**DOI:10.23873/2074-0506-2018-10-2-87-97**

# Morphofunctional evaluation of liver grafts obtained from standard donors and expanded criteria donors

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*Received: 28 September 2017*

*Accepted for publication: 8 February 2018*

*Donor organ shortage stimulated an active use of donors with expanded evaluation criteria. The main evaluation method was a histological examination of liver graft biopsy specimens before (time-zero biopsy) and after reperfusion (time-1 biopsy).*

*Severe ischemic and reperfusion injuries among recipients who received a liver graft made 20.4%, and 16.6%, respectively.*

*The study showed no impact of small droplet, medium droplet, or even large droplet steatosis (less than 50%) on graft reperfusion injury.*

**Keywords:** standard donors, expanded criteria donors, histological evaluation of hepatic graft, steatosis

**Khubutiya M.Sh., Zimina L.N., Galankina I.E., et al. Morphofunctional evaluation of liver grafts obtained from standard donors and expanded criteria donors. *Transplantologiya. The Russian Journal of Transplantation.* 2018;10(2):87–97. (In Russian). DOI:10.23873/2074-0506-2018-10-2-87-97**

ALT, alanine aminotransferase

AP, alkaline phosphatase

AST, aspartate aminotransferase

BP, blood pressure

GGTP, gamma-glutamyl transpeptidase

GRI, graft reperfusion injury

MELD, Model for End-Stage Liver Disease Evaluation, a scoring system for assessing the severity of chronic liver disease

PAS, periodic acid-Schiff

## Introduction

The shortage of donor organs stimulated an active use of donors with expanded evaluation criteria. However, that has led to the increased number of both transplantations, and complications such as a poor graft function, biliary complications, etc. [1]. The expanded criteria donor (ECD) category includes: donors over 60 years old, those with a body mass index over 27, those having large-droplet steatosis over 15%;; hemodynamically unstable donors (BP below 60/40 mmHg for 60 minutes or longer), those who stayed on mechanical lung ventilation for more than 5 days, and those having a high serum Na concentration (≥ 165 mmol/L) [2].

Liver dysfunction for the first 7−10 days after transplantation is a fairly common phenomenon and has numerous causes. The most significant of these are large-droplet steatosis, early post-transplant graft rejection, the initial condition of the recipient, and vascular and biliary surgical complications that developed in the early postoperative period [3, 4].

Morphological examination of the graft is the "golden standard" to assess its condition and predict the postoperative course. The studies conducted for many years in N.V. Sklifosovsky Research Institute for Emergency Medicine have shown the important role of morphological studies of biopsy specimens, namely, the "time-zero biopsy" performed at

organ retrieval before the transplantation, and "time-1 biopsy" performed after organ reperfusion and the inclusion of the transplanted organ into the bloodstream [5].

The comparison of morphological parameters of biopsy at time-0 when the organ is removed from the donor and at time-1 after the organ inclusion in the recipient's bloodstream makes it possible both to evaluate the graft, and to assess the recipient's preparation for surgery. Besides, it is precisely the graft biopsy after reperfusion that makes it possible both to assess the organ morphological structure at its function recovery, and to predict the postoperative outcome [5].

The donor liver assessment using the primary liver graft biopsy including the comparison of the organ macro- and microscopic patterns revealed an unjustified graft discarding in 32 (36.5%) of 85 cases. An urgent morphological study would increase the donor pool and the number of transplantations by 10% [6, 7].

**The aim of the study was** to make a comparative analysis of morphological and functional parameters of liver grafts from optimal versus marginal donors (ECDs) at organ removal and after its inclusion in the blood flow, to determine the relationship between the graft morphological and reperfusion injury, and to predict the postoperative recovery of the graft function.

## Material and methods

Of 85 liver grafts, 44 (51.8%) were obtained from optimal donors, and 41 (48.2%) were from ECDs. The optimal donor group included those donors who, after being declared brain-dead, had the variables (blood enzymes, electrolytes, etc.) and constants (age, hepatosis, etc.) consistent

with the acceptable levels, and the ECD group (marginal donors) included those in whom the parameters exceeded the acceptable values. The mean donor age was 38 ± 9 years old; there were 59 men (69.4%), and 26 women (30.6%). At liver removal, a cooled Custodiol preservative solution in a volume of 300 ml/kg/body weight was used for preservation. Any complications in a recipient, i.e. hepatic venous or arterial thromboses, were recorded as potential factors of parenchymal injuries and those recipients were excluded from the study.

The liver resistance to reperfusion injury, and the graft functional recovery in a recipient were assessed by studying the peak concentrations of cytolysis enzymes: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltranspeptidase (GGTP), alkaline phosphatase (AP) for 72 hours, monitoring the blood coagulation parameters for up to one week, and the time of normal bile secretion recovery within 2 weeks [6].

To assess the morphological pattern, the obtained before reperfusion liver biopsy specimen (time-zero biopsy) was divided into two fragments. On one fragment fixed with 10% neutral formalin or without fixation (immediate biopsy), the sections were obtained on the freezing microtome and stained with Oil Red-O (ORO), hematoxylin and eosin (H&E) for the estimation of fat content. The second fragment of the liver was embedded in paraffin. The paraffin sections were stained with H&E, picrofuxine up to Van Gieson's method. Glycogen was studied by PAS reaction with the control sections being treated with amylase. HBs antigen in hepatocytes, the elastic fibers and copper-protein complexes were detected by Shikata stain. Puncture biopsy specimens were examined using the above described techniques [6].

Moreover, they investigated bioptic samples taken after reperfusion (1-biopsy), that were processed the same way as bioptic samples taken before reperfusion.

The degree of hepatocyte steatosis in the absence of small droplet or large droplet fatty degeneration was defined according to the amount of affected hepatocytes and graded as zero (0) (less than 1/3 hepatocytes affected), grade 1 (from 1/3 to 2/3 of hepatocytes affected), grade 2 (over 2/3 of hepatocytes being affected). (Fig. 1−4).

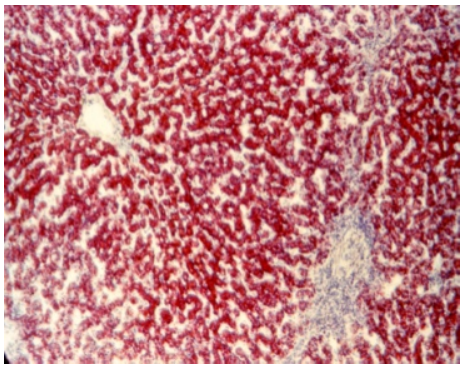

**Fig. 1. Fatty degeneration (ORO-stained, magnification x 80)**

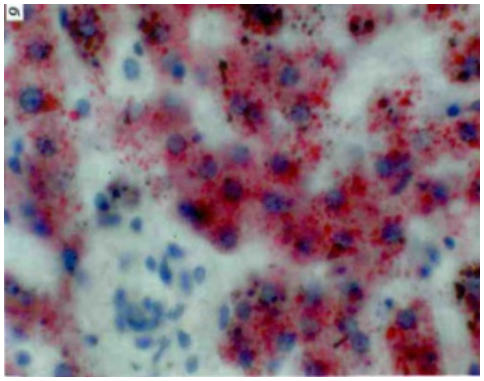

**Fig. 2. Focal small droplet fatty degeneration (ORO-stained, magnification x 200)**

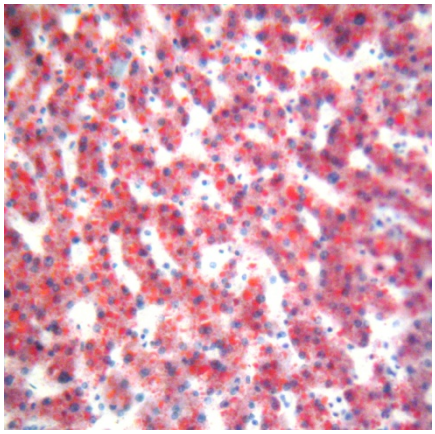

**Fig. 3. Diffuse small droplet fatty degeneration with individual large droplet collections (ORO-stained, magnification x 200)**

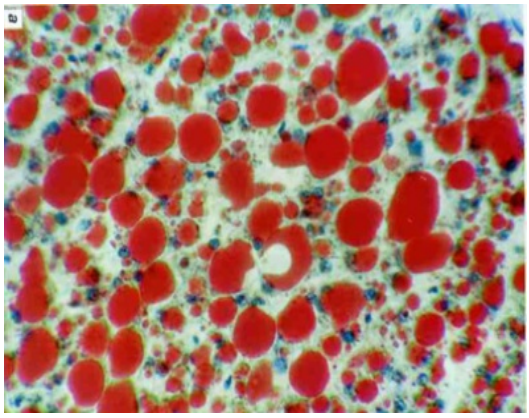

**Fig. 4. Diffuse large droplet fatty degeneration (ORO-stained, magnification x 200)**

The necrosis was assessed as grade 0 without necrotic damage, or 1 with monocellular or individually grouped of necrotizing hepatocytes being present in the field of vision (Fig. 5−7), grade 2 at small-focal necrosis (Fig. 8), and grade 3 at large-focal necrosis of hepatocytes (centrilobular, bridge-shaped) (Fig. 9−11).

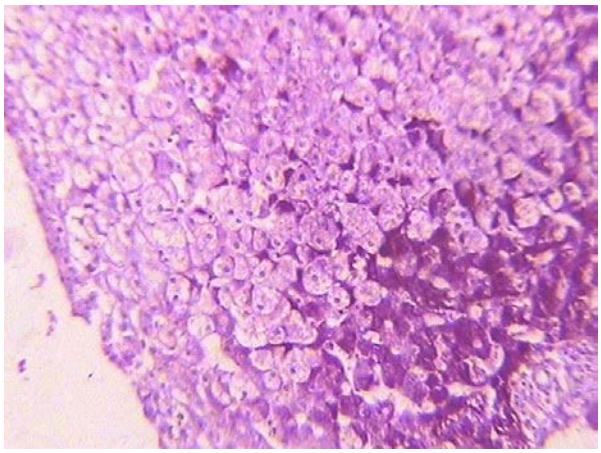

**Fig. 5. Uneven distribution of glycogen (PAS reaction, magnification x 200)**

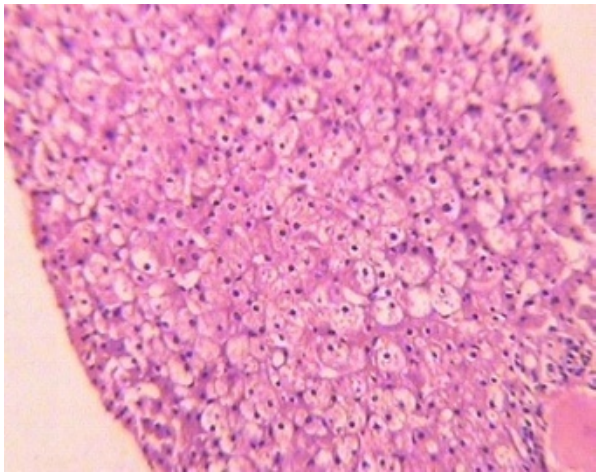

**Fig. 6. Focal vacuolar degeneration of hepatocytes (H&E-stained, magnification x 80)**

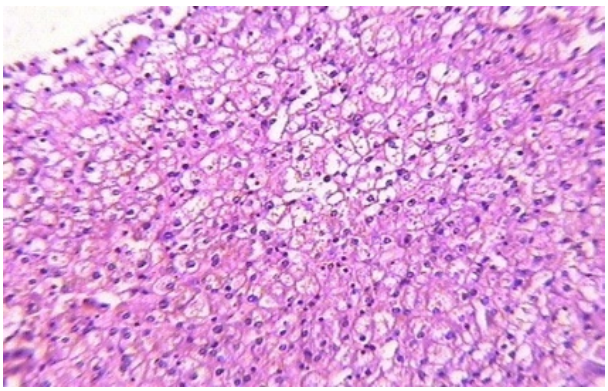

**Fig. 7. Ischemic abnormalities in hepatocytes: vacuolar and ballooning degeneration (magnification x 80, H&E-stained)**

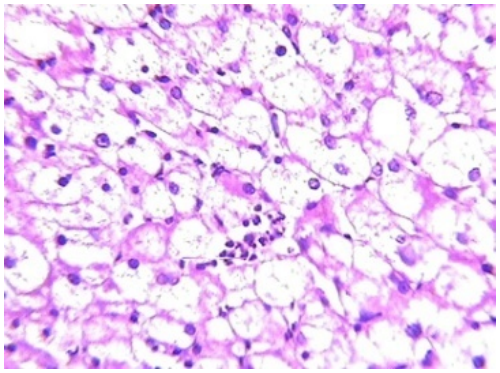

**Fig. 8. Trabecular disintegration (H&E-stained, magnification x 200)**

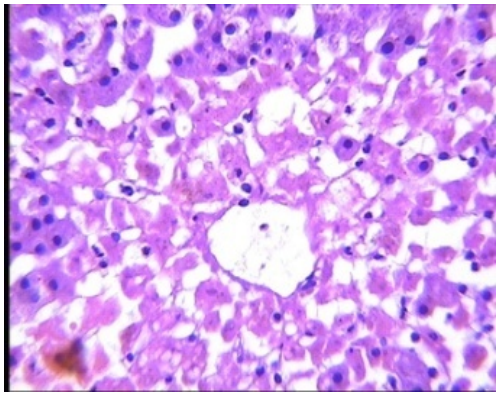

**Fig. 9. Centrilobular (bridge-shaped) necrosis (H&E-stained, magnification x 200)**

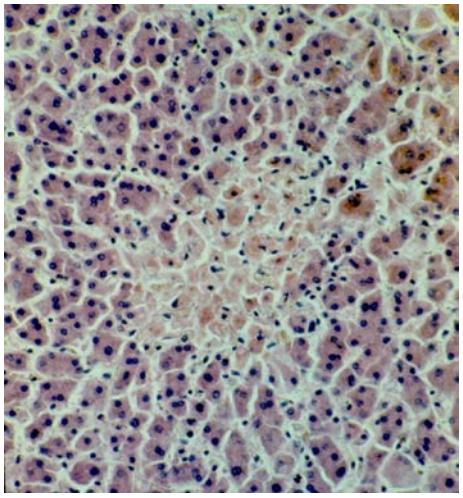

**Fig. 10. Necrosis of zone III hepatocytes (H&E-stained, magnification x 200)**

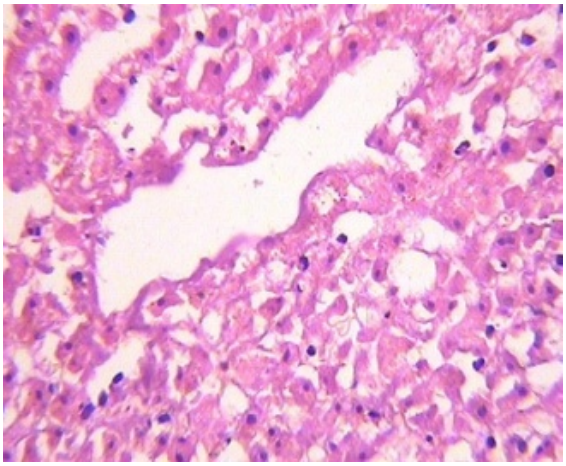

**Fig. 11. Coagulation necrosis of hepatocytes (H&E-stained, magnification x 80)**

The study was performed basing on the results of histological biopsy material analysis. To compare the morphological changes in the liver between the recipients who received the organ from standard and marginal donors, the correlation coefficient between individual histological signs was determined. The statistical significance was defined as $P \leq 0.05$.

**Study results**

Table 1 shows the results obtained at primary and secondary liver biopsies on presented parameters. But it was not always possible to reflect completely the histological diagnosis of "ischemic injury" of the liver, for example: such histostructural abnormalities as hepatocyte degeneration changes (vacuolar, balloon, fatty), glycogen content in hepatocytes, disrupted histoarchitectonics, and trabecular disintegration.

**Table 1**. **Morphological assessment of primary and secondary biopsies of liver grafts from 44 optimal donors**

| Morphological parameters of liver graft. Histological diagnosis | Before reperfusion | | After reperfusion | | Δ% |
|---|---|---|---|---|---|
| | abs. | M ± m,% | abs. | M ± m,% | |
| Ischemic injury | 18 | 40.9 ± 1.1 | 44 | 100 ± 0.0* | + 159 |
| Glycogen content in hepatocytes | 42 | 95.5 ± 0.6 | 4 | 9.1 ± 0.7* | - 87.8 |
| Hepatocyte necroses | 11 | 22.7 ± 1.0 | 37 | 84.1 ± 0.7* | + 270 |
| Damage to liver histocellular structure | 15 | 34.1 ± 1.1 | 24 | 59.1 ± 1.1* | + 73.3 |
| Large droplet steatosis | 7th | 15.9 ± 0.8 | 8 | 18.21 ± 0.9 * | + 13.8 |
| Small droplet steatosis | 19 | 40.9 ± 1.1 | 22 | 47.7 ± 1.2* | + 14.2 |
| Mixed steatosis | 7th | 15.9 ± 0.8 | 11 | 25.0 ± 1.0* | + 57.2 |
| Cholestasis | 6th | 13.6 ± 0.3 | 6th | 13.6 ± 0.3 | 0 |
| Infiltration of portal tracts | 15 | 36.4 ± 1.1 | 24 | 52.2 ± 1.2* | + 43.7 |
| Fibrosis | 29 | 65.9 ± 1.0 | 27th | 63.6 ± 1.1 | - 3.4 |

* $P \leq 0.05$, statistical significant

Ischemic alterations manifested themselves in hepatocyte changes with the signs of focal and diffuse balloon and vacuolar dystrophy (see Fig. 5−7). A complete removal of glycogen from hepatocyte cells was found in all "time-1" biopsy specimens after reperfusion (Fig. 12, 13), but the glycogen content had been high enough before the organs were switched in the recipient's bloodstream.

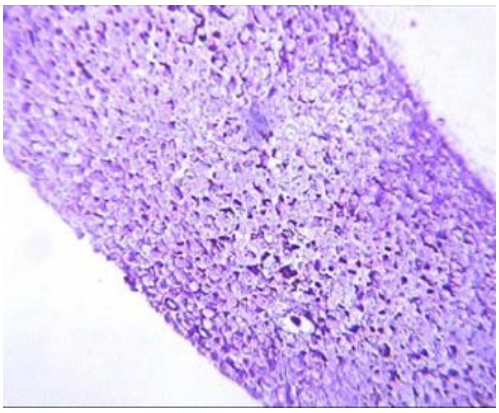

**Fig. 12. The content of glycogen in the liver (PAS reaction, magnification x 80)**

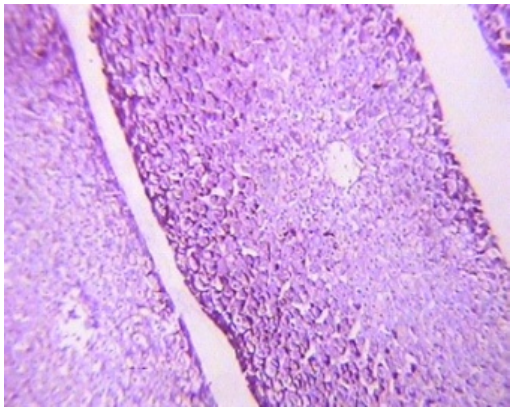

**Fig. 13. A rapid decrease in glycogen, glycogen disappearance from the cytoplasm of hepatocytes after reperfusion (PAS reaction, magnification x 200)**

GRI and ischemic alterations often damaged the liver histoarchitectonics causing trabecular disintegration (see Fig. 8), destructive changes increase in sinusoids (+ 73.3%), which subsequently contributed to appearing dystrophic processes in hepatocytes per se (see Fig. 7, Fig. 14) with the development of balloon dystrophy and coagulation necrosis (+270%), being both monocellular and grouped with granulocyte infiltration (see Fig. 9−11).

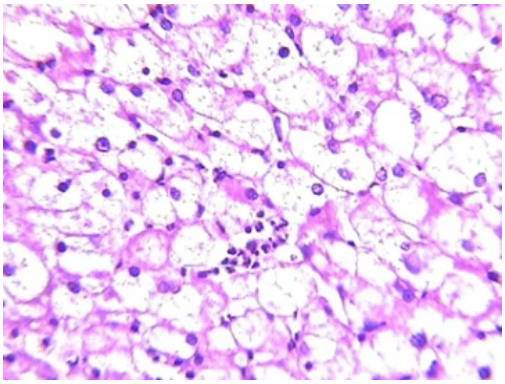

**Fig. 14. Balloon dystrophy of hepatocytes (H&E-stained, magnification x 200)**

Less pronounced abnormalities of liver histoarchitectonics with solitary coagulation necrosis or hepatocyte dystrophy were noted in time-0 biopsies, but much less frequently. The infiltration of portal tracts with mononuclear lymphocytes was seen in 40.1% of cases in the primary time-0 biopsy, but it increased by 52.2% due to granulocyte inclusion after the organ having been switched into the bloodstream. The decreased fibrosis (-3.4%) seen in secondary biopsies was related to the specific nature of the incisional material obtained at primary biopsy with a more pronounced subcapsular fibrosis of the left lobe compared to the liver fragment taken from its deeper layers after the reperfusion.

GRIs were classified as mild, moderate, severe, or critical. They were assessed by measuring the cytolytic ALT and AST enzyme content and defined as light at up to 600 U/L, moderate at 601−2000 U/L, severe at 2001−5000 U/L, and critical at over 5000 U/L.

The distribution of liver grafts according to GRI severity in this group is shown in Diagram 1.

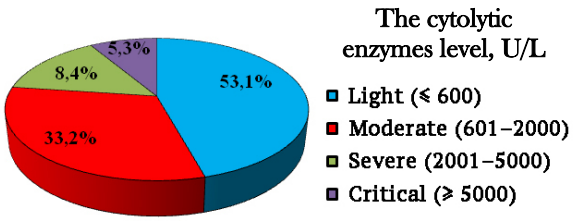


**Diagram 1. The recipient distribution according to GRI severity in the group of those who received the organ from an optimal donor (n = 44)**

Critical and severe GRIs accounted for 13.7% in the group of recipients who received the organ from optimal donors. The results of time-0 and time-1 biopsies of liver grafts obtained from marginal donors are presented in Table 2.

**Table 2. Morphological assessment of primary and secondary biopsies of liver grafts obtained from 41 marginal donors**

| **Morphological parameters of the liver graft. Histological diagnosis** | **Before reperfusion** | | **After reperfusion** | | **Δ%** |
|---|---|---|---|---|---|
| | abs. | M ± m,% | abs. | M ± m,% | |
| Ischemic injury | 17 | 41.4 ± 1.4 | 41 | 100 ± 0.2* | + 140 |
| Glycogen content in hepatocytes | 38 | 92.6 ± 0.8 | 3 | 7.4 ± 0.7* | - 90.9 |
| Hepatocyte necrosis | 14 | 34.1 ± 1.3 | 23 | 56.1 ± 1.4* | + 66.7 |
| Damage to liver histocellular structure | 15 | 36.6 ± 1.3 | 28 | 68.3 ± 1.3* | + 92.2 |
| Large droplet steatosis | 9 | 25 ± 1.4 | 12 | 33.3 ± 1.3* | + 33.2 |
| Small droplet steatosis | 17 | 47.2 ± 1.4 | 23 | 63.8 ± 1.3* | + 35.2 |
| Mixed steatosis | 6 | 16.7 ± 1.0 | 7 | 19.4 ± 1.1* | + 16.2 |
| Cholestasis | 2 | 4.9 ± 0.3 | 2 | 4.9 ± 0.3 | 0 |
| Infiltration of portal tracts | 14 | 38.9 ± 1.4 | 18 | 50 ± 1,4* | + 28.5 |
| Fibrosis | 19 | 52.7 ± 1.4 | 17 | 47.2 ± 1.4 | - 10.4 |

***** $P \leq 0.05$, statistical significant

Reperfusion injuries of liver cells in the form of edema, vacuolization, balloon dystrophy were identified in 41.4% of time-0 biopsies, and in 41 cases (100%) after the liver was switched in the recipient's bloodstream. Glycogen content in hepatocytes was noted in 38 samples (92.6%); but after reperfusion, it retained only in 3 (7.4%), and was absent in the rest transplanted organs.

The liver graft ischemic and reperfusion injuries of various severity in the form of necrosis were revealed in secondary biopsy samples in 56.1% of the transplanted organs which resulted in increased hepatocyte necrosis by 66.7%. Both in primary and secondary biopsy specimens, the cholestasis signs were noted only in 2 (5.5%), but the graft ischemic and reperfusion injury did not affect their increase. Prior to the switching the liver graft into the bloodstream, the portal tract infiltration was detected in 38.9% of cases, and it increased after the reperfusion by 28.5% due to granulocytes.

The minimal morphological changes in the graft after reperfusion were seen in 29 recipients of organs either from optimal or from marginal donors. They are included in Tables 1 and 2, but not allocated separately. The causes of the changes were different, perhaps, associated with the optimization of surgical technique, the reduction of the warm and cold ischemia time, better recipient condition, etc. It should be noted that severe GRIs were noted in 17.1% and 13.7% of recipients who received the organ from marginal and optimal donors, respectively.

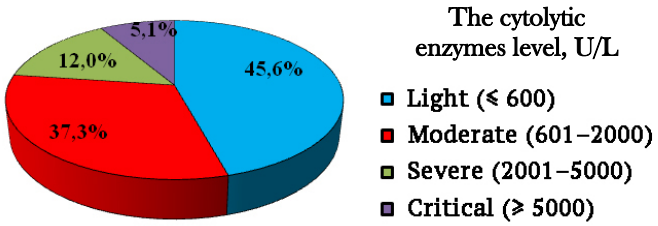


**Diagram 2. The GRI severity indicators in the recipients who received the organ from marginal donors (n = 41)**

Severe and critical injuries were observed in the early postoperative period; morphologically, they were seen as centrilobular and bridge-shaped coagulation necroses of hepatocytes after reperfusion. That can become a useful indicator for the evaluation of graft function recovery; and in a relatively unaffected recipient, the transplanted organ acquires an additional potential for functional recovery. That was confirmed by other investigators in making histological examinations after reperfusion [6, 7]. The extent of liver graft ischemic and reperfusion injury in the recipients of the organ from standard donors and ECDs did not depend on the steatosis severity found in time-0 biopsy specimens.

## Discussion

The problems associated with GRI have been widely discussed in literature. A number of authors find no critical liver injury at histological examination or evaluate the injury as insignificant [8].

The attitude to steatosis has been the most heatedly debated. Hepatocytes with fatty degeneration in GRI are most prone to release free lipids, providing a substrate for lipid peroxidation and the formation of free

radicals [9]. In primary ischemic injury, new injuries occur after the liver has been switched into recipient's bloodstream, as a rule, even in absent steatosis. Only 29% of recipients in both groups did not show a significant worsening of the histological pattern after GRI.

The recipients who received an organ from standard donors, showed an increased number of individual monocellular or small-focal necroses in the biopsy specimens; and in the second group, there were single-cell and even bridge-shaped necroses of hepatocytes revealed in a few cases among the patients with critical or severe GRI. Hepatocyte injury in the form of centrilobular necrosis in the recipients of both the first and second groups correlated with the signs of severe and critical GRI, regardless of time-0 biopsy results. Despite the increased number of recipients who received the organ with large droplet steatosis from marginal donors, we noticed no increase in the centrilobular necrosis amount nor in GRI severity, although the steatosis degree was assessed from 10 to 60%.

A number of investigators believe that the GRI associated with large droplet steatosis occurs due to the mechanical occlusion of the sinusoidal microcirculatory region, which can lead to hepatocyte ischemic necrosis and increase the damage area through involving the humoral mechanisms in this process [10, 11].

GRIs were manifested by hepatocyte ischemic injury of focal and diffused nature, by a rapid decrease in their cytoplasm glycogen down to complete disappearance, by disrupted histoarchitectonics with the trabecular disintegration and sinusoid destruction, monocellular to widespread necrosis of hepatocytes. However, those abnormalities were observed in the recipients of the first and second groups and did not correlate with the steatosis severity. The increased number of biopsies with large droplet

steatosis after reperfusion could apparently explained by an uneven distribution of fatty-degeneration-affected hepatocytes throughout the liver graft.

The increased incidence of small droplet steatosis after reperfusion in the recipients of liver graft from optimal donor and ECDs can be explained by the prolonged inhibition of mitochondrial β-oxidation of fatty acids, which most often occurs both during preservation and reperfusion when several mechanisms are switched on: the ischemic injuries and the effect of under-oxidized radicals [4, 12].

Some researchers consider that small droplet steatosis potentially threatens the graft functional recovery [13]. In our study, we did not find an expected correlation either with the GRI severity, or with subsequent functional disorders.

Because of a small number of observations and a low incidence of primary graft non-function, hepatocyte necrosis or apoptosis was determined both in primary biopsies and after reperfusion. However, the absence of such abnormalities before organ retrieval indicates that they can be detected quite quickly after reperfusion [14]. Our study has shown that extended necrosis is detected after GRI, although the mechanism of its occurrence is not clear [15, 16].

Glycogen as the main energy substrate was present in hepatocytes of 80 primary biopsies (94.1%), but after reperfusion, it was completely absent in 72 grafts (84.7%), and its content was extremely decreased in 13 (15.3%).

Mild and moderate ischemic and reperfusion injuries were seen in 38 (86.3%) recipients who had received the organ from the standard criteria donors and in 34 (82.9%) recipients of the organ from marginal donors. Severe and critical GRIs were noted in 6 (13.6%) and 7 (17.1%) graft biopsy

specimens, respectively, and were morphologically manifested by centrilobular necrosis. Almost all biopsies displayed a combination of large-droplet and small-droplet steatosis. All time-0 biopsies showed focal ischemic lesions, including 7 cases (8.2%) where we identified the injury progression up to colliquated or coagulation necrosis.

Despite the increased number of recipients who had received the organ affected by large droplet steatosis from marginal donors, we did not notice an increase in GRI severity, although the steatosis degree was from 10 to 60%.

Thus, the study showed that the ischemic injuries, as well as steatohepatosis detected in the biopsy material before the organ removal contribute to the development of ischemic and reperfusion injuries, but do not always lead to the liver graft dysfunction. The graft with moderate steatosis and vacuolization of hepatocytes can function successfully without specific therapy. However, if the primary biopsy reveals centrilobular necrosis of the liver, then such an organ should be discarded from transplantation. Trabecular disintegration, focal infiltration, glycogen absence, monocellular and small-focal necroses, and small droplet steatosis of hepatocytes do not significantly affect the graft function recovery. Massive centrilobular and multilobular hepatocyte necroses were seen only among the recipients with critical reperfusion injury in whom the disease severity exceeded MELD score of 24. But the ischemic and reperfusion injuries of the liver did not correlate with the donors' characteristics (standard or marginal) and did not even depend on the steatosis degree found in the primary biopsies.

An accurate evaluation of the liver graft remains a rather difficult task even in experienced hands, but, structurally, the morphological alteration

revealed after reperfusion could predict the liver graft functional recovery and postoperative course more accurately [6].

## Conclusions

1. Large-droplet steatosis up to 50% of graft hepatocytes does not correlate with an increased incidence of centrilobular necrosis and the severity of reperfusion injuries.

2. Small droplet steatosis affects neither the severity of reperfusion injury, nor subsequent functional disorders.

3. Centrilobular necrosis in the recipients of both the first and second groups correlated with severe and critical reperfusion injuries regardless time-0 biopsy results.

4. The recipient disease severity exceeding MELD score of 24 poses is an impact both on the increase of centrilobular and multilobular hepatocyte necroses number and on the morphofunctional pattern of severe and critical graft reperfusion injuries.

**Conflict of interests.** Authors declare no conflict of interests.

**Financing.** The study was carried out without external funding.

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