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# Prognostic value of perioperative assessment of plasma cardiac troponin I in patients undergoing liver transplantation

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**Abstract. An elevation in plasma cardiac troponins is an indicator of increased perioperative risk in orthopaedic and vascular surgery, however, data on liver transplantation (LTx) are scarce. The aim of the study was to evaluate the prevalence of cardiac troponin I (cTnI) elevation in the perioperative period of LTx, and its potential relationship with 1-year mortality. Material and methods. Analysis included 79 patients with liver cirrhosis. During LTx all patients underwent hemodynamic measurements. cTnI level was determined before the operation, 24, 48 and 72 hours afterwards. One-year mortality was assessed. Results. 12.7% patients died, all during in-hospital period. cTnI level on day 1. was identified as the most promising marker of increased death risk with optimal cut-off value of 0.215 ng/mL (the sensitivity of 60.0%, specificity of 87.0%, positive predictive value of 40.0%, negative predictive value of 93.8%). The most important predictor of cTnI increase was the duration of the LTx procedure followed by amount of packed red blood cells transfused, basic stroke volume index, and cardiac output index. In conclusion: value of cTnI level assessed 24 hours post-surgery was a reliable predictor of death following LTx with optimal cut-off value of 0.215 ng/mL. The surgery time was the most important predictor of cTnI elevation.**

**Key words**: cardiac troponin I, liver transplantation, surgery time

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**Abbreviations**: LTx, liver transplantation; cTnI, cardiac troponin I; cTnT, cardiac troponin T; MELD, Model of End-Stage Liver Disease; PRBCs, packed red blood cells; FFP, fresh frozen plasma; CI, cardiac output index; SI, stroke volume index; sPAP, systolic pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; $SvO_2$, mixed venous oxygen saturation; $SaO_2$, arterial oxygen saturation; MAP, mean arterial blood pressure; Hb, haemoglobin concentration; Hbmin, minimal concentration of haemoglobin during surgery

## INTRODUCTION

An elevated cardiac troponin I (cTnI) concentration not only identifies acute cardiac injury but has also been proven useful in predicting poor outcomes for patients with cardiac and non-cardiac conditions (e.g. heart failure, chronic obstructive pulmonary disease, pulmonary embolus, end-stage renal disease with haemodialysis, and others). cTnI was evaluated to be elevated in up to 30% of asymptomatic patients with liver cirrhosis with normal electrocardiograms and without a history of cardiovascular disease. This is considered to reflect subendocardial damage. At the same time, we know that the increase of cTnI allows only for the diagnosis of myocardial injury but does not identify the aetiology of the damage. It needs to be emphasized that there exists no clearly defined cut-off point for cTnI, which would allow for the separation of the group of patients with acute myocardial infarction (Pateron *et al*., 1999; Higham *et al*., 2004; Watt *et al*., 2010).

An increase in cTnI level in the perioperative period was observed in a large proportion of patients undergoing vascular and orthopaedic surgery. In addition, it was proven that such increase is a good predictor of cardiovascular events in the follow-up (Filipovic *et al*., 2003; Landesberg *et al*., 2003; Devereaux *et al*., 2005; Bolliger *et al*., 2009).

Very few papers which discuss the importance of an increased cTnI level following LTx have been published so far.

## AIM OF THE STUDY

The initial hypothesis was that elevated serum troponin I levels in the perioperative period of liver transplantation would strongly correlate with post-transplant mortality. The primary goal of the study was to evaluate the prevalence of cTnI elevation in the perioperative period of LTx, to identify the optimal time of cTnI measurement, and to analyse the relationship between elevated cTnI level and 1-year mortality. Secondary goal was to assess which of the selected clinical, biochemical or operation procedure related parameters correlate with cTnI elevation.

## MATERIAL AND METHODS

We conducted a retrospective analysis of 80 patients referred to the Department of Internal Medicine and Cardiology between 2008 and 2011 and subsequently operated within 6 to 12 months. The patients underwent a routine cardiac assessment prior to the liver transplantation.

The study was reviewed and approved by the Ethics Committee of the Medical University of Warsaw.

None of the studied patients had history of coronary artery disease or myocardial infarction. All patients underwent rigorous pre-transplant cardiovascular evaluation (including clinical assessment, echocardiography, stress test, coronary angiography – if necessary), that ruled out major coronary artery disease. The preoperative cardiac

evaluation was carried out in accordance with the ESC guidelines for the preoperative evaluation of the cardiac patients for non-cardiac surgery (Poldermans *et al.*, 2009).

One of the patients from the initial group had to be excluded from the study due to accidental rupture of the steatotic graft during liver transplantation which was followed by massive bleeding requiring a transfusion of 14 units of packed red blood cells (PRBCs). ST elevation, myocardial infarction type 2 and cardiogenic shock was recognized. The primary graft non-function was diagnosed and the patient underwent urgent re-LTx. He died 2 days after re-LTx.

For the purpose of further analysis, the data of the remaining 79 patients (mean age 52.1±7.48 years, 26 (32.9%) female) were compiled. Sixteen (23.2%) patients were diagnosed with hypertension, probably resulting from immunosupressive therapy. In most of the studied cohort, viral inflammation was the dominating cause of liver cirrhosis (54.4%). Twenty (25.3%) patients were previously diagnosed with hypertension. Eighteen (22.8%) persons had a previously diagnosed diabetes, in 30 (38.0%) cases a history of smoking was present.

Pre-transplant MELD scores (Model of End-Stage Liver Disease) were calculated for all patients immediately before the transplantation. In patients who were operated because of HCC (hepatocellular carcinoma), the MELD score was calculated without correction (no added points).

All patients had total intravenous anaesthesia. Fluid therapy was guided by hemodynamic measurements and aimed at optimum cardiovascular stability. PRBCs were transfused when haemoglobin level fell below 8 g/dL. Based on routine coagulation screen and thromboelastometry, haemostatic disorders were corrected using fresh frozen plasma (FFP), cryoprecipitate, platelet concentrates and antifibrinolytics. All the recipients received whole liver grafts from the deceased donors which were implanted according to piggy back method. During the surgery, all patients had standard hemodynamic measurements performed with the use of a pulmonary catheter and a radial artery line. According to the protocol that was adopted in our centre, hemodynamic and biochemical values were obtained at four independent time points: directly after anaesthesia induction, within 30 minutes prior to reperfusion, 30 minutes after reperfusion and at the end of the surgery (and at more time points, if necessary). The obtained values were collected, among them: cardiac output index (CI), stroke volume index (SI), systolic pulmonary artery pressure (sPAP), pulmonary artery wedge pressure (PAWP), mixed venous oxygen saturation ($SvO_2$), and arterial oxygen saturation ($SaO_2$). All of them were taken into account in our analysis. Based on four haemoglobin concentration measurements, ΔHb value was calculated for each patient. It represented the difference between the haemoglobin concentration before surgery and the lowest concentration registered during operation. Total blood loss was monitored as well.

The duration of the surgery, from skin incision to final wound dressing (skin-to-skin time), the duration of functional anhepatic phase, from portal vein closure to organ reperfusion, and amount of transfused units of blood products, were recorded.

Restrictive fluid therapy (4 mL/kg/h) was used in 22 (27.85%) patients. This kind of fluid therapy was implemented in our hospital in 2011 in order to limit blood loss during hepatectomy. The procedure was introduced only in patients without known renal disease. The restrictive fluid therapy was conducted from the beginning of anaesthesia to the clamping of the portal vein. After that, the intravascular volume was restored by infusion of crystalloids.

The patient's hemodynamic status was monitored at all times. During surgery vasopressors or/and inotropes were infused to maintain hemodynamic stability. Norepinephrine was continuously infused in case of the patients with low systemic vascular resistance index and mean arterial blood pressure (MAP) < 65 mmHg. The patients with severe hypotension (MAP < 50 mmHg) were treated with adrenaline bolus (10–100 mcg). Dobutamine was infused only if hemodynamic parameters indicated a reduction of cardiac contractility.

The concentration of cTnI was determined directly before the operation, 24, 48 and 72 hours after surgery. The blood sample for testing cTnI was transferred to the laboratory immediately after the collection and the measurement was performed without delay. cTnI determination was performed with a colorimetric measurement technique (Simens Dimension Cardiac Troponin I system with heterogeneous immunoassay module), according to the kit producer. cTnI value of 0.07 ng/mL was considered to be the upper limit of the reference range.

A 12-lead ECG (electrocardiogram) was performed routinely in all patients starting from the first postoperative day. New myocardial ischemia signs were the objective of the research: ST depression > 1 mV, T-wave inversion, new Q waves or a new left bundle branch block. ECG was repeated in all patients with elevated cTnI level during the second and third day.

During the in-hospital post-transplant period the occurrence of the following cardiovascular events requiring immediate treatment was investigated: acute coronary syndrome, acute heart failure, stroke and/or serious, potentially fatal cardiac arrhythmias, and the cardiac and all-cause death.

After at least one year from the hospital discharge, telephone interview was carried out in all patients, during which we established the medical history since leaving hospital, with particular attention to any cardiovascular events and hospitalization for cardiac reasons.

**Statistical analysis**. Mann-Whitney test was used in all comparisons of continuous variables and median with range was reported in group descriptions.

For nominal variables $Chi^2$ or Fisher's exact tests were employed depending on the expected count's distribution.

Receiver operating curve (ROC) analysis was applied to determine the area under the curve (AUC) and optimal cut-off value of troponin I level for predicting 1-year mortality.

Confidence intervals for AUC were estimated using bootstrapping (20 000 samples).

Due to the presence of outliers and non-normality of the distribution of many variables, non-parametric coefficients (Spearman's rho) were reported in the analysis of troponin I correlates.

Differences were considered significant at $p<0.05$. R software (R Core Team, 2014) and SPSS (ver. 23) were used for statistical calculations.

## RESULTS

The whole cohort of 79 studied patients was divided into two groups. Sixty nine (87.3%) patients survived and ten patients died (12.7%) during the in-hospital period. For the period of discharge from hospital until

the end of 1-year follow-up none of the patients died, as confirmed by telephone interviews. Neither cardiac events nor hospitalisations due to cardiovascular reasons were reported by interviewed patients.

The group of patients who survived did not differ significantly from the group of deceased patients in the median values of most of the pre-surgery measures including age and the degree of hepatic insufficiency defined by MELD score. Between group comparisons of all the other parameters are available in Table 1.

All patients underwent ECG on the first day after the transplantation. We found no signs of ischemia in the ECG curves. In some, but not in all of the patients, ECG was repeated on the second and third day, even without evidence of ischemia.

**Table 1. The characteristics of survivors and non-survivors groups**

| Parameter | Survivors | | Non-survivors | | *P* value |
|---|---|---|---|---|---|
| | N | Med (range) | N | Med (range) | |
| Pre-operative patient characteristics | | | | | |
| Age [years] | 69 | 54 (36–64) | 10 | 56.5 (37–61) | 0.447 |
| Sex (F) | 69 | 23 (33.3%) | 10 | 3 (30%) | 1.000 |
| MELD [points] | 69 | 14 (6–27) | 10 | 14 (6–26) | 0.842 |
| Preoperative creatinine [mg/dL] | 69 | 0.9 (0.6–2.4) | 10 | 1.05 (0.4–1.9) | 0.270 |
| HR [$min^{-1}$] | 68 | 72 (53–102) | 10 | 69 (66–97) | 0.946 |
| BPsys [mmHg] | 68 | 106 (110–167) | 10 | 107 (86–132) | 0.776 |
| BPdia [mmHg] | 68 | 58.5 (39–89) | 10 | 59 (48–69) | 0.917 |
| Dialysis [N(%)] | 69 | 6 (8.7) | 10 | 5 (50) | 0.002 |
| Peri-operative parameters | | | | | |
| CI [L/min/$m^2$] | 66 | 3.91 (1.82–8.05) | 10 | 3.9 (2–5.82) | 0.951 |
| SI [L/min/$m^2$] | 66 | 56.50 (20.2–91.6) | 10 | 53.85 (30.3–57.6) | 0.701 |
| sPAP [mmHg] | 68 | 24 (12–32) | 10 | 25.5 (18–38) | 1.000 |
| PAWP [mmHg] | 68 | 13 (5–26) | 10 | 12 (7–16) | 0.680 |
| $SvO_2$ [%] | 67 | 84 (71.8–93.4) | 9 | 81.9 (74.4–89.8) | 0.879 |
| $SaO_2$ [%] | 67 | 98.8 (94.2–100) | 9 | 99.2 (97.4–99.6) | 0.089 |
| Hbmin [g/L] | 69 | 8.6 (5.4–13.7) | 10 | 7.65 (3.9–12) | 0.583 |
| Δ Hb [g/L] | 69 | 2.7 (0–9) | 10 | 3.25 (0.5–8.4) | 0.072 |
| Blood loss [mL] | 67 | 1500 (100–8060) | 10 | 3000 (800–12000) | 0.011 |
| PRBCs [units] | 69 | 2 (0–16) | 10 | 6 (0–26) | 0.002 |
| Adrenaline bolus in reperfusion phase [n(%)] | 69 | 42 (60.9) | 10 | 7 (70) | 0.794 |
| Noradrenaline [n(%)] | 69 | 20 (29) | 10 | 2 (20) | 0.432 |
| Dobutamine [n(%)] | 69 | 20 (29) | 10 | 2 (20) | 0.432 |
| ANHEP [min] | 69 | 156 (75–345) | 10 | 175 (90–270) | 0.364 |
| Skin-to-skin time [min] | 69 | 395 (270–580) | 10 | 475 (365–600) | 0.005 |
| Restrictive fluid therapy [n(%)] | 69 | 20 (29) | 10 | 2 (20) | 0.432 |
| Troponin I concentration | | | | | |
| cTnI-0 [ng/mL] | 64 | 0.02 (0–0.07) | 10 | 0 | 0.796 |
| cTnI-1 [ng/mL] | 69 | 0.08 (0.00–0.87) | 10 | 0.23 (0.01–31.58) | 0.008 |
| cTnI-2 [ng/mL] | 69 | 0.06 (0.00–2.40) | 10 | 0.99 (0.00–37.14) | 0.018 |
| cTnI-3 [ng/mL] | 69 | 0.04 (0.00–1.81) | 10 | 0.23 (0.00–13.43) | 0.186 |
| cTnImax [ng/mL] | 69 | 0.09 (0.00–2.40) | 10 | 1.04 (0.00–37.10) | 0.009 |

MELD, Model of End-Stage Liver Disease; HR, heart rate; BPsys, systolic arterial pressure; BPdia, diastolic arterial pressure; Hbmin, minimal concentration of haemoglobin during surgery; ΔHb, difference between the haemoglobin concentration before surgery and the lowest concentration registered during operation. PRBCs, packed red blood cells; ANHEP, anhepatic functional phase time; Skin-to-skin time, time of surgery; cTnI, troponin I concentration (determined before surgery, on the first, second and third day after the surgery and maximal value). **Hemodynamic parameters determined immediately before surgery**: CI, cardiac output index; SI, stroke volume index; sPAP, systolic pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; $SvO_2$, mixed venous oxygen saturation, $SaO_2$, arterial oxygen saturation. *P* values for continuous variables were obtained using Mann-Whitney test. Differences in distributions of binary variables (sex, dialysis, restrictive fluid therapy, adrenaline, noradrenaline, dobutamine) were tested using $Chi_2$ or exact Fisher's test – depending on the distribution of expected counts.

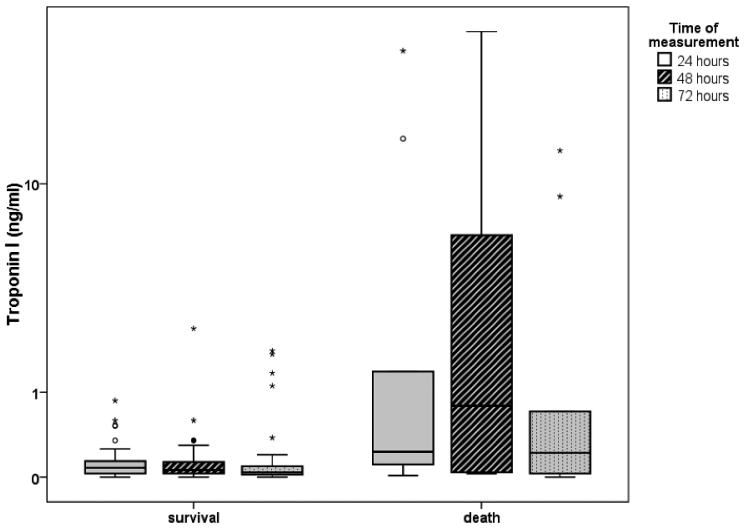


**Figure 1. Plasma cardiac troponin I concentration determined after the surgery according to the treatment outcome (survivors *vs* non-survivors).**
Vertical axis values were square-root transformed for clarity of illustration.

Cardiovascular events occurred rarely during the peri- and post-operative period. In one patient, an episode of asystole with the need of short time cardiopulmonary resuscitation occurred during the liver graft reperfusion. The patient survived. In another patient (without cTnI elevation in early post-surgery period) atrial fibrillation occurred on the fourth day after the transplantation. Electrical cardioversion was successful but the patient died some days later due to sepsis. Yet in another patient, sudden cardiac arrest occurred immediately after the end of the session of physical rehabilitation as a result of ventricular fibrillation on the sixth day after LTx. Cardiopulmonary resuscitation was ineffective. In this patient, on the second day after the operation, cTnI level increased to the maximal value of 6.2 ng/mL. Signs of ischemia in ECG and segmental left ventricular contractility abnormalities in echocardiography were not observed at that time. The patient did not consent to coronary angiography and the eventual invasive treatment. In other 8 patients, the cause of death was multiple organ failure in the course of sepsis.

Among all the studied patients, the values of cTnI level in the blood samples collected prior to surgery did not exceed the cut-off point determined by kit producer (producer range: 0–0.07 mg/mL, mean value in studied group 0.02±0.02 ng/mL). Maximum cTnI levels observed post-surgery exceeded that criterion value in the majority of cases: 43 (62.3%) patients from the survival group and 8 (80.0%) of the dead patients (no significant difference). Notably, there was also no significant difference in cTnI concentration, determined before surgery.

However, significant differences were observed in the peri- and post-operative period. Deceased patients had significantly higher median values of cTnI concentration determined 24 and 48 hours after surgery. Levels of cTnI were also significantly higher when maximal observed values were compared. Since between group differences were most pronounced on day 1 and for the maximum cTnI levels (Table 1, Fig. 1), these two variables were used for further ROC analysis.

ROC analysis was applied to determine the AUC and optimal cut-off values of cTnI levels for predicting all-cause mortality. In the first analysis, the measurements collected on day 1. were used as a predictor. The AUC was 0.759 (bootstrap 95% CI 0.564–0.923, Fig. 2). The cTnI cut-off value of 0.215 ng/mL resulted in the sensitivity of 60.0%, specificity of 87.0%, positive predictive value (PPV) of 40.0%, and negative predictive value (NPV) of 93.8%.

The second ROC analysis was based on maximal cTnI values. Obtained AUC values were comparable (0.755, bootstrap 95% CI 0.559–0.926), however, the optimal cut-off value was much higher than in the previous analysis and amounted to 1.79 ng/mL. This classificator had the sensitivity of 50.0%, specificity of 98.6%, positive predictive value (PPV) of 83.3% and negative predictive value (NPV) of 93.2%.

Due to large confidence intervals of AUC, it is not possible to decide which of the two classifiers performs better. However, cTnI level estimated on day 1. has a clear practical advantage over maximum cTnI – it is available earlier and does not require repeated measurements. That is why further analysis of cTnI correlates focused on day 1. measurements only.

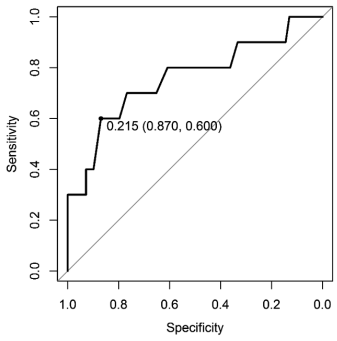


**Figure 2. Receiver operating characteristic curve for cTnI (ng/mL) level on 1. post-surgery day as predictor of all-cause mortality.**

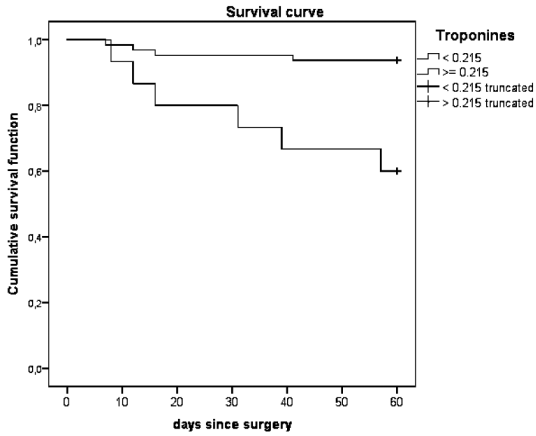


**Figure 3. Kaplan-Meier plot illustrating deaths in two groups selected using optimal cut-off value of plasma cardiac troponin I concentration established in ROC analysis.**
Since all deaths occurred within the first 56 days post-surgery, the horizontal axis was truncated at 60 days.

**Table 2. Statistically significant correlates of troponin I concentration determined on the 1st day after surgery**

| | cTnI-1 | | |
|---|---|---|---|
| | N | Spearman's rho | *P* value |
| Age [years] | 79 | 0.227 | 0.044 |
| MELD [points] | 79 | 0.278 | 0.013 |
| BPsys [mmHg] | 78 | 0.240 | 0.034 |
| SI [L/min/m²] | 79 | 0.278 | 0.013 |
| CI [L/min/m²] | 76 | 0.325 | 0.004 |
| Bloodloss [mL] | 76 | 0.303 | 0.008 |
| Hbmin [g/L] | 79 | –0.296 | 0.008 |
| PRBCs [units] | 79 | 0.319 | 0.004 |
| ANHEP [min] | 79 | 0.268 | 0.017 |
| Skin-to-skin time [min] | 79 | 0.430 | <0.001 |

MELD, model of end-stage liver disease; BPsys, systolic arterial pressure; SI, stroke volume index; CI, cardiac output index; Hbmin, minimal concentration of haemoglobin during surgery; PRBCs, packed red blood cells; ANHEP, anhepatic functional phase time; Skin-to-skin time, surgery time (BPsys, SI, CI – determined immediately before surgery)

Kaplan-Mayer plot (Fig. 3) illustrates the temporal distribution of deaths in the studied sample. Kaplan-Mayer statistics were not reported here, as patients were classified into two groups based on the optimal cut-off score determined using the same group of patients and the same dependent variable.

All the biochemical and hemodynamic variables significantly correlated with the troponin concentration determined 24 hours after the surgery (cTnI-1) are listed in Table 2. The most important predictor cTnI-1 was surgery time followed by amount of transfused packed red blood cells, basic stroke volume index, and cardiac output index. Weaker correlation was observed for anhepatic functional phase time, minimal concentration of haemoglobin during surgery (Hbmin), packed red blood cells (PRBCs) used for transfusion, systolic arterial pressure, cardiac output index (CI) and stroke volume index (SI) (last three parameters determined immediately before surgery).

## DISCUSSION

According to the guidelines of the European Society of Cardiology, the LTx is classified as a group of surgical procedures with a high risk of cardiovascular complications (the risk is estimated to be > 5%) (Poldermans *et al.*, 2009).

The course of the liver transplantation is often related to: severe blood loss and transient reduction of the preload during cross-clamping of the portal circulation (anhepatic functional phase), partial clamping of the inferior vena cava, the risk of hemodynamic complications, and acute myocardial injury. Therefore, the patients referred for LTx should undergo precise cardiac diagnostics, including coronary angiography in selected cases. It is important not only as part of the risk assessment preceding the surgical procedure, but also in the context of the lifetime immunosuppressive therapy following the transplantation. It was shown that the consequences of immunosuppressive therapy may include hypertension, dyslipidaemia, and new-onset diabetes, considered as classical risk factors for atherosclerosis (Howell *et al.*, 1960; Fellström, 2001; Berzigotti *et al.*, 2005; Balla & Chobanian, 2009; Kockx *et al.*, 2010).

Elevation of cTnI in patients undergoing orthopaedic and vascular surgery was demonstrated in literature. The incidence of perioperative ischemia was estimated to be 14–47% and the incidence of myocardial infarction to be 1–26%. These episodes were asymptomatic on numerous occasions (Higham *et al.*, 2004; Chong *et al.*; 2009; Flu *et al.*, 2010).

Available data draws attention to the fact that most of the acute coronary episodes in the perioperative period occurred within the first 2–3 days after the surgery, when part of the patients received analgesics. Some patients are intubated at this time or in a condition which prevents complaints. Incidentally, symptoms associated with necrosis of the heart muscle can be explained by the presence of postoperative complications (e.g. hypotension and/or tachycardia which may be associated with blood loss or hypovolemia) (Devereaux *et al.*, 2005).

Many papers indicate an elevated postoperative troponin concentration to be an independent predictor of mortality, particularly during the first year after non-cardiac surgery. In their meta-analysis of 16 papers, Levy *et al.* suggested, for example, that the majority of these patients are likely to have some degree of underlying coronary artery stenosis. It is therefore justifiable to consider the management with known beneficial secondary prophylactic cardiac interventions like aspirin, beta-blocker and statin for patients with a perioperative troponin elevation who survived the hospital period (Levy *et al.*, 2011).

In the VISION Study, the peak postoperative fourth-generation plasma cardiac troponin T (cTnT) measurement during the first 3 days after non-cardiac surgery allowed to predict a 30-day mortality and substantially improved risk stratification (Devereaux *et al.*, 2012; Szczeklik & Devereaux, 2012).

The fact that peripheral vascular and orthopaedic surgery is often performed in elderly patients' populations needs to be taken into account. Patients with liver cirrhosis comprise mainly middle-aged population. The mean age of patients in our study did not exceed 55 years of age. They were asymptomatic and the significant coronary artery disease was unlikely. Therefore, the elevation of cTnI in more than half of the patients in the perioperative period was rather surprising. At the same time, the predictive status of these measurements in LTx patients remains unknown.

It should be emphasized that both groups of the studied patients did not differ significantly in the incidence of risk factors (including diabetes) and good systolic and diastolic function of the left ventricle was noted in both groups (as evidenced by the comparison of the mean values of both of the relevant echocardiographic parameters).

Most investigators chose to measure troponin I instead of cTnT because of the lower impact of renal insufficiency on the result of the test in comparison with cTnT measurements (Jaffe, 2006). At the time when our study group was formed, cTnI was used as standard testing procedure in our hospital laboratory.

Ischemia was found in none of the patients according to the ECG conducted on the first day after the transplantation. Unfortunately, only a few patients had ECG performed serially in successive days. Nevertheless, if the ECG results were available, even then the records showed no characteristics of myocardial ischemia.

As stated above, there were no significant differences in cTnI concentration determined before surgery. De-

ceased patients, in comparison with those who survived, had significantly higher median values of subsequently determined cTnI (day 1, 2) level, and median maximum values of the parameter (0.09 *vs* 1.04 ng/mL, $p$=0.009). Nonetheless, no median basic value of cTnI was observed before the surgery. Significant differences were found in the surgery time; it was significantly longer in the group of patients who died. In addition, within this group the blood loss was significantly greater and followed by a greater number of PRBCs units transfused. This suggests that elevated cTnI level should be considered as a predictor of mortality risk after LTx. It should be pointed out once again that all of the patients underwent pre-transplant cardiovascular testing that excluded major coronary artery disease. Therefore, the objective was to find other potential factors which may have influenced the outcome.

We took into account only selected clinical, biochemical and hemodynamic parameters in our analysis. It is clear that the list of variables which potentially affected the outcome of liver transplantation could be much longer. What was discovered was that the degree of hepatic insufficiency defined by MELD score, anhepatic functional phase time, blood loos, PRBCs transfused, minimal haemoglobin concentration in the course of the operation, basic SI and CI were significantly correlated with maximal troponin I concentration. The surgery time was the most important predictor of the increase in cTnI levels in studied patients.

Patkowski *et al.* identified, among others, cold and warm ischemic times (integral parts of liver transplantation) to be the prognostic factors predicting the postoperative course and 1-year survival among liver transplant recipients in a group of 215 patients (cold ischemic time – the time from the beginning of donor liver perfusion up to the insertion of the liver into the recipient; warm ischemic time – the time from the insertion of the liver into the recipient up to the graft reperfusion) (Patkowski *et al.*, 2006).

In an interesting paper, which included 20 Chinese cirrhotic patients, Hei *et al.* observed the dynamic changes of serum creatine kinase (CK), its MB fraction (CK-MB), and cTnI concentration during liver transplantation. Variables were recorded on seven occasions: immediately after the induction of anaesthesia, 15 minutes before the onset of the anhepatic phase, 30 minutes after the onset of the anhepatic phase, 15 and 30 minutes after the graft reperfusion (respectively), at the end of the operation, and 24 hours after surgery. CK and CK-MB increased continuously during the operation and afterwards. Thirty minutes after graft reperfusion, cTnI declined significantly and remained low by the end of operation. Nonetheless, it did significantly increase 24 hours after the operation ($p$<0.01). CO and ejection fraction did not correlate with cTnI level (Hei *et al*, 2006). In our material, CI and SI measured just before the surgery significantly correlated with maximal cTnI concentration.

The significance of cTnI elevation following the transplantation is difficult to assess, especially considering the acuity of such patients. Snipelinsky *et al.* showed in a group of 78 patients that those with elevated TnT concentration were found to have a higher mortality rate (all-cause and cardiac) than those with either normal or intermediate levels. Authors suggested that troponin I evaluation following LTx may aid in the prognostic assessment of these patients (Snipelinsky *et al.*, 2013).

Observations made by Siniscalchi *et al.* are also most interesting as they discovered that elevated early postoperative cTnT concentrations were associated with a greater decrease in GFR and increased incidence of acute kidney injury in the first week after the transplantation. It is noteworthy that the statistical association was stronger for cTnT than for MELD (Siniscalchi *et al.*, 2012).

Coss *et al.* in the group of 230 patients who underwent LTx were investigating the risk factors of cardiac episodes in post-transplant period. They found out that the pre-transplant increased troponin levels, apart from diabetes and a history of cardiovascular disease, alone or in combination, were strongly associated with the occurrence of cardiovascular events in median 8.2 years follow-up. Interestingly, they accepted a troponin I level >0.07 ng/mL as the cut-off point for myocardial injury (Coss *et al.*, 2011).

In our study we employed ROC curve analysis to determine the optimal cut-off value of cTnI for both day 1. and maximal TnI levels. Both cut-off scores obtained (0.215 and 1.79, respectively) exceeded significantly the value of 0.07 ng/mL recommended by Siemens. Even though our results did not provide empirical data allowing to choose between the two measures of TnI increase, it is clear that day 1. troponin offers a significant practical advantage: it can be assessed earlier than maximal TnI level and it does not require repeated measurement.

A potential limitation of our study is the lack of echocardiography examination performed after liver transplantation in all patients with elevated cTnI to assess segmental left ventricular contractility. Myocardial infarction is the most common perioperative complication in major non-cardiac surgery associated with a poor prognosis. The monitoring of cardiac biomarkers in high-risk patients, both prior to and 48–72 hours after a major surgery, is therefore recommended. Devereaux *et al.* recommended to broaden the definition of myocardial infarction in the perioperative period by the outcome of echocardiography demonstrating new segmental wall motion abnormalities (Devereaux *et al.*, 2011). In the study group an echocardiogram was performed only in 15 patients and proved no segmental wall motion abnormalities in any of them. However, it is not possible to determine the number of patients with perioperative acute myocardial infarction. Multivariate models could not be estimated due to the limited sample size and low number of critical events (10 deaths) (Ploeg van der, 2014). Future studies are, therefore, needed to establish unique contribution of the studied predictors in explaining cTnI elevation.

The results of our study suggest that the value of cTnI assessed 24 hours post-surgery could be a reliable predictor of death following LTx surgery with optimal cut-off value of 0.215 ng/mL. The surgery time was the most important predictor of cTnI elevation.

## REFERENCES

Balla A, Chobanian M (2009) New-onset diabetes after transplantation: a review of recent literature. *Curr Opin Organ Transplant* **14**: 375–379. doi: 10.1097/MOT.0b013e32832dbb98

Berzigotti A, Bonfiglioli A, Muscari A, Bianchi G, Libassi S, Bernardi M, Zoli M (2005) Reduced prevalence of ischemic events and abnormal supraaortic flow patterns in patients with liver cirrhosis. *Liver Int* **25**: 331–336

Bolliger D, Seeberger MD, Lurati-Buse GAL, Christen P, Rupinski B, Gurke L, Filipovic M (2009) Preliminary report on the prognostic significance of preoperative brain natriuretic peptide and postoperative cardiac troponin I in patients undergoing major vascular surgery. *Anesth Analg* **108**: 1069–1075. doi: 10.1213/ane.0b013e318194f3e6

Coss E, Watt K, Pedersen R, Dierkhising R, Heimbach J, Charlton M (2011) Predictors of cardiovascular events after liver transplantation: a role for pre-transplant serum troponin levels. *Liver Transpl* **17**: 23–31. doi: 10.1002/lt.22140

Chong CP, Lam QT, Ryan JE, Sinnappu RN, Lim WK (2009) Incidence of post-operative troponin I and 1-year mortality after emergency orthopaedicburgery in older patients. *Age and Ageing* **38**: 168–174. doi: 10.1093/ageing/afn231

Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, Wang CY, Garutti RI, Jacka MJ, Sigamani A, Srinathan S, Biccard BM, Chow CK, Abraham V, Tiboni M, Pettit S, Szczeklik W, LuratiBuse G, Botto F, Guyatt G, Heels-Ansdell D, Sessler DI, Thorlund K, Garg AX, Mrkobrada M, Thomas S, Rodseth RN, Pearse RM, Thabane L, McQueen MJ, VanHelder T, Bhandari M, Bosch J, Kurz A, Polanczyk C, Malaga G, Nagele P, Le Manach Y, Leuwer M, Yusuf S; Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators (2012) Association between postoperative troponin I levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* **307**: 2295–2304. doi: 10.1001/jama.2012.5502

Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH (2005) Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review. *CMAJ* **173**: 779–788

Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Rao-Melacini P, Chrolavicius S, Yang H, Macdonald C, Avezum A, Lanthier L, Hu W, Yusuf S; POISE (PeriOperativeI-Schemic Evaluation) Investigators (2011) Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med* **154**: 523–528. doi: 10.7326/0003-4819-154-8-201104190-00003

Fellström B (2001) Risk factors for and management of post-transplantation cardiovascular disease. *Bio Drugs* **15**: 261–278

Filipovic M, Jeger R, Probst C, Girard T, Pfisterer M, Gürke L, Skarvan K, Seeberger MD (2003) Heart rate variability and cardiac troponin I are incremental and independent predictors of one-year all-cause mortality after major noncardiac surgery in patients at risk of coronary artery disease. *J Am Coll Cardiol* **42**: 1767–1776

Flu W-J, Schouten O, Kuijk J-P, Poldermans D (2010) Perioperative cardiac damage in vascular surgery patients. *Eur J VascEndovasc Surg* **40**: 1–8. doi: 10.1016/j.ejvs.2010.03.014

Hei Z, Liu D, Luo C, Li S, Ma W, Luo G (2006) Perioperative changes of ventricular function and three indicators of myocardial injury during orthotopic liver transplantation. *Chinese Med J* **119**: 939–943

Higham H, Sear JW, Sear YM, Kemp M, Hooper RJL, Foex P (2004) Peri-operative troponin I concentration as a marker of long-term postoperative adverse cardiac outcomes – a study in high-risk surgical patients. *Anaesthesia* **59**: 318–323

Howell WL, Manion WC (1960) The low incidence of myocardial infarction in patients with portal cirrhosis of the liver: a review of 639 cases of cirrhosis of the liver from 17731 autopsies. *Am Heart J* **23**: 259–260

Jaffe AS, Babuin L, Apple FS (2006) Biomarkers in acute cardiac disease: the present and the future. *J Am Coll Cardiol* **48**: 1–11

Kockx M, Jessup W, Kritharides L (2010) Cyclosporin A and atherosclerosis-cellular pathways in atherogenesis. *Pharmacol Ther* **128**: 106–118. doi: 10.1016/j.pharmthera.2010.06.001

Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y, Weissman C, Mosseri M (2003) Association of cardiac troponin I, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol* **42**: 1547–1554

Levy M, Heels-Ansdell D, Hiralal R, Bhandari M, Guyatt G, Yusuf S, Cook D, Villar JC, McQueen M, McFalls E, Filipovic M, Schünemann H, Sear J, Foex P, Lim W, Landesberg G, Godet G, Poldermans D, Bursi F, Kertai MD, Bhatnagar N, Devereaux PJ (2011) Prognostic value of troponin and creatine kinase, muscle and brain isoenzyme measurement after noncardiac surgery. A systematic review and meta-analysis. *Anesthesiology* **114**: 796–806. doi: 10.1097/ALN.0b013e31820ad503

Pateron D, Beyne P, Laperche T, Logeard D, Lefilliatre P, Sogni P, Moreau R, Langlet P, Elman A, Bernuau J, Valla D, Erlinger S, Lebrec D (1999) Elevated circulating cardiac troponin I in patients with cirrhosis. *Hepatology* **29**: 640–643

Patkowski W, Zieniewicz K, Skalski M, Krawczyk M (2009) Correlation between selected prognostic factors and postoperative course in liver transplant recipients. *Transplant Proc* **41**: 3091–3102. doi: 10.1016/j.transproceed.2009.09.038

Ploeg van der T, Austin PC, Steyerberg EW (2014) Modern modelling techniques are data hungry: a simulation study for predicting dichotomous endpoints. *BMC Med Res Methodol* **14**: 137. doi: 10.1186/1471-2288-14-137

Poldermans D, Bax JJ, Boersma E, De Hert S, Eeckhout E, Fowkes G, Gorenek B, Hennerici MG, Iung B, Kelm M, Kjeldsen KP, Kristensen SD, Lopez-Sendon J, Pelosi P, Philippe F, Pierard L, Ponikowski P, Schmid JP, Sellevold OF, Sicari R, van den Berghe G, Vermassen F (2009) Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery; European Society of Cardiology (ESC). *Eur Heart J* **30**: 2769–2812. doi: 10.1093/eurheartj/ehp337

Siniscalchi A, Gamberini L, Mordenti A, Bernardi E, Cimatti M, Riganello I, Toccaceli L, Vecchiatini T, Diamanti M, Faenza S (2012) Postoperative troponin T elevation as a predictor of early acute kidney injury after orthotopic liver transplantation: a preliminary retrospective study. *Transpl Proc* **44**: 1999–2001. doi: 10.1016/j.transproceed.2012.06.039

Snipelisky D, Donovan S, Levy M, Satyanarayana R, Shapiro B (2013) Cardiac troponin I elevation predicts mortality in patients undergoing orthotopic liver transplantation. *J Transplant* **2013**: 252838. doi: 10.1155/2013/252838

Szczeklik W, Devereaux PJ (2012) Troponin T level and mortality risk after noncardiac surgery: practical implications of the VISION study. *Pol Arch Med Wewn* **122**: 499–503 (in Polish)

Watt K, Coss E, Pedersen R, Dierkhising R, Heimbach J, Charlton M (2010) Pretransplant serum troponin I levels are highly predictive of patient and graft survival following liver transplantation. *Liver Transpl* **16**: 990–998. doi: 10.1002/lt.22102