continue cancer therapy, to recognize patients at higher risk, and to better monitor the liver.

Keywords: chemotherapy-associated hepatotoxicity; solid malignancies; biochemical biomarkers; quantitative ultrasound; liver stiffness; attenuation coefficient

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INTRODUCTION

Although targeted therapies and immunotherapy are becoming more and more important in the treatment of solid malignancies, chemotherapy still plays a key role in many of these disease entities [1]. However, systemic anticancer treatment is frequently limited by treatment-related toxicities, among which hepatic injury is clinically important because the liver is the principal organ responsible for drug metabolism, biotransformation, and elimination. Hepatotoxicity associated with chemotherapy can be present with subtle rises in liver enzymes, steatosis, steatohepatitis, cholestatic injury, sinusoidal obstruction, fibrosis, or,

in rare cases, acute liver failure. Liver toxicity can require dosage reduction, treatment interruption, or even permanent discontinuation and could affect the oncologic outcome [2,3].

The major serum markers of liver function used for routine hepatic monitoring during chemotherapy are alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, bilirubin and albumin [4]. These biomarkers are easily accessible and are useful for diagnosis of liver injury but are less predictive of liver injury before the onset of clinically significant liver injury. The

aminotransferase elevations are generally more indicative of hepatocellular injury than of hepatic functional reserve, and bilirubin and albumin levels may be relatively spared until more significant dysfunction occurs. Moreover, metabolic disease, other co-medications, infection, nutritional impairment, hepatic metastases, and pre-existing liver abnormalities complicate the interpretation of abnormal liver biochemistry in patients with cancer [5,6].

Quantitative ultrasound (qUS) has become a non-invasive technique for objective evaluation of hepatic tissue characteristics [7]. The measurements of attenuation obtained from ultrasound allow a quantitative assessment of fat accumulation in the liver, while shear-wave elastography allows assessment of liver stiffness. These measurements might be able to detect subclinical structural and biomechanical abnormalities that are not obvious from conventional laboratory measurements or qualitative ultrasonography [8,9]. Hepatic attenuation may be increased in the presence of steatosis and metabolic vulnerability, and liver stiffness may be increased with fibrosis or inflammation, vascular congestion, or sinusoidal injury due to treatment. These changes may make it more likely for the liver to be harmed during systemic chemotherapy [10,11].

The potential of using the combination of biochemical and imaging markers is especially relevant as the two types of markers offer complementary biological information. Biochemical parameters reflect hepatocellular injury and hepatic synthetic reserve, while quantitative ultrasound is able to assess tissue composition and mechanical properties [12,13]. An integrated approach could therefore identify at-risk patients before the conventional toxicity thresholds are attained, and may facilitate individualized monitoring and appropriate earlier intervention to continue anticancer treatment safely [14].

Although conventional biochemical markers have been used to assess hepatotoxicity, the number of prospective studies combining the use of biochemical markers with quantitative ultrasound parameters for prediction of hepatotoxicity is still limited, especially in the context of heterogeneous solid malignancies and chemotherapy. The majority of prior studies have assessed laboratory abnormalities and imaging parameters alone, and there remains some doubt as to the added value of combining both methods [15-18]. Therefore, this prospective cohort study aimed to evaluate biochemical and quantitative ultrasound predictors of chemotherapy-associated hepatotoxicity in patients with solid malignancies and to determine whether an integrated biochemical-ultrasound model provides superior predictive performance compared with biochemical or ultrasound parameters alone.

MATERIALS AND METHODS

Study Design and Setting:

This prospective cohort study was conducted from January 2025 to January 2026 through collaboration between the Department of Biochemistry, Mekran Medical College, Turbat, Pakistan, and the Department of Clinical and Radiation Oncology, Neurospinal and Cancer Care Institute (NCCI), Karachi, Pakistan. Clinical recruitment, chemotherapy administration, and follow-up were done at NCCI, and biochemical assessment was done with the Department of Biochemistry, Mekran Medical College. The study was performed following the Declaration of Helsinki, and all participants signed a written informed consent form.

Study Population:

Eighty consecutive adult patients with solid tumors confirmed by biopsy, who were to receive systemic cytotoxic chemotherapy, were entered into the study. Eligible patients were ≥ 18 years of age, with sufficient hepatic function and an ECOG performance status of 0–2. Patients with primary liver malignancy, extensive liver metastases, cirrhosis, active viral hepatitis, biliary obstruction, acute liver disease, or heavy alcohol consumption were excluded. Patients who had an ALT or AST > 2 times the upper limit of normal (ULN) and/or a bilirubin > 1.5 times ULN and/or an ALP > 2 times ULN for which no explanation was given were also excluded.

Clinical and Biochemical Evaluation:

Baseline data consisted of age, gender, BMI, diabetes mellitus, hypertension, malignancy type and stage, chemotherapy protocol, and co-medications. Venous blood samples were collected prior to the start of chemotherapy and prior to subsequent cycles of chemotherapy. The biochemical parameters were: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin, serum albumin, and lactate dehydrogenase (LDH). Prediction analyses were performed using baseline measurements; the serial measurements were used to show hepatic injury that occurred during the treatment.

Quantitative Ultrasound Assessment:

Quantitative liver ultrasound was conducted before first-cycle chemotherapy with an ultrasound system that had attenuation imaging and 2D shear wave elastography. Measurements were acquired with a right intercostal approach avoiding major vessels, bile ducts, focal lesions, and artefacts. The attenuation coefficient (AC) was measured in dB/cm/MHz and liver stiffness measurement (LSM) in kilopascals (kPa). Technically acceptable measurements were taken multiple times, and the median value was used for analysis.

Definition of Hepatotoxicity:

The main outcome was hepatotoxicity due to chemotherapy during follow-up. Hepatic injury was identified as ALT $\geq 5 \times$ ULN, ALP $\geq 2 \times$ ULN and attributed to hepatic injury, or ALT $\geq 3 \times$ ULN and total bilirubin $> 2 \times$ ULN. The pattern of injury was categorized by R ratio (ALT/ALT ULN / ALP/ALP ULN with R ratio > 2 indicating hepatocellular injury; R ratio < 2 indicating cholestatic injury; and R ratio > 2 and < 5 indicating mixed injury. Other hepatotoxic medications, infection, ischemic injury, disease progression, and viral hepatitis were ruled out before the attribution to chemotherapy.

Follow-Up and Outcomes:

These patients were monitored during chemotherapy with clinical assessment and liver biochemical tests prior to each chemotherapy cycle. Data were collected on the rate of hepatotoxicity, the timing of hepatotoxicity, the pattern of hepatotoxicity, severity of hepatotoxicity, and chemotherapy interruption, dose modification, or discontinuation. The main aim was to evaluate the predictive efficacy of biochemical biomarkers, quantitative ultrasound parameters, and an integrated biochemical-ultrasound model.

Statistical Analysis:

Continuous variables were presented as mean $\pm$ standard deviation, or median (interquartile range), and categorical variables were presented as frequencies and percentages. Independent-samples t-test or Mann-Whitney U test was used for continuous variables, and chi-square or Fisher's exact test was used for categorical variables for between-group comparisons. Independent associations of hepatotoxicity were determined by multivariable logistic regression models and presented as adjusted odds ratios and 95% confidence intervals. Biochemical and ultrasound models were compared with an integrated model using receiver operating characteristic analysis. The area under the curve, sensitivity, specificity, positive predictive value, and negative predictive value were determined. A two-sided p-value < 0.05 was considered statistically significant.

RESULTS

Participant Characteristics:

A total of 80 patients with solid malignancies were included in the final analysis, comprising 40 males (50.0%) and 40 females (50.0%). The mean age of the cohort was 52.6 ± 11.2 years. The most frequent malignancies were colorectal cancer (22.5%), lung cancer (21.3%), breast cancer (20.0%), prostate cancer (12.5%), ovarian cancer (10.0%), and other solid tumors (13.7%). Twenty-four patients (30.0%) received anthracycline/taxane-based chemotherapy, 21 (26.3%) received fluoropyrimidine/oxaliplatin-based regimens, 19 (23.8%) received platinum-

containing regimens, and 16 (20.0%) received other cytotoxic combinations.

During follow-up, 20 patients (25.0%) developed chemotherapy-associated hepatotoxicity, whereas 60 (75.0%) did not. Sex distribution was identical between outcome groups and was not associated with hepatotoxicity. Patients who developed hepatotoxicity had significantly higher baseline body mass index (BMI), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), attenuation coefficient (AC), and liver stiffness measurement (LSM), together with lower serum albumin. Diabetes mellitus was also more frequent among patients who developed hepatic injury (Table 1).

Table 1. Baseline Characteristics According to Chemotherapy-Associated Hepatotoxicity

Variable	Hepatotoxicity (n=20)	No hepatotoxicity (n=60)	p-value
Age, years	54.2 ± 10.5	52.1 ± 11.5	0.474
Male sex, n (%)	10 (50.0)	30 (50.0)	1.000
Female sex, n (%)	10 (50.0)	30 (50.0)	1.000
BMI, kg/m ²	28.2 ± 4.1	25.8 ± 4.0	0.025
Diabetes mellitus, n (%)	8 (40.0)	9 (15.0)	0.018
ALT, U/L	35 (27–43)	27 (21–34)	0.007
AST, U/L	32 (25–40)	27 (22–34)	0.064
GGT, U/L	48 (35–63)	31 (24–42)	< 0.001
ALP, U/L	113 (91–137)	103 (84–126)	0.205
Total bilirubin, mg/dL	0.77 ± 0.22	0.70 ± 0.19	0.172
Albumin, g/dL	3.80 ± 0.38	4.07 ± 0.36	0.005

AC, dB/cm/MHz	0.70 ± 0.08	0.61 ± 0.07	<0.001
LSM, kPa	6.5 ± 1.4	5.2 ± 1.2	<0.001

Values are presented as mean ± SD, median (IQR), or n (%). Continuous variables were compared using the independent-samples t-test or Mann-Whitney U test, as appropriate; categorical variables were compared using the chi-square or Fisher exact test.

Pattern and Clinical Course of Hepatotoxicity:

Among the 20 patients who developed chemotherapy-associated hepatotoxicity, 14 (70.0%) demonstrated a hepatocellular pattern, three (15.0%) had mixed injury, and three (15.0%) had a cholestatic pattern. The median time from initiation of chemotherapy to development of hepatotoxicity was 10.8 weeks (IQR 7.6–15.2).

Most hepatic events were reversible following clinical monitoring and modification of treatment. Six patients (30.0% of hepatotoxicity cases) required temporary chemotherapy interruption or dose reduction, while one patient required permanent discontinuation of the suspected regimen. No patient developed acute liver failure or died directly from chemotherapy-associated hepatotoxicity.

Biochemical and Quantitative Ultrasound Changes:

Patients who subsequently developed hepatotoxicity demonstrated higher pretreatment GGT and ALT concentrations and lower serum albumin compared with those who remained free of hepatic injury. Quantitative ultrasound also demonstrated significant baseline differences. Mean AC was 0.70 ± 0.08 dB/cm/MHz in patients who developed hepatotoxicity compared with 0.61 ± 0.07 dB/cm/MHz in those who did not (p<0.001). Similarly, mean LSM was 6.5 ± 1.4 kPa versus 5.2 ± 1.2 kPa, respectively (p<0.001).

Serial assessment showed greater increases in ALT, GGT, hepatic attenuation, and liver stiffness among patients who developed hepatotoxicity, supporting the presence of progressive biochemical and structural hepatic changes during chemotherapy.

Independent Predictors of Hepatotoxicity:

Variables showing clinically relevant associations were assessed using multivariable logistic regression. To reduce overfitting in the 80-patient cohort, the final model was restricted to the strongest clinically relevant predictors. Higher baseline GGT, AC, and LSM remained independently associated with subsequent chemotherapy-associated hepatotoxicity (Table 2).

Each 10-U/L increase in GGT was associated with a 28% increase in the adjusted odds of hepatotoxicity.

Every 0.05-dB/cm/MHz increase in AC was associated with approximately 1.7-fold greater odds, while each 1-kPa increase in LSM increased the odds of hepatotoxicity by approximately 46%.

Table 2. Independent Predictors of Chemotherapy-Associated Hepatotoxicity

Predictor	Adjusted OR	95% CI	p-value
GGT, per 10-U/L increase	1.28	1.05–1.57	0.016
AC, per 0.05-dB/cm/MHz increase	1.71	1.18–2.48	0.005
LSM, per 1-kPa increase	1.46	1.09–1.95	0.011

Adjusted odds ratios were obtained using multivariable binary logistic regression. OR, odds ratio; CI, confidence interval.

Predictive Performance:

The biochemical model incorporating baseline ALT, GGT, and serum albumin demonstrated moderate discriminatory performance, with an AUC of 0.76 (95% CI 0.65–0.87). The quantitative ultrasound model combining AC and LSM showed improved discrimination, with an AUC of 0.81 (95% CI 0.71–0.91).

The integrated model combining GGT, AC, and LSM demonstrated the strongest predictive performance, achieving an AUC of 0.89 (95% CI 0.81–0.96). At the optimal probability threshold, the integrated model provided 85.0% sensitivity, 81.7% specificity, 60.7% positive predictive value, and 94.2% negative predictive value. Bootstrap internal validation yielded an optimism-corrected AUC of 0.87, indicating good model stability (Table 3).

Table 3. Predictive Performance of Biochemical, Ultrasound, and Integrated Models

Model	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV
Biochemical model	0.76 (0.65–0.87)	70.0%	70.0%	43.8%	87.5%

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Quantitative ultrasound model	0.81 (0.71–0.91)	75.0%	75.0%	50.0%	90.0%
Integrated model	0.89 (0.81–0.96)	85.0%	81.7%	60.7%	94.2%

AUC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value.

Overall, the findings demonstrated that quantitative ultrasound parameters provided predictive information beyond conventional biochemical testing. Combining GGT, hepatic attenuation coefficient, and liver stiffness yielded the highest discrimination for chemotherapy-associated hepatotoxicity; sex was not related to the risk for hepatic injury.

DISCUSSION

This prospective cohort study shows that biochemical markers with quantitative ultrasound could be more useful in predicting hepatotoxicity due to chemotherapy in solid malignancy patients. Hepatotoxicity developed in 25.0% of the cohort, with hepatocellular injury representing the predominant biochemical pattern. Baseline GGT, hepatic attenuation coefficient (AC), and liver stiffness measurement (LSM) were independently associated with hepatotoxicity, and the integrated model had significantly better discrimination than biochemical or ultrasound assessment alone [1,2].

Systematic liver surveillance during cytotoxic chemotherapy is clinically important, as seen by the frequency of hepatic injury observed. Patients with cancer make liver injury assessment especially difficult, as liver function tests may also be abnormal due to metabolic disorders, infection, co-administration of other drugs, nutritional deficits, or tumour-related factors [3]. ALT, AST, ALP and bilirubin are still key biochemical markers for drug-induced liver injury, but are mainly used to diagnose the injury after biochemical alterations have occurred and do not reflect the underlying susceptibility of the liver [4].

GGT was the only biochemical parameter that was found to be an independent predictor of hepatotoxicity among conventional biochemical markers [5]. Patients who later developed hepatic injury had significantly higher baseline GGT, although they were deemed eligible for chemotherapy. GGT may indicate oxidative stress, microsomal enzyme activity,

metabolic dysfunction, or mild hepatobiliary damage not fully captured by aminotransferases. Patients who developed hepatotoxicity were also found to have lower baseline albumin, but this association was reduced after multivariate adjustments. This could suggest that decreased hepatic or nutritional reserve plays a role in susceptibility, but is not as specific as markers of altered liver function per se [6].

An important result was the independent predictive value of quantitative ultrasound. The baseline AC and LSM were significantly higher in patients who developed hepatotoxicity. Contemporary multiparametric ultrasound guidance allows ultrasound attenuation to be used for liver fat characterization, a non-invasive means of quantitative information [5,6]. Subclinical steatosis can be a risk factor for chemotherapy-induced mitochondrial dysfunction, oxidative damage, and inflammatory damage. Thus, more attenuation prior to treatment could indicate a liver phenotype less likely to withstand subsequent cytotoxic insult [7].

Similarly, increased baseline liver stiffness independently predicted hepatotoxicity. Liver stiffness should not be used as a sole indicator of fibrosis because it can also be influenced by inflammation, vascular congestion, and alteration of liver tissue architecture [8]. This is especially true in oncology as multiple chemotherapy drugs can cause sinusoidal or vascular hepatic injury. Liver stiffness changes during chemotherapy with oxaliplatin have been shown in previous shear-wave elastography studies, suggesting a possible role of elastographic monitoring in chemotherapy-induced liver damage [9].

The most clinically relevant finding was that which was achieved by combining biochemical and imaging parameters. The biochemical model showed an AUC of 0.76 and the quantitative ultrasound model showed an AUC of 0.81 [10]. The AUC was 0.89 when the three tests (GGT, AC, LSM) were combined, and 0.87 after internal validation. The integrated model also achieved a high level of sensitivity (85.0%) and specificity (81.7%), suggesting biochemical and imaging metrics yield complementary information. A high negative predictive value (94.2%) could be very helpful for the identification of patients at relatively low risk of clinically relevant hepatic toxicity [11].

The results may have implications for the monitoring of individual chemotherapy. Patients with an unfavorable biochemical-ultrasound profile might benefit from more frequent monitoring of liver function, earlier repeat ultrasound, and more careful evaluation of concurrent hepatotoxic drugs, and more aggressive metabolic-risk factor management [12]. These risk categorizations shouldn't be seen as a reason not to administer effective chemotherapy. Rather, it is important to recognise patients who might

require closer monitoring and earlier intervention before the liver is damaged enough to require substantial treatment changes [13].

The study can also help to usher in a wider trend of multimodal assessment of drug-induced liver injury. New biomarkers like glutamate dehydrogenase, microRNA-122, cytokeratin-18, and osteopontin may be able to give more insights into hepatocyte injury and cell death [10-12]. But because they are not widely available or affordable, their use is currently limited. The biochemical tests and quantitative ultrasound currently available on the market, on the other hand, represent a much more widely available and potentially suitable method for repeated clinical assessment [13].

There are some caveats to be noted. The number of hepatotoxicity events was modest (20); thus, only a few predictors could be retained in the final multivariable model. Bootstrap validation confirmed good model stability, but external validation is needed before clinical use [14]. There were heterogeneous chemotherapy regimens, and mechanisms of hepatotoxicity may vary among drug classes. Additionally, there was no routine use of liver biopsy or magnetic resonance imaging (MRI) based quantitative assessment, and ultrasound measurements may be equipment- and operator-dependent. Finally, clinical recruitment was performed in a single center for oncology, which may not be generalizable to other populations [15-17].

Despite these limitations, the prospective design, balanced inclusion of male and female patients, standardized pretreatment biochemical and ultrasound assessment, temporal separation of predictors from outcomes, and direct comparison of biochemical, imaging, and integrated models strengthen the study. Further multicenter studies, with larger numbers of patients, should confirm and assess the validity of this proposed model and whether serial quantitative ultrasound adds to the prediction beyond baseline quantitative ultrasound [18-20].

CONCLUSION

Chemotherapy-associated hepatotoxicity occurred in 25% of the patients with solid malignancies and was independently associated with higher baseline GGT, hepatic attenuation coefficient, and liver stiffness. Quantitative ultrasound was able to add value over routine biochemical assessment, and biochemical and ultrasound parameters combined together achieved the best discrimination of future hepatic injury. Biochemical-quantitative ultrasound strategy could thus offer a convenient and non-invasive way to risk-stratify before treatment and monitor livers individually during chemotherapy. The model needs to be validated in a larger study before it can be applied in routine clinical decision-making.

Authors' Contributions

AA contributed to study conception, biochemical methodology, data interpretation, and manuscript drafting. **AB** contributed to quantitative ultrasound assessment, imaging interpretation, and data acquisition. **AR** contributed to oncology assessment, chemotherapy-related clinical evaluation, patient follow-up, and interpretation of hepatotoxicity outcomes. **WA** contributed to study methodology, pharmacological interpretation, statistical review, and critical revision of the manuscript. **KN** contributed to hepatology-related interpretation, clinical assessment, and manuscript revision. **NA** contributed to biochemical analysis, laboratory interpretation, data validation, and critical review. All authors reviewed and approved the final manuscript.

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The datasets generated and analyzed during the study are available from the corresponding author on reasonable request, subject to institutional and ethical requirements.

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