

Diagnostic approaches to identifying cardiotoxicity in patients with hepatocellular carcinoma undergoing antineoplastic therapy

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INTRODUCTION

According to Global Cancer Statistics (GLOBOCAN 2022), Africa, Europe, and Asia account for up to 90% of all cases of primary liver cancer, with 70.1% of cases occurring on the Asian continent. In the Republic of Kazakhstan in 2023, the incidence of liver cancer was 5.6 per 100,000 population, and the mortality rate was 2.7. Between 2014 and 2023, liver cancer had the lowest five-year survival rate among all malignant neoplasms in Kazakhstan¹.

Hepatocellular carcinoma (HCC) is the most common malignant tumor of the liver, accounting for up to 85% of all forms of primary cancer².

HCC therapy varies depending on the stage of the disease and includes a variety of clinical strategies: from targeted and immunotherapy to liver transplantation³. Sorafenib remains the main drug for the treatment of HCC^{4,5}, while doxorubicin is used in transarterial chemoembolization of the hepatic artery (TACE)⁶.

However, the use of modern methods of HCC treatment is accompanied by the risk of developing cardiotoxicity⁷, leading to cancer therapy-related cardiac dysfunction (CTRCD)⁸.

However, the use of modern methods of treating GCC is accompanied by the risk of developing cardiotoxicity⁷, leading to cancer therapy-related cardiac dysfunction (CTRCD)⁸. CTRCD is accompanied by the development of reversible or irreversible, functional or structural changes in the myocardium and manifests itself with symptoms of cardiovascular disease^{8,9}. Complications that develop during chemotherapy negatively affect both the quality of life and overall survival of patients, regardless of the prognosis associated with the underlying disease¹⁰.

Confirmation of cardiotoxicity requires a comprehensive diagnostic approach, including clinical evaluation, electrocardiography (ECG), echocardiography (TTE), and cardiac biomarkers (high-sensitivity troponin (hs-cTn), brain natriuretic peptide (NT-proBNP))^{11,12}. Among these, TTE (namely global longitudinal strain (GLS) and NT-proBNP levels) are the most sensitive tools for diagnosing early preclinical LV dysfunction and monitoring the dynamics of cardiotoxicity¹³. And considering clinical practicality, sensitivity, and specificity, GLS, hs-cTn, and NT-proBNP are the most preferred diagnostic methods¹⁴.

Unfortunately, not all laboratories in Kazakhstan are capable of measuring hs-cTn and NT-proBNP levels, and not all cancer centers are equipped with the necessary equipment to detect early markers of myocardial dysfunction, such as GLS. Nevertheless, in recent years there

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has been a steady trend towards wider implementation of these methods in oncology practice due to their high diagnostic value and improved technical accessibility.

Currently, there is extensive data on increased levels of cardiac biomarkers in patients receiving sorafenib and doxorubicin¹⁵⁻¹⁷.

In our study, we analyzed changes in laboratory parameters of hs-cTn I and NT-proBNP in patients with HCC receiving targeted therapy and targeted therapy in combination with TACE. The analysis was performed before treatment and 6 months after the start of therapy, both within groups and between groups.

MATERIALS AND METHODS

The result of the article is a subanalysis in a prospective study performed under grant from the Ministry of Science and High Education of the Republic of Kazakhstan (Individual Registration Number AP19176025). The study was carried out from October 2024 to September 2025. The research was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the of nJSC «Astana Medical University» (No. 21 from 09/2023). All participants provided written informed consent prior to enrollment in the study.

A total of 69 patients with HCC were included in the study. The patients were divided into two groups based on the treatment protocol. The first group consisted of 29 patients who received daily targeted therapy with sorafenib at a dose of 800 mg per day. The second group included 40 patients who, in addition to receiving sorafenib at the same dose, underwent TACE with doxorubicin at a dose of 50 mg.

Exclusion criteria included patients under 18 years of age, those with metastatic liver cancer, other types of malignancies, cardiovascular diseases, any intraventricular conduction abnormalities, heart rhythm disturbances, ejection fraction less than 50% and a glomerular filtration rate (GFR) less than 30 mL/min.

All patients underwent laboratory testing (validated equipment from Roche Diagnostics, Mannheim, Germany) of cardiac biomarkers (hs-cTn I и NT-proBNP) before the initiation of therapy (4 ± 1 days) and 6 months after the start of treatment.

To assess the probability of developing chronic heart

failure, a logistic regression model was constructed, where the predictors were indicators of left ventricular systolic function, and the dependent variable was the occurrence of CHF 6 months after the start of target therapy. Equation (a) was constructed to reflect the dependence of the probability of CHF on GLS indicators.

The equation was as follows:

$$P = \frac{1}{1 + e^{-z}} \quad (a)$$

where P is the theoretical probability of developing CHF 6 months after the start of therapy, $z = (\text{FAC in \%} \times 0.938) + (\text{GLS in \%} \times 0.478) + 410.467$.

The cut-off value in the model was set at 0.2. If, after calculations, P was less than 0.2, the risk of developing CHF was considered to be higher.

Statistical analysis was performed using SPSS version 26 (IBM, USA). For variables with a non-normal distribution, non-parametric methods were applied: the Mann–Whitney U test (for intergroup comparisons) and the Wilcoxon test (for intragroup comparisons). For variables with a normal distribution, Student's t-test was used. Statistical significance was set at $p < 0.05$. Data are presented as means with standard deviations, and binary variables are presented as frequencies in absolute values and percentages.

Ethical approval

The study was approved by the Astana Medical University ethics committee

RESULTS

Table 1 presents the general characteristics of patients receiving both targeted therapy and targeted therapy combined with transarterial chemoembolization (TACE). The total number of patients with hepatocellular carcinoma included in the study was 69. Women prevailed in the targeted therapy group, accounting for 19 people (66%), and in the targeted therapy combined with TACE group, accounting for 23 women (57%). The average age of patients was 57 ± 8.1 and 59 ± 7.7 , respectively. Body mass index, hemoglobin, leukocyte, and platelet levels were within normal limits, with no differences between the two groups. Both groups were at stage C2 of GFR (glomerular filtration rate).

Table 1. Characteristics of patients on Targeted Therapy and Targeted therapy with TACE

Indicator	Targeted therapy group (n=29)	Targeted therapy and TACE group (n=40)	p
Female sex, n (%)	19 (66%)	23 (57%)	0,42
Age, years	57±8,1	59±7,7	0,643
BMI, kg/m ²	24,8±3,4	25,6±4,4	0,581
Hemoglobin, g/L	122,1±19,4	117,1±12,1	0,334
Leukocytes, x10 ⁹ /L	6,9±3,0	7,1±2,9	0,213
Platelets, x10 ⁹ /L	221,4±92,1	201,2±81,2	0,39
GFR ml/min/1,73m ²	78,1±3,2	86,4±2,9	0,08

GFR – glomerular filtration rate

To assess cardiotoxicity, laboratory parameters (hs-cTn I and NT-proBNP) and echocardiography data (ejection fraction (EF) and global longitudinal strain (GLS)) – indicators of left ventricular systolic function – were evaluated. Before starting therapy, there were no differences in hs-cTn I and NT-proBNP levels or echocardiography parameters between the subgroups.

Table 2. Baseline laboratory and Echocardiography Parameters of Patients in Both Groups before starting therapy

Indicator	Targeted therapy group (n=29)	Targeted therapy and TACE group (n=40)	p
hs-cTn I, ng/ml	3,8±0,9	3,1±0,6	0,29
NT-proBNP, pg/ml	117±9,1	122±8,4	0,194
EF, %	57±4	59±3	0,098
GLS, %	-19,1±2,1	-18,9±1,9	0,23
Resting heart rate, bpm	74±9	70±11	0,188

We evaluated laboratory and echocardiographic parameters 6 months after the start of therapy. An increase in NT-proBNP levels (p=0.029) and a decrease in GLS (p=0.041) were observed. There were no significant differences in the dynamics of hs-cTn I, EF, and heart rate parameters.

Table 3. Laboratory and Echocardiography Parameters of Patients in Both Groups after 6 months of therapy

Indicator	Targeted therapy group (n=29)	Targeted therapy and TACE group (n=40)	p
hs-cTn I, ng/ml	3,2±0,6	3,7±0,9	0,21
NT-proBNP, pg/ml	148,4±3,9	152,1±3,1	0,029
EF, %	58±3	58±4	0,124
GLS, %	-14,9±2	-15,2±1,7	0,041
Resting heart rate, bpm	72±7	79±12	0,21

In patients in the targeted therapy group, statistically significant differences in NT-proBNP levels were observed at 6 months: 117±9.1 vs. 148.4±3.9 (p=0.044) and GLS -19,1±2,1 vs -14,9±2, p=0.038 (Table 4)

Table 4. Laboratory and Echocardiography Parameters of Patients in Targeted Group in dynamics after 6 Months of Treatment

Indicator	Targeted therapy group (n=29)	Targeted therapy group after 6 months (n=29)	p
hs-cTn I, ng/ml	3,8±0,9	3,2±0,6	0,046
NT-proBNP, pg/ml	117±9,1	148,4±3,9	0,044
EF, %	57±4	58±3	0,21
GLS, %	-19,1±2,1	-14,9±2	0,038
Resting heart rate, bpm	74±9	72±7	0,132

In patients in the Targeted Group with TACE in dynamics after 6 months, we also detected changes in NT-proBNP and GLS levels. NT-proBNP levels changed dynamically, increasing from 122±8.4 before the start of therapy to 148.4±3.9 six months after the start of treatment (p=0.02). Meanwhile, GLS levels decreased from -18.9±1.9 before therapy to -14.9±2, p=0.04 6 months after the start of treatment (p=0.04). Table 5.

Table 5. Laboratory and Echocardiography Parameters of Patients in Targeted Group with TACE in dynamics after 6 Months of Treatment

Indicator	Targeted therapy and TACE group (n=40)	Targeted therapy and TACE group after 6 months (n=40)	p
hs-cTn I, ng/ml	3,1±0,6	3,2±0,6	0,441
NT-proBNP, pg/ml	122±8,4	148,4±3,9	0,02
EF, %	59±3	58±3	0,153
GLS, %	-18,9±1,9	-14,9±2	0,04
Resting heart rate, bpm	70±11	72±7	0,28

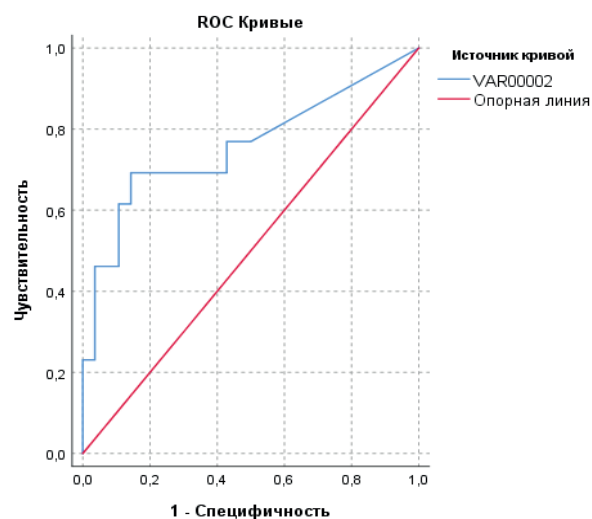
Predicting the risk of developing CHF in patients with IHD based on echocardiography parameters in patients with hepatocellular carcinoma

Logistic regression analysis was used to assess the relationship between the probability of developing CHF and the condition of the left ventricle, as well as the prognostic value of left ventricular GLS.

Among all covariates significant according to the correlation analysis, the seven most significant in terms of correlation coefficient were selected. According to the general principle of selecting predictors for regression analysis, their number is ten times less than the total number of observations in the study. In this case, $n=69$, therefore, the number of covariates should not exceed 69. Among the included covariates, using the stepwise inclusion method, the left ventricular GLS index and had the highest significance.

To evaluate the quality of the resulting model, a ROC curve was constructed (Figure 1). The area under the curve for the predicted probability was 0.725 ($p<0.001$, 95% CI (0.621-0.828), indicating “good” quality of the predicted model. The area under the curve for the predicted group with a classification threshold of 0.2 was 0.684 ($p=0.004$, 95% CI (0.577-0.792).

To characterize the binary classifier presented above with a cut-off point of 0.2, the following parameters were calculated: sensitivity = 86%; specificity = 50.6%; positive predictive value = 40%; negative predictive value = 90.4%.



True Positive Rate • False Positive Rate

Figure 1- ROC curve

DISCUSSION

Cardiotoxicity remains one of the most significant problems in modern cardio-oncology, as an increasing number of patients experience cardiovascular complications during anticancer therapy. Manifestations of cardiotoxicity range from asymptomatic reduction in ejection fraction to clinically significant heart failure, arrhythmias, myocardial ischemia, and hypertension, requiring special attention from the medical community when treating cancer patients¹⁸.

In clinical practice, biomarkers of myocardial damage and cardiac overload are used for early detection of cardiotoxicity. Among them, high-sensitivity troponin (hs-Tn I) and natriuretic peptide (BNP/NT-proBNP) are of particular importance. If cardiac troponin reflects sensitive and specific biomarkers of cardiomyocyte damage¹⁹, NT-proBNP is considered a sensitive marker of myocardial overload and dysfunction^{20,21}. NT-proBNP concentration strongly correlates with the severity, prognosis, and effectiveness of therapy in heart failure²².

Recently, there have been increasing reports that NT-proBNP may be an independent predictor of fatal outcomes in cancer patient^{23,24}. In oncology practice, BNP and NT-proBNP are becoming increasingly important as biomarkers of early cardiotoxicity associated with chemotherapy and targeted therapy. An increase in its level may precede clinical manifestations

and a decrease in ejection fraction, making it a useful monitoring tool in cardio-oncological surveillance²⁵. In our study, we also determined changes in NT-proBNP levels in patients receiving both targeted therapy and targeted therapy with TACE across 6 months after start of therapy $148,4 \pm 3,9$ vs $152,1 \pm 3,1$ ($p=0.029$). Similarly, NT-proBNP levels changed in patients within the target therapy ($117 \pm 9,1$ vs $148,4 \pm 3,9$, $p=0,044$) and target therapy combined with TACE groups (in dynamics $122 \pm 8,4$ vs $148,4 \pm 3,9$, $p=0.02$).

However, despite the active use of NPs as sensitive biomarkers of heart failure and chemotherapeutic cardiotoxicity, their role in oncology remains insufficiently studied. To date, there are no clear clinical guidelines for interpreting elevated NT-proBNP levels in cancer patients outside the context of overt cardiac dysfunction, which creates diagnostic uncertainty.

For example, in a study by Wieshammer S et al, in cancer patients with dyspnea and concomitant cardiovascular disease, an NT-proBNP threshold value of 100 ng/L has high sensitivity for the diagnosis of Heart Failure²⁶.

Troponins are cardiac biomarkers that have always been used to diagnose acute coronary syndromes, but have proven useful in detecting cardiotoxicity. Cardiac troponin T (cTnT) and cardiac troponin I (cTnI), released when heart muscle cells are damaged, are markers specific to the heart but not to a specific disease²⁷. According to some studies, after anthracycline chemotherapy, an increase in troponin levels is consistently observed in 21–40% of patients, regardless of the type of analysis²⁸. However, in our study, we did not find a significant change in troponin levels in either subgroup. This may be due to the short observation period.

Echocardiography is the gold standard for assessing myocardial systolic function. This method is easily reproducible, accessible, and noninvasive. The most important in identifying cardiotoxicity is its early, reversible detection²⁹. Undoubtedly, GLS determination is the primary noninvasive method for the early detection of left ventricular systolic myocardial dysfunction^{30,31}. Yes, GLS has some limitations: high software requirements, an experienced physician, a normal heart rate, and sinus rhythm. However, these should not be

a limitation in identifying myocardial dysfunction in cancer patients³².

We identified a decrease in GLS in patients in both subgroups, which characterizes an early decline in left ventricular systolic function. In targeted group in dynamics - GLS $-19,1 \pm 2,1$ vs $-14,9 \pm 2$, $p=0.038$, and from -18.9 ± 1.9 before therapy to -14.9 ± 2 , $p=0.04$.

After correlation, the GLS indicator was included in the ROC curve construction, and sufficient predictive ability of this indicator in the development of heart failure in patients with HCC was revealed.

CONCLUSION

In patients with HCC without pre-existing cardiovascular pathology, a comparison between the targeted therapy group and the targeted therapy combined with TACE group, as well as within-group dynamics over 6 months after therapy initiation, revealed the following: an increase in NT-proBNP and GLS. These results highlight the importance of thorough laboratory monitoring and Echocardiography during targeted therapy and TACE in patients with HCC, particularly given the potential risk of adverse cardiovascular events.

Overall, our findings contribute to the growing body of evidence on chemotherapy-associated laboratory and echocardiographic changes in HCC patients, underscoring the need for comprehensive cardiac monitoring and individualized treatment strategies for this patient population.

Author's contribution

Data gathering and idea owner of this study: Saule Kubekova, Niyaz Malayev, Natalya Zagorulya

Study design: Saule Kubekova, Natalya Zagorulya

Writing and submitting manuscript: Saule Kubekova, Natalya Zagorulya

Editing and approval of final draft: Niyaz Malayev, Natalya Zagorulya, Oksana Zagorulya

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