



( ) , . .

-

, 2016.



UNIVERSITY OF NI<sup>TM</sup>  
FACULTY OF MEDICINE



Gordana (D) Petrovi , spec. dr med.

CLINICAL AND BIOCHEMICAL  
CHARACTERISTICS OF NON-ALCOHOLIC  
FATTY LIVER DISEASE AS  
MANIFESTATIONS OF METABOLIC  
SYNDROME

DOCTORAL DISSERTATION

Ni–, 2016. godina



## Подаци о докторској дисертацији

: . , ,

: -

: . (NAFLD)  
 ,  
 5 %  
 .  
 NAFLD;  
 I148M PNPLA3 NAFLD.  
 . 55  
 , ,  
 (UZ)  
 NAFLD (MS).  
 31 . 16  
 . -18 (CK-18)  
 .  
 PNPLA3 rs738409  
 PCR-RFLP .  
 NAFLD  
 , , AST, ALT, GGT, CRP,  
 , HOMA-  
 IR (p<0,001), LDL (p<0,05), HDL  
 (p<0,05).  
 NAFLD

, DM 2, MS  
 (p<0,001).  
 UZ  
 II III (p<0,01) UZ  
 I , ,  
 DM 2 (p<0,05).  
 MS (p<0,001)  
 NAFLD.  
 CK-18 NASH  
 (p<0,05). NAFLD,  
 G PNPLA3 ,  
 AST ALT  
 (p<0,05).  
 . PNPLA3 I148M  
 NAFLD.

: ,  
 :

: -18, PNPLA3 ,

: 616.36-008.6-071

: B 550,

: **CC BY-NC-ND**

## Data on Doctoral Dissertation

Doctoral  
Supervisor:

Proffesor Goran Bjelakovi , gastroenterologist, University of Ni-,  
Faculty of medicine

Title:

Clinical and biochemical characteristics of non-alcoholic fatty liver  
disease as manifeastations of metabolic syndrome

Abstract:

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease, characterized by the accumulation of triglycerides in more than 5% of hepatocytes in the absence of alcohol intake harmful to the liver.

The aims of the study were to determine the clinical and biochemical characteristics of patients with NAFLD, to establish the association between polymorphism of the I148M variant in the PNPLA3 gene and NAFLD.

The study encompassed 55 patients, who were diagnosed with NAFLD and metabolic syndrome (MS), based on anamnestic data, anthropometric measurements, blood test results, and abdominal ultrasound. The control group included 31 healthy participants. Liver biopsy was performed in 16 patients. Measuring of CK-18 concentration in blood plasma was done by ELISA. For the detection of the PNPLA3 rs738409 polymorphism, we used a PCR-RFLP method.

The patients with NAFLD had statistically significantly higher mean values of AST, ALT, GGT, triglycerides, urates, CRP, ferritin, FBG, insulin, HOMA-IR ( $p < 0.001$ ), LDL ( $p < 0.05$ ), whereas the levels of HDL were higher in the control group ( $p < 0.05$ ). MS as well as obesity, hypertension, and type 2 DM were statistically more present in patients with NAFLD comared to the control group ( $p < 0.001$ ) and in patients with grade 2 and 3 ultrasound findings fatty liver in

relation to grade 1 ( $p < 0.05$ ).

A univariate logistic regression analysis showed that MS statistically significantly ( $p < 0.001$ ) increases the probability of the occurrence of NAFLD.

The highest mean value of plasma CK-18 was found in patients with NASH, and it was statistically higher with regard to patients with common steatosis ( $p < 0.05$ )

Patients with NAFLD, homozygotes for the G allele PNPLA3 gene polymorphism, had statistically significantly higher activities of AST and ALT compared to the carriers of a normal allele ( $p < 0.05$ ).

NAFLD is the hepatic manifestation of MS. PNPLA3 I148M polymorphism is a predisposing factor for the development of NAFLD.

Scientific Field:

Medical science, internal medicine

Scientific  
Discipline:

Gastroenterology and hepatology

Key Words:

non-alcoholic fatty liver disease, metabolic syndrome, cytokeratin 18, PNPLA3 gene polymorphism

UDC:

616.36-008.6-071

CERIF  
Classification:

B 550, Gastroenterology

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Commons  
License Type:

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## Садржај

1.	.....	1
2.	.....	4
2.1.	.....	4
2.2.	NAFLD .....	5
2.3	NAFLD .....	8
2.3.1	.....	8
2.3.1.1.	NAFLD .....	8
2.3.1.2.	NAFLD .....	10
2.3.1.3.	NAFLD .....	12
2.4.	NAFLD .....	18
2.4.1.	š      ð .....	19
2.4.2.	.....	19
2.4.3.	, .....	20
2.4.4.	, .....	20
2.4.4.1.	.....	20
2.4.4.2.	.....	22
2.4.4.3.	.....	23
2.4.4.4.	.....	24
2.4.4.5.	.....	24
2.4.5.	.....	25
2.4.5.1.	<i>Patatin like phospholipase domain containing -3</i> (PNPLA3) .....	25
2.5.	.....	27
2.6.	NAFLD .....	29
2.7.	NAFL NASH .....	36
2.8.	.....	41
2.9.	NAFLD .....	44
2.9.1.	.....	44
2.9.2.	NAFLD .....	45
2.9.2.1.	.....	46
2.9.2.2.	.....	48
2.9.2.3.	.....	49
2.9.2.4.	-3 .....	50
3.	.....	51
4.	.....	53
5.	.....	54
5.1.	.....	55
5.2.	.....	56



5.2.1.	.....	57
5.2.1.1.	, <i>body mass index</i> -BMI .....	57
5.2.2.	.....	57
5.2.3.	.....	58
5.2.4.	.....	58
5.2.5.	.....	59
5.2.6.	.....	59
5.2.7.	.....	60
5.2.8.	.....	60
5.2.9.	18 .....	61
5.2.10.	.....	63
5.2.10.1.	DNK .....	64
5.2.10.2.	PCR-RFLP PNPLA3 rs738409 (C10109G) .....	65
5.2.10.3.	DNK .....	66
5.2.10.4.	PNPLA3 rs738409 (C10109G) .....	67
5.2.11.	.....	68
6.	.....	69
6.1.	(NAFLD) .....	69
6.2.	NAFLD .....	69
6.3.	NAFLD .....	71
6.3.1.	NAFLD .....	71
6.3.2.	NAFLD .....	72
6.4.	NAFLD .....	74
6.5.	NAFLD.....	76
6.6.	, NAFLD .....	78
6.7.	, NAFLD BMI .....	80
6.8.	, NAFLD 2 .....	82
6.9.	, NAFLD NAFLD .....	85

6.10.	.....	90
6.10.1.	.....	96
6.10.1.1	.....	96
6.11.	NAFLD	
	.....	99
6.12.	18	104
6.12.1.	ROC	
	CK-18	
	NASH NAFLD	111
6.13.	,	
	PNPLA3 rs738409 (C10109G) .....	114
7.	.....	121
8.	.....	144
9.	.....	150

## 1. УВОД

(NAFLD, . *Non-alcoholic Fatty Liver Disease*)

(NASH, . *Non-alcoholic Steatohepatitis*),  
(HCC, engl. *hepatocellular carcinoma*).

(TG) 5%

NAFLD

NAFLD

(MS),

(IR)

NAFLD.

NAFLD

NAFLD.

30% 75%

NASH

HCC.

NASH

NASH : , ( ), .  
NAFLD .  
,  
,  
(ATP) ,  
,  
NAFLD.

I148M *patatin like phospholipase domain containing-3* (PNPLA3) .  
PNPLA3 ,  
148.

NAFLD .  
, :  
, , , ,

NAFLD .  
,  
š õ .

78% NAFLD NASH

(UZ) *imaging* NAFLD

*imaging* (MR),  
(MRS) (TE) (*FibroScan*).

, NAFLD

NAFLD, NASH .  
NASH  
HCC  
NAFLD.  
(NAFL, . Non-  
*alcoholic Fatty Liver*) NASH, -18 (CK-18)  
NASH,  
š ð  
NAFLD,  
NASH,  
NAFLD,

## 2. ПРЕГЛЕД ЛИТЕРАТУРЕ

### 2.1. Дефиниција и подела неалкохолне масне болести јетре

[1].

NAFLD (DM) 2, NAFLD [2, 3].

1980. Ludwig š õ ,

[4].

[5, 6]. NAFLD

[7, 8]. NAFLD :

- ( 5% )  
*imaging*
- (>21  
>14 )

[9].

[9].

, , 5%

, NASH ( / )

( ),

[1, 8, 9].

NAFLD , NASH 23%

10-15 HCC. NASH

. NASH

о [10, 11, 12].

NAFLD C, Wilsonove ,

( , , Mauriac Weber Christian

), ,

, ( , ,

, .),

( )

( , by-pass

), .

NAFLD [9, 13].

## 2.2. Епидемиологија NAFLD

, NAFLD .

NAFLD 6,3% 33%, 20%

, NASH 3% 5%.  
 NAFLD MS NAFLD  
 [14].  
 )  
 NAFLD [15].  
 NAFLD , ,  
 , NAFLD  
 NAFLD  
 ,  
 (CT), MR MRS [14].  
 , Williams .  
 (SAD) 46%, NASH  
 12,2% , 29,9% UZ  
 ( 58,3%  
 35,1%), (74% NAFLD 22% NASH),  
 ( 58,9%), ( ),  
 (BMI, . *body mass index*) [16].  
 Lee ., NAFLD ,  
 589 , 51%. 30%  
 10,4% NASH 2,2%  
 [17].  
 Zois .  
 , 31% 39% [18].



NAFLD

*Dionysos*  
NAFLD

20% 25% <sup>[5]</sup>.

12

91% (85% 98%), NASH- 37% (24% 98%)

1,7% (1% 7%) <sup>[2]</sup>.

Dvorak . DM 2

NAFLD 79%. 93%

NAFLD

(BMI, (OS) ) <sup>[19]</sup>. , Leite

NAFLD 69% DM 2 <sup>[20]</sup>.

Caballeria . 766 ,

NAFLD 33% 20%

<sup>[21]</sup>.

NAFLD.

NAFLD,

I148M PNPLA3 ,

<sup>[22]</sup>. NAFLD MRS,

30%. 45% .

NAFLD 33% 24% <sup>[23]</sup>.

, Friht .

NAFLD ,

( 60 ), ( 50 60 )

( 50 ),

NAFLD,

<sup>[24]</sup>.

NAFLD

26.527 31%

16% [25].

NAFLD, NASH,  
NAFLD [14].

### 2.3. Етиологија NAFLD

#### 2.3.1. Ризични фактори

2, MS [2, 3, 5, 6, 8, 9, 26, 27]. NAFLD, DM

##### 2.3.1.1. NAFLD и гојазност

(SZO) 2014. , 1,9  
18 0,6  
BMI 30 kg/m<sup>2</sup>  
, MS [28].  
20 , [29].  
, : DM 2,  
,  
( , , , , )  
) IR HCC.  
BMI 40 kg/m<sup>2</sup> 50% 60%  
[30, 31].  
NAFLD.  
57% 74% , 90%  
NASH [2, 27].

HCC

, HCC

, NAFLD [14, 32]

HCC Fassio . 22

NASH, BMI [33]

, MS, DM 2 NAFLD, NASH

[34]

, [28]

), ( ),

( )

( )

NASH [34]

BMI

. BMI

. BMI

25 kg/m<sup>2</sup>. BMI : BMI Ö 18,5 kg/m<sup>2</sup>

, BMI 18,5 kg/m<sup>2</sup> 24,9 kg/m<sup>2</sup>, BMI 25

kg/m<sup>2</sup> 29,9 kg/m<sup>2</sup> BMI × 30,0 kg/m<sup>2</sup>

kg/m<sup>2</sup> BMI. BMI 30 kg/m<sup>2</sup> 34,99  
 , BMI 35 kg/m<sup>2</sup> 39,99 kg/m<sup>2</sup>  
 BMI 40 kg/m<sup>2</sup>  
 [28, 35].  
 BMI 30 kg/m<sup>2</sup>  
 [28, 29].  
*Prospective Studies*  
 Collaboration BMI 5 kg/m<sup>2</sup> 25 kg/m<sup>2</sup>,  
 30% [35].  
 BMI,  
 ,  
 . MS  
 , DM 2,  
 (KVB) NAFLD [28, 36, 37].  
 NAFLD/NASH  
 , NASH [15].  
 BMI,  
 , [28] NAFLD [27].

### 2.3.1.2. NAFLD и дијабетес

347

2030.

NAFLD ( )  
 , IR, MS [19, 20, 27, 38].  
 NAFLD .  
 ,  
 NAFLD DM 2.

DM 2

[39].

NAFLD 69% 79%

[16, 19, 20]. NAFLD 27%

, 43%

, 62% DM 2 [40].

NAFLD NASH

Williams . 2011.

NAFLD NASH

74% vs. 46% 22% vs. 12%.

NASH

[16].

DM 2

NAFLD, , HCC [39].

NASH

NAFLD :

(GGT)

(AST)/ (ALT) [41].

Leite . 2011.

NAFLD DM 2. 78%

NASH, 36% 60%

(HDL ) ALT

NASH.

DM

2 UZ [42].

Younosi .  
 NAFLD  
 (25% vs. 10%, p=0,04)  
 (56,8% vs. 27,3%, p=0,001), (18,2% vs.  
 2,3%, p =0,02) [43].

Targher .  
 NAFLD DM 2  
 , (p<0,001)  
 NAFLD. NAFLD  
 ,  
 MS.  
 NAFLD DM 2  
 [44, 45].

### 2.3.1.3. NAFLD и метаболички синдром

80 .  
 MS. Reaven 1988.  
 X, DM 2,  
 , IR [46]. De Fronzo Ferrannini  
 ,  
 IR [47].  
 , X  
 ,  
 , DM 2 .  
 ,  
 , [48, 49]. MS  
 NAFLD, *sleep* ,

MS 4,7 NAFLD

[50]. Treeprasertsuk , HDL NAFLD

( , )

(63,7%), 73,8% [51].

NAFLD,

3,6 [52].

Chituri 87% NAFLD

(94% , 82%

50% ) 98%

IR, NASH

C [53].

1998.

MS,

SZO

MS.

1. *The National Cholesterol Educational Programm (NCEP) Adult Treatment Panel III (ATP III),* 2001. A (AHA, engl. American Heart Association) 2005.

NCEP/ATP III HDL [49,50] MS ( 1).

1.  
NCEP/ATP III.

	× 102 cm × 88 cm
	× 1,7 mmol/l,
HDL	< 1,03 mmol/l < 1,29 mmol/l
	× 130 mmHg / × 85 mmHg,
	× 5,6 mmol/l, dijabetes melitus 2

2. (IDF, *International Diabetes Federation*) 2005.

( ) , [54] ( 2).



2.

IDF.

	× 94 cm × 80 cm
	× 1,7 mmol/l,
HDL	< 1,03 mmol/l < 1,29 mmol/l
	× 130 mmHg / × 85 mmHg,
	× 5,6 mmol/l, dijabetes melitus 2

MS.

MS NHANES (National Health and Nutrition Examination Survey) 5% , 22%  
60% [55]. Weiss  
50% [56].  
MS  
7% 20 29 42% 60 69  
[57].  
13% 18%  
[58].  
MS :  
▪ ( 44% 50 MS),  
▪ ( MS ,  
)

■ ( , - - ),

■ HDL , ,

■ ( MS 7,4%) 1 cm

■ ( , ).

NAFLD [58, 59] , IR, NASH

MS.

IR [60].

[61]

IR

(VLDL, . Very Low Density Lipoproteins) [62], (HDL, . High Density Lipoprotein)

(LDL, . Low Density Lipoprotein).

[63].

NASH [64].

NAFLD

NAFL NASH.

MS [65].

MS KVB [66].

IR,

MS [34].

: (TNF- ), (IL)-6, IL-8 C- (CRP). Ridker Women Helth Study, 14.719 C- (hs-CRP engl. high sensitive- C reactive protein) >3mg/l

KVB [67]. Zimerrman BMI hs-

CRP 20% [68].

NAFLD.

BMI 10%

hs-CRP

MS

DM 2.

,

MS

DM 2.

500-1000

,

0,5 1 kg

.

7% 10%, 6 12

(30 )

,

DM 2

e [69].

MS,

( ,

, , ),

MS.

MS,

MS [70].

### 2.4. Патогенеза NAFLD

NAFLD

,

,

... [71]

#### 2.4.1. Теорија „два ударца“

NAFLD NASH ... [72]

... [73]

... [73, 74]

HCC, ... [75]

#### 2.4.2. Инсулинска резистенција

... [76]

PPAR *Peroxisome proliferator-activated receptor gamma* [77]

-1c (SREBP-1c, *Sterol regulatory element binding protein-1c*) jetri [78]. PPAR

PPAR ( ) , ,  
 , IR [79]. SREBP-1c  
*de novo* [78].

### 2.4.3. Липидна акумулација, стеатоза јетре

. ,  
*de novo* .  
*de novo*, ,  
 / .  
 [80] , 60%  
 , [73].  
 (CoA).  
 CoA,  
 kappa B (NF-kB) [81].  
 B ( po B)  
 (MTP) VLDL .  
 NAFLD MTP/apoB ,  
 [82].

### 2.4.4. Инфламација, стеатохепатитис

#### 2.4.4.1. Цитокини

:  
 , ,  
 [73].

,  
: TNF- , IL-6 .  
NAFLD.  
[83].  
NASH  
NASH,  
NAFLD NASH TNF- [84].  
kappa (IKK- ) [85]  
SREBP-1c,  
, TNF- ,  
TNF- ,  
c  
TNF- , TNF- 1 TNF- 2, TNF- 1  
[75]. Hotamisligil . TNF-  
NASH [86]. NASH  
TNF- TNF-  
NASH [87, 88, 89].  
NASH *pentoxifyllinom* ( TNF- )  
[90].  
(TGF- )  
Hasegawa . TGF-  
NASH [91],

Dass [92].

Mahmoud .

TGF-

NASH [93].

IL-6,

NAFLD

NASH

[84, 94].

2.4.4.2. Адипокини

, ,

NAFLD.

AMP-

, PPAR-

-CoA

[78].

20% 60%

NAFLD

[95].

NASH

, ,

[75, 87].

NAFLD.

NASH,

IR [95, 96].

TNF- ,

-

,

[73].

,

TGF- .

NAFLD,

[97].

, ,



### 2.4.4.3. Оксидативни стрес и митохондријална дисфункција

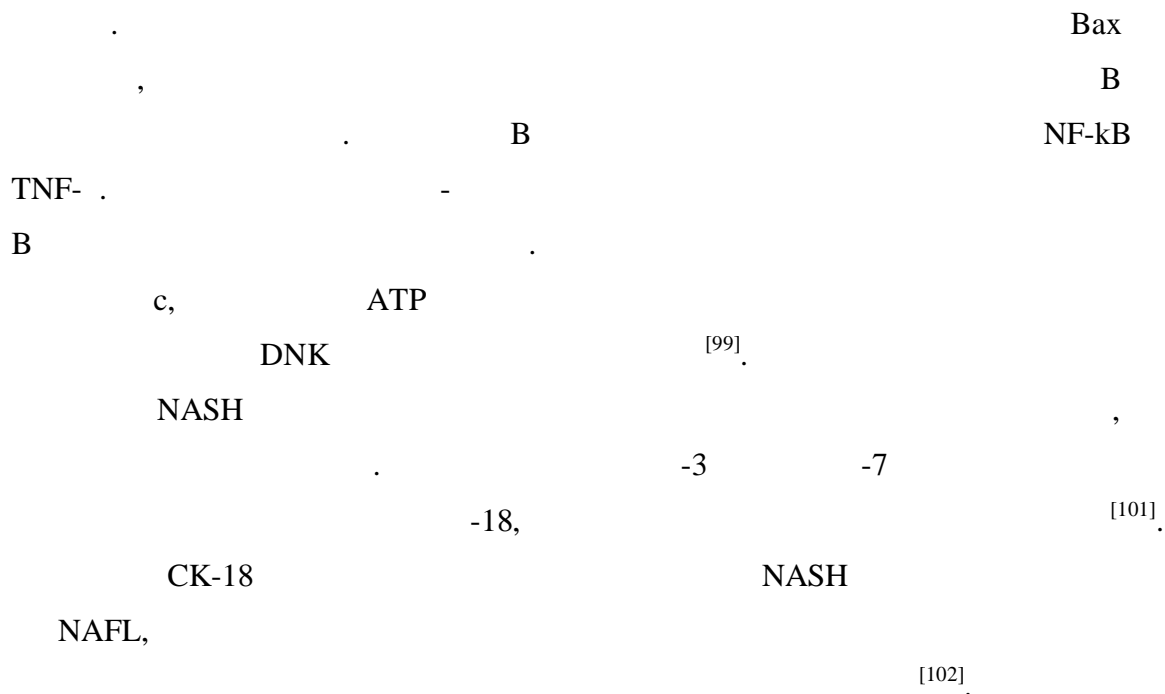
NASH .  
NASH.  
[98] .  
NF-kB  
[81] .  
NF-kB,  
HCC.  
(DNK).  
(MDA) 4-  
(HNE). MDA HNE  
[99] .  
(TNF , IL-6, IL-8, TGF ),  
ATP.  
NAFLD  
*citohrom* P-450E1 (CYP2E1)  
CYP (CYP2E1 CYP4A)

CYP2E1

NASH

[100]

#### 2.4.4.4. Апоптоза хепатоцита



#### 2.4.4.5. Ендоплазматски ретикулум стрес и раст бактерија

NASH

[103]

NAFLD [104].

NAFLD

[105].

*by-passom* NASH

#### 2.4.5. Генетска предиспозиција

NAFLD.

NAFLD

NAFLD

NAFLD,

IR,

[106].

MS NAFLD,

IR,

PPAR

TNF-

[106, 107].

##### 2.4.5.1. *Patatin like phospholipase domain containing-3* ген (PNPLA3)

(GWS, . *Genome wide assotiation study*)

PNPLA3 (SNP rs 738409, I148M),

, NAFLD. Romeo . 2008. ,

DNK , PNPLA3 ,

22,

PNPLA3

148,

. PNPLA3 481 ,  
53 kD 14 .  
I148M PNPLA3  
,  
PNPLA3 [22, 108, 109].  
Romeo .  
G  
PNPLA3  
, BMI,  
,  
NAFLD [22].  
[109].  
,  
NAFLD,  
Speliotes . G rs738409  
,  
[110].  
Valenti .  
NAFLD, I148M 3,3  
NASH [111]. PNPLA3 I148M  
,  
GG 3,24  
3,2 CC  
[112].

Liu . PNPLA3 rs738409  
C>G HCC NAFLD (p<0,0001).  
G ,  
, , , , .  
GG HCC 4  
CC [113].  
I148M  
NAFLD ,  
,  
,  
[108].

## 2.5. Клиничке манифестације и лабораторијски налази

,  
.  
, , , .  
, , , .  
[3, 8].  
,  
NASH  
[114].  
*imaging* ,  
NAFLD [9].  
NAFLD : ALT, AST, (ALP),  
GGT, , (PT)  
(KKS) [115].

3 4 ,  
 ALT AST, AST  
 NASH . AST/ALT  
 1 (bridging/ciroz ) [38].  
 80% NAFLD ,  
 [17, 116]. *Dallas Heart Study*  
 79% NAFLD ALT [23].  
 Mofrad . ALT  
 NAFLD [117]. NAFLD  
 .  
 š ð NAFLD,  
 , , ,  
 :  
 , , ,  
 [118]. ,  
 , AST/ALT>1  
 , NASH  
 , [38].  
 NAFLD

(AASLD, . *American Association for The Study of Liver Diseases*),

[9].  
 ALP NAFLD,  
 NASH [13].  
 ALP NAFLD  
 [119]. AST GGT  
 ALT [58].  
 Tahan . GGT  
 NAFLD . GGT

96,5 U/L, GGT 83%  
 69% [120].

NASH [13].

### 2.6. Дијагноза NAFLD

NAFLD . , , ,  
 60% 94%, 66% 97% [121].  
 NAFLD  
 (š õ ),  
 , [122, 123].  
 UZ  
 NAFLD 40% [124].  
 UZ 30% [125].

[115,126].  
 Lijima . NAFLD UZ  
 , 20  
 NASH  
 [127].  
 , , .  
 CT  
 , ,  
 (HU).

-10 HU - 1

95% 100% [128]

CT [123]

UZ CT

3%. MR, MRS, MR

MRS

NAFLD,

NASH [126]

*FibroScan*,

UZ

kPa *Young-* [129]

50 (8.433 ) AUROC ( .

*area under the receiver operated curve*) 0,87 0,98, 0,94

( 13,01 kPa), 0,75 0,93,

0,84 ( 7,65 kPa) [130]. *FibroScan* ,

Yoneda . *FibroScan* 67

NAFLD .



FibroScan AUROC 0,87,  
0,90 0,99 [131].

NAFLD.

NAFLD,

NAFLD

C282Y

HFE ,

NAFLD

AASLD

21

14

[9].

NAFLD

, *imaging*

NAFLD,

NAFL

NASH

š

õ

NASH [126].

NAFLD,

[132]

[133]

NAFLD

NASH

HCC

NAFLD,

TNF- , hs-CRP,

-6, 3

NASH [115, 126, 134, 135]

NASH

-18. -18

3 7

CK-18. CK-18

, CK18Asp396 ( 30)

30,

(ELISA). ELISA, 65

M65ED, CK-18,

CK-18

ELISA C.

Wieckowska . 44 NAFLD

CK-18 . CK-18

NASH

( : 766 U/L [480-991] vs. 202 U/L [160-258] vs.

215 U/L [150-296], p<0,01). CK-18 395

U/L NASH (AUROC

0,93, 85,7%, 99,9%)<sup>[136]</sup>.

Feldstein .

CK-18

NASH . CK-18

( : 305 (192, 493)

vs. 193 (151, 261); p<0.001), 2 3

0-1 ( : 304 (211, 575) vs. 211 (154, 363); p<0.002).

CK-18 NASH 90%,

80%<sup>[102]</sup>.

Shen . NAFLD CK-18 30, 65

65ED ELISA .

30 65 65ED,

NAFLD ,

NASH (AUROC 0,8). 30

80%

NASH, 65ED 81% 74%

[137].

Joka ELISA

CK-18, 65/ 65ED 30

[138].

/ CK-18

NASH,

1000 NAFLD

CK-18 NASH (AUROC 0,82) [139].

CK-18 60% [140].

CK-18

CK-18

[9].

NASH

NAFLD

NASH

NASH, : HAIR ( , ALT

), NAFIC ( , IV ),

NAFLD ( , BMI, CK-18), NASH

test ( , , , , GGT, , 2

, AST, ALT, 1,

), NASH Diagnostic (CK-18, , ), Palekar

( , , AST, BMI, AST/ALT ) .

:  
 AST/ALT , FIB-4 ( , ( R), AST, ALT), APRI index  
 (AST, R), BARD (BMI, AST/ALT , ), FibroMeter ( ,  
 , , AST, ALT, , R), NAFLD [115, 126,  
 134, 135]

NAFLD [9].  
 Angulo . 2006. NAFLD  
 NAFLD 6 ,  
 (F3-F4)  
 (F1-F2). : ,  
 BMI, , , AST/ALT ,  
 .  
 ,  
 NAFLD  
 0,676, NAFLD  
 -1,455. -1,455,  
 (  
 93%). 0,676,  
 (  
 90%). ,  
 .  
 NAFLD Angulo ..  
 75% ,  
 90% [141].

NAFLD/NASH ,

. NAFLD  
NASH .  
,  
NAFLD/NASH.  
NAFLD NAFLD/NASH.  
NAFLD  
,  
AASLD 2012. , NAFLD  
,  
NAFLD  
NAFLD  
NAFLD  
[9].

**2.7. Патохистолошке карактеристике NAFLD и NASH**

NAFLD NAFLD/NASH.  
[142]  
NAFLD :

■ , ,

AASLD NASH 2002.

NASH.

NASH.

NAFLD ,

NAFLD 5%

[1].

NAFLD

NAFLD

NAFLD 3 ,

[143].

: 5% 33% , 33% 66% >66%

[144].

NAFLD,

NASH

:

) ( NASH<sup>[11]</sup> 3

). NASH

, NASH,

[145]

,

/

8 18

8 18

( ) NASH

,

[146]

18.

mm<sup>2</sup> (*acidophil body index*)

NASH

[142]

( , ,

). (

) *satellitosis*.

( )

( , )

NASH<sup>[146, 147]</sup>

NAFLD/NASH

.

, ( C

).



NAFLD  
NASH.

NASH

3

3

/

, bridging

(NASH

).

,

š

õ

NASH,

[142,146]

[148]

a

NASH

:

,

,

3

8

18,

p62 [149].

NASH,

p

NASH,

p

NASH,

NASH

/

[142]

NAFLD.

Brunt . 1999.  
 NAFLD,  
 NASH, p  
 p  
 ( )  
 ), Brunt . NASH  
 : 1 ( ), 2 ( ) 3 ( ) ( )  
 3.).  
 : 1, 3  
 ; 2, 1  
 / ; 3,  
 4, [144].

3. Brunt .

	*		
1 ( )	1-2	0-1	0-1
2 ( )	2-3	- 3	2 1-2
3 ( )	3	- 3	3 1-2

Легенда:  
 \* ( 1. 33% , 2. 33% 66% , 3. 66 % )

NASH *Clinical Research Network (CRN)* 2005.  
 1 3 : 1  
 3, 1B 3 1C  
 /  
 NASH CRN NAFLD *activity score (NAS)*,  
 p NAFLD  
 NAFLD , p  
 p .

(0-3), (0-3) (0-2),  
 NAS 0-8 ( 4.)<sup>[150]</sup>.  
 NAS×5 p  
 NASH, p NASÖZ šnot NASHö.  
 (borderline). Brunt  
 976 p NASH CRN,  
 75% NASH NAS 5, 28%  
 , 7% šnot NASHö NAS 5 29% NAS 4  
 NASH. NASH  
 NAS<sup>[151]</sup>.

4. p NAFLD activity score.

p		Score
	5%	0
	5%-33%	1
	>33% 66%	2
	>66%	3
	2	0
	2-4	1
	4	2
		3
p		Score
		0
		1
		2

2.8. Природни ток болести и прогноза

NAFLD  
 .  
 AASLD  
 2012. , :  
 ) NAFLD

) NAFLD NASH

) NASH ( NAFL)

[9]

NAFLD

[10, 152, 153]

, NAFLD,

[154, 155]

[156] NAFLD

, NAFLD

[153]

NASH

NAFL,

NASH, NASH

[154]

, NASH

26% 37%

20-30% [33, 145, 157, 158] NASH

20% *Child-Pugh* 45 %

10

NASH HCC (2,6% ) [158]

NAFLD

NASH [7, 38, 59] ( 45

), , AST/ALT 1

(*bridging* / ) [38]

(DM 2, ),

NAFLD [155,159] 2

70%

NASH,  
NASH

[9, 14, 32, 155]

AASLD NASH 2012.

NASH

HCC [9].

40% 62%

NASH

HCC 5 7 [152, 159].

NASH

HCC

[160]. Bugianesi . 2002. 641

HCC. 641 , 6,9% HCC

HCC HCV

, HBV

NASH,

[32]

NASH

[14]

(SRTR) , NASH- *end-stage*

C

NASH,

1,2% 2001. 9,7 % 2009. [12].

, NASH

NASH

[160].

## 2.9. Терапија NAFLD

NAFLD. , NAFLD , NAFLD , NAFLD .

NAFLD š

ō š , :

a) ( / ),

b)

c) [161].

### 2.9.1. Промена животних навика

NAFLD [161, 162].

Musso . 2012.

5% ,

NAFLD,

7% ,

[163].

Promrat .

31 NASH

7% ,

, NAS,

[164].

AASLD 2012. ,  
3% 5% ,  
10% [9].  
NAFLD  
NAFLD  
[165, 166] .  
š õ  
š õ .  
[161] .  
NAFLD IR. 400 kcal,  
30 60 .  
[9, 156, 161] .  
NAFLD,  
NAFLD [9] .

### 2.9.2. Фармакотерапија NAFLD

NAFLD  
DM 2, IR, ,  
NAFLD  
[156] .

NAFLD

2.9.2.1. **Метформин и тиазолидини**

NAFLD,

NAFLD.

NAFLD/NASH

( )

(

) [167].

NAFLD,

, MS

Razavizade

NAFLD.

(1g/ )

(30mg/ )

, IR

(HOMA-IR, *Homeostasis model insulin resistance*

[168].

*assessment index*)

Li

, HOMA-IR,

[169].

TONIC

(500mg

)

(400IU

)

NAFLD.



, ,  
, [170],  
, Haukeland .  
NAFLD  
CT ,  
[171],  
NASH, AASLD 2012.  
NAFLD [9].  
PPAR ,  
PPAR ( )  
( )  
( )  
(TNF- ) ( ).  
NAFLD  
Belforta . 55 2  
NASH  
(45mg/ )  
HOMA-IR  
[172],  
Aithal .  
[173],  
PIVENS  
247 ,

IU/ , n=84 vs. NASH ( 30 mg/ , n= 80 vs. 800 , n=83; 96 ).

Score. NAFLD Activity

, IR,

47%

21%

[79].

)

NASH,

[174].

NASH,

NASH

AASLD 2012.

NASH

### 2.9.2.2. Витамин Е

NASH

NAFLD NASH.

NAFLD

PIVENS

[79]

NASH  
NASH

800 IU/  
, NAFLD

NASH

[9]

NASH,

[175]

### 2.9.2.3. Хиполипемии

NAFLD,  
NAFLD

NAFLD

LDL

NAFLD.

[176]

1980. 2012.

NAFLD/NASH.

[177, 178]

AASLD 2012.

NAFL NASH.

NASH,

[9]

#### 2.9.2.4. **Омега-3 масне киселине и урсодеоксихолна киселина**

Zhu . -3

NAFLD

[179]

AASLD

NAFLD

NAFL NASH.

NAFL NASH [9].

( , , TNF-

, *glukagon-like-peptide-1* ,

-4 .)

NAFL NASH,



- -18. -18 NASH
- CK-18 NAFLD NASH, NAFL NASH,
- I148M PNPLA3
- -18
- -18
- I148M PNPLA3 (AST ALT),
- PNPLA3 I148M
- PNPLA3 I148M NAFLD.

#### 4. ЦИЉЕВИ ИСТРАЖИВАЊА

1. -  
,
2. NAFLD.
3. NAFLD.
4. ( )  
, )  
, NAFLD .
5. -18  
NAFLD.
6. I148M PNPLA3  
NAFLD,  
.
7. I148M PNPLA3  
-18 .

## 5. ПАЦИЈЕНТИ И МЕТОДЕ РАДА

2012.

2014.

55, 32, 23, 24

71.

18

6

54





- Centrifuga
- DNK *QIAcube*, *Qiagen*, *SAD*
- *QIAxcel*, *Qiagen*, *SAD*
- Intel CORE i5
- *Olympus BX50*
- PCR , *Thermal Cycler, Veriti 96-well, Applied Biosystems*, *SAD*
- PCR , *Ehret Mini 2*
- *Rainin*, LTS pipeta 0,5 ó 10 µl, 10 ó 100 µl i 20 ó 200 µl
- "*Immunoscan plus-Labsystem*", *Finland*

## 5.2. Методе рада

,  
.  
.  
.  
.  
.  
.  
6  
.  
(  
,  
, DM 2, ...), : (  
) a  
(  
,  
,  
)

### 5.2.1. Антропометријска мерења

(TV) . ( ) ,  
 , ,  
 (kg),  
 .  
 (cm)  
 .  
 , ,  
 .

#### 5.2.1.1. Индекс телесне масе, *body mass index*-BMI

BMI, kg<sup>2</sup>  
 (kg/m<sup>2</sup>). BMI :

- BMI 18,5 kg/m<sup>2</sup> ,
- BMI 18,5 kg/m<sup>2</sup> 24,9 kg/m<sup>2</sup> ,
- BMI 25 kg/m<sup>2</sup> 29,9 kg/m<sup>2</sup> , ,
- BMI 30 kg/m<sup>2</sup> 34,99 kg/m<sup>2</sup> ,
- BMI 35 kg/m<sup>2</sup> 39,99 kg/m<sup>2</sup> .
  
- BMI 40 kg/m<sup>2</sup> .

#### 5.2.2. Мерење крвног притиска

10 .  
 (SKP)  
 (DKP), (mmHg).

### 5.2.3. Биохемијске анализе крви

,  
 ,  
 .  
 , CRP,  
 , ALP, GGT, (UBIL)  
 (DBIL), , , , ,  
 , (HOL), HDL , LDL  
 , TG, , (PT,  
 (INR, . *international normalized ratio*),  
 ). AST/ALT.  
 HOMA [180] .

$$\text{HOMA IR} = \frac{(\text{mmol/L}) \times (\text{mU/L})}{22.5}$$

NAFLD ( , BMI, (TR),  
 / , AST/ALT ) :  

$$\text{NAFLD} = -1,675 + 0,037 \times \text{AST/ALT} + 0,094 \times \text{BMI (kg/m}^2\text{)} + 1,13 \times \text{TR}$$
 (x109/L) -0,66 x (g/dl)  
 NAFLD -1,45  
 , 0,675 , .

### 5.2.4. Присуство метаболичког синдрома

NCEP/ATPIII [49,50] .

- je
- :
- - ( × 102 cm , × 88 cm ),
  - : × 1.7 mmol/l,
  - HDL : < 1,03 mmol/l , < 1.29 mmol/l ,
  - : × 130 mmHg / × 85 mmHg,
  - : × 5.6 mmol/l, DM 2.

#### 5.2.5. Допунске анализе

- ( )
- B C (HBs Ag, HCV At)
  - (IgG, IgA, IgM)
  - ( , , At),
- 1 .

#### 5.2.6. Ултразвук

ACUSION

Simens X 300 3,5 MHz.

,

,

,

UZ .

- UZ :
- I, UZ ;
  - II, ;
  - III, , [181, 182]

### 5.2.7. Биопсија јетре

### 5.2.8. Патохистолошка анализа

10%

24

10:1.

4-5 ,  
 37°C .  
 , ,  
 - (HE)  
 Leica DM1000, Leica EC3.  
 (Mayer's hematoxylin, Bio Optica, ) (1%  
 , BioGnost, ).

Brunt .<sup>[144]</sup> :

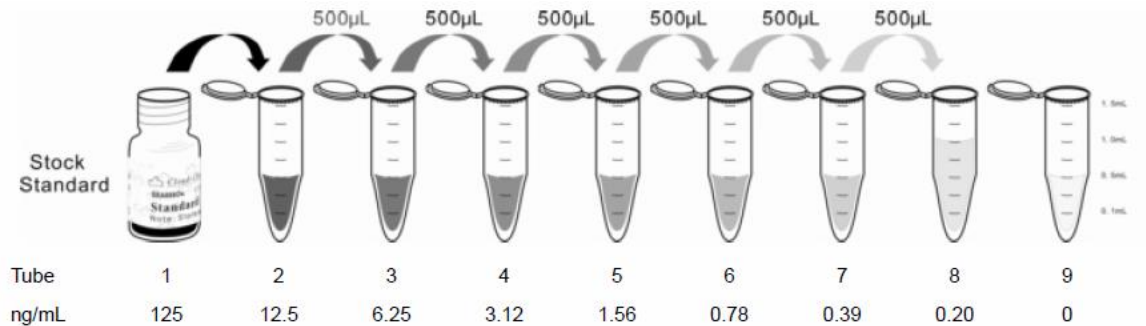
- ,
- ,
- NASH ( ,  
 , ) ,
- 
- .

### 5.2.9. Квантитативно мерење цитокератина-18 у крвној плазми

-18  
 ó ELISA  
 .  
*sandwich Enzyme-linked immunosorbent assay kit for  
 cytokeratin 18,* , ,  
 -18 ,  
*Cloud-Clone Corp (SAD).*

CK-18, 100 µl 100µl ( )  
 ).  
 2  
*horseradish peroxidase-* (HRP).  
 TMB , ( )  
 , ) CK-18,

CK-18  
 ELISA  
 CK-18  
 (OD)  
 60 ( 18°C 25°C).  
 125 ng/ml.  
 125 ng/ml 12,5 ng/ml.  
 (12,5 ng/ml)  
 1 ml  
 10  
 450 nm.  
 ( 1).



1.

500 µl

12,5 ng/ml,

500

µl



6,25 ng/ml.

šblankõ.

: 12,5 ng/ml, 6,25 ng/ml, 3,12 ng/ml, 1,56 ng/ml, 0,78 ng/ml, 0,39 ng/ml, 0,20 ng/ml 0 ng/ml.

CK-18, 100 µl

šblankõ-

120 37°C.

100 µl *etection Reagent* 30 37°C.

350 µl

100 µl *detection reagent B* 30 37°C.

350 µl

90 µl (*substrate solution*)

20 37°C.

20

50 µl (*stop solution*),

### 5.2.10. Молекуларна дијагностика

PNPLA3 rs738409

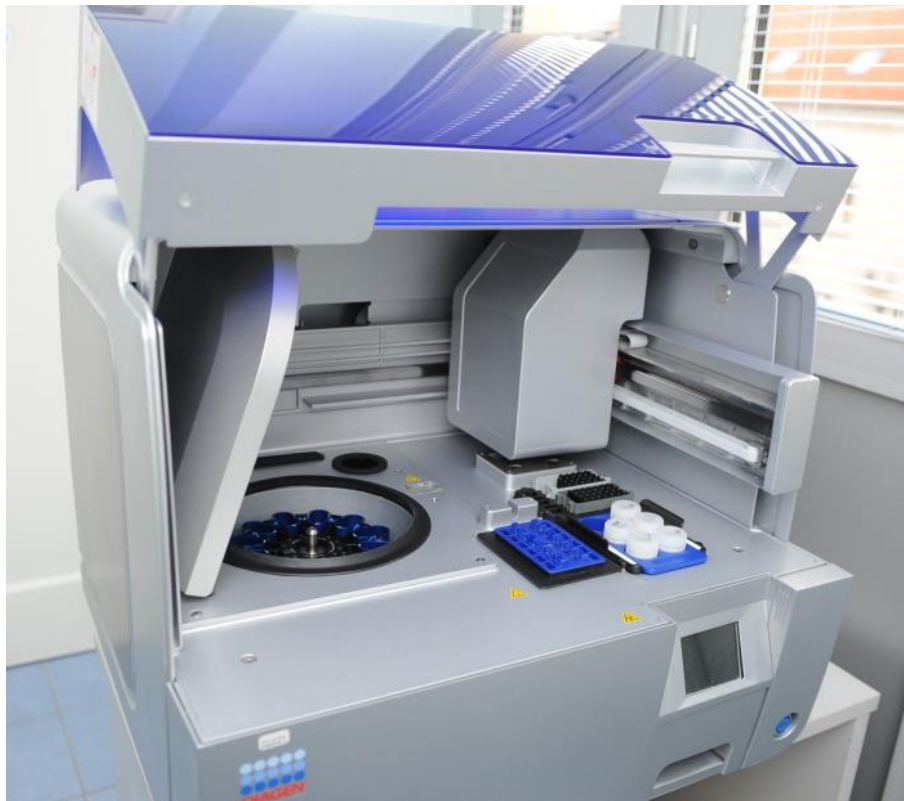
NAFLD

PNPLA3 I148M (PCR  
. Polymerase chain reaction) 5ml  
EDTA. -20°C.

### 5.2.10.1. Екстракција ДНК

ДНК

ДНК QIAcube (Qiagen, SAD)



2. QIAcube (Qiagen, SAD)

ДНК.

5.2.10.2. PCR-RFLP метода за дијагностику полиморфизма PNPLA3 rs738409 (C10109G)

PNPLA3 rs 738409 (C10109G)

PCR , PCR  
 BtsCI (New England Biolabs), PCR-RFLP  
 Dutta, 2012<sup>[183]</sup>.  
 . PCR 20 µl  
 10 1 HotStarTaq Master Mix (Qiagen, ), 7 1 (RNase-free  
 Water, Qiagen, ), 0,5 PLA3\_F (TGG GCC TGA AGT  
 CCG AGG GT), 0,5 1 PLA3\_R (CCG ACA CCA GTG CCC TGC  
 AG) 2 1 DNK. (Bio Basic Canada Inc.,  
 ) 0,25 M. PCR  
 (NK) DNK 2 1  
 (RNase-free Water, Qiagen, ), ( 5.).

5. PCR

Hot StarTaq Master Mix (Qiagen)	10	1
RNAse-Free Water (Qiagen)	7	1
	(5-3):	
PLA3_R	TGG GCC TGA AGT CCG AGG GT	0,5 1
PLA3_R	CCG ACA CCA GTG CCC TGC AG	0,5 1
DNK		2 1
		20 1

20 1, PCR „Thermal Cycler“, Veriti 96-well, Applied Biosystems.

PCR  
 95°C 15 , 35 94°C  
 30 , 66°C 30

72°C 30 , ,  
72°C 7 ( 6.).

6. PCR .

1		95°C/15 min.
2	35	94°C/30 sec.
		66°C/30 sec.
		72°C/30 sec.
4		72°C/7 min.

BtsCI

15 µl 10 µl PCR , 3,3 µl (*RNase-free Water, Qiagen*), 1,5 µl *Cut Smart pufera (New England Biolabs)* 0.2 µl BtsCI (*New England Biolabs*) 4 50°C „*Thermal Cycler*“, *Veriti 96-well, Applied Biosystems*.

*QIAxcel (Qiagen)* .

### 5.2.10.3. Визуелизација продукта умножавања DNK

DNK

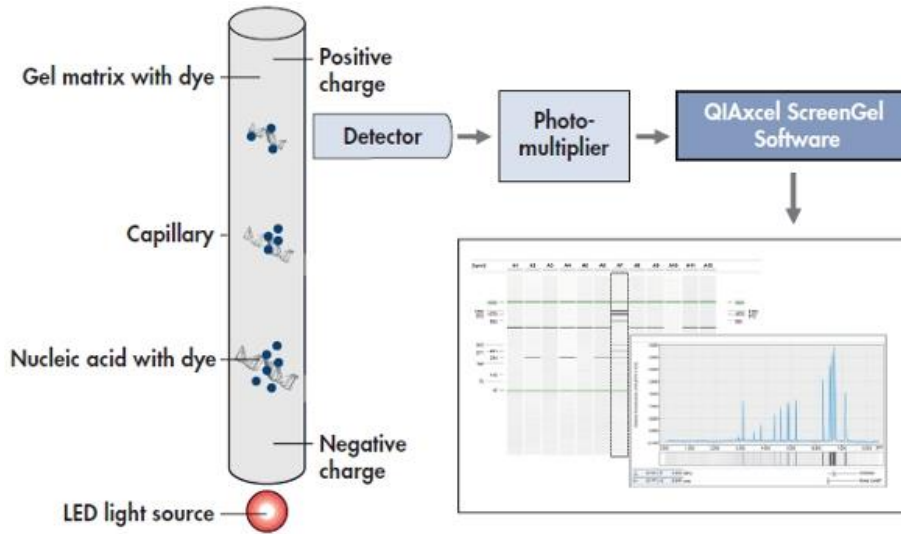
*QIAxcel (Qiagen, САД)*.

*QIAxcel* -

( )

QIAxcel ScreenGel software.

( 2.).



2. 6

QIAxcel

5.2.10.4. Детекција полиморфизма PNPLA3 rs738409 (C10109G)

PNPLA3 rs738409 (C10109G)

PCR-RFLP

BCSP-31.

333 bp ( ).

PCR 333 bp

QIAxcel (Qiagen, )

QIAxcel BioCalculator.

PCR

BtsCI (New England Biolabs)

(C10109C), (C10109G)

(G10109G).

DNK

333 bp

200 bp 133 bp,  
 333 bp, 200 bp 133 bp,  
 333 bp ( 7.).

7.

	(C10109C)	(C10109G)	(G10109G)
PCR-RFLP (bp)		333	333
	200	200	
	133	133	

5.2.11. Статистичка обрада резултата

Shapiro-Wilk Kolmogorov-Smirnov  
 Mann-Whitney  
 - , 3 Kruskal-Wallis ANOVOM ( ).  
 Pearson- (r) Spearman- (ρ)  
 . Pearson-  $\chi^2$  ,  
 2x2, Mantel-Haenzel- Fisher-  
 SPSS 15.0,  
 p<0,05.

## 6. РЕЗУЛТАТИ

### 6.1. Демографски параметри пацијената студијске (NAFLD) и контролне групе

NAFLD ( ) 55 (63,95%) , 31  
 (36,05%) . NAFLD  
 49,29±12,95, 52 ,  
 47,84±10,08 49 . Mann-Whitney  
 NAFLD  
 .  
 NAFLD 23 (41,82%) 32 (58,18%),  
 10 (32,26%) 21 (67,74%).  
 NAFLD  
 ( 8.)

8. NAFLD

	NAFLD , n=55		, n=31	
( )	49,29 ± 12,95	52	47,84 ± 10,08	49
( / )	23 (41,82%)	32 (58,18%)	10 (32,26%)	21 67,74%)

### 6.2. Антропометријски параметри пацијената NAFLD и контролне групе

. NAFLD  
 , ,  
 (p<0,001)  
 ( 9.).

9. NAFLD

	NAFLD	n=55		n=31
OS (cm)	106,36 ± 8,44 <sup>***</sup>	105	78,87 ± 7,18	79,00
TT (kg)	92,22 ± 14,83 <sup>***</sup>	92	65,00 ± 8,90	62,00
TV (m)	1,68 ± 0,12	1,65	1,70 ± 0,09	1,68
BMI (kg/m <sup>2</sup> )	32,83 ± 4,20 <sup>***</sup>	32,87	22,52 ± 2,08	22,77

\*\*\* – p<0,001

NAFLD 16 OS × 102 cm ( 10.).  
 × 88 cm NAFLD ( 11.).

10. NAFLD

OS,	NAFLD n=23		
	n	%	
OS (cm) × 102	16	69,57	110,00
OS (cm) < 102	7	30,43	101,29

11. NAFLD

OS,	NAFLD n=32		
	n	%	
OS (cm) × 88	32	100,00	106,00
OS (cm) < 88	0	0,00	0,00

NAFLD 17 (30,91%)  
 38 (69,09%) ( 12.).  
 22 (40,00%)  
 , 13 (23,64%) 3 (5,45%)  
 , 29



NAFLD (p<0,001)

( 12.).

12.

NAFLD

BMI

	NAFLD n=55		n=31	
	n	%	n	%
BMI (kg/m <sup>2</sup> )				
BMI < 18,5 kg/m <sup>2</sup>	0	0,00%	1	3,23%
BMI 18,5 kg/m <sup>2</sup> 24,9 kg/m <sup>2</sup>	0	0,00%	29	93,55%
BMI 25 kg/m <sup>2</sup> 29,9 kg/m <sup>2</sup>	17	30,91%	1	3,23%
BMI (kg/m <sup>2</sup> ) × 30,0 kg/m <sup>2</sup>	38	69,09%***	0	0,00%
BMI 30 kg/m <sup>2</sup> 34,99 kg/m <sup>2</sup>	22	40,00% <sup>x***</sup>	0	0,00%
BMI 35 kg/m <sup>2</sup> 39,99 kg/m <sup>2</sup>	13	23,64%	0	0,00%
BMI 40 kg/m <sup>2</sup>	3	5,45%	0	0,00%

\*\*\* – p<0,001, x –

### 6.3. Клинички и биохемијски параметри пацијената NAFLD и контролне групе

#### 6.3.1. Клинички параметри пацијената NAFLD и контролне групе

NAFLD 40 (72,73%) 26  
 DM 2 (47,27%). , 4  
 (12,90%) . DM 2  
 NAFLD (p<0,001) ( 13.).

13.

DM 2

NAFLD

	NAFLD n=55		n=31	
	n	%	n	%
	40	72,73%***	4	12,90%
DM 2	26	47,27%***	0	0,00%

\*\*\* – p<0,001

NAFLD  
 137,18±18,60 mmHg  
 , 116,45±13,86 mmHg (p<0,001).  
 NAFLD  
 84,73±10,69 mmHg  
 72,90±9,98 mmHg (p<0,001) ( 14.).

14.  
 NAFLD

	NAFLD	n=55		n=31
SKP (mmHg)	137,18 ± 18,60***	140	116,45 ± 13,86	120
DKP (mmHg)	84,73 ± 10,69***	90	72,9 ± 9,98	70

\*\*\* – p<0,001

6.3.2. Биохемијски параметри пацијената NAFLD и контролне групе

NAFLD  
 LDL ,  
 (p<0,05), (p<0,01), TG, , CRP,  
 (p<0,001), HDL (p<0,05)  
 .  
 NAFLD ,  
 .  
 INR ( 15.).

15.

NAFLD

	NAFLD	n=55	n=31	
( $\mu\text{mol/l}$ )	373,01 $\pm$ 94,55 <sup>***</sup>	375,1	239,98 $\pm$ 56,57	237,4
UBIL ( $\mu\text{mol/l}$ )	12,78 $\pm$ 5,66 <sup>*</sup>	12,2	10,17 $\pm$ 2,91	9,9
DBIL ( $\mu\text{mol/l}$ )	2,23 $\pm$ 1,08	2	1,81 $\pm$ 0,54	1,6
(g/l)	45,1 $\pm$ 3,09	45,2	44,05 $\pm$ 3,84	44,9
HOL (mmol/l)	5,86 $\pm$ 1,06 <sup>**</sup>	5,82	5,16 $\pm$ 1,08	5,12
HDL (mmol/l)	1,15 $\pm$ 0,25	1,13	1,28 $\pm$ 0,28 <sup>*</sup>	1,34
LDL (mmol/l)	3,76 $\pm$ 0,92 <sup>*</sup>	3,8	3,26 $\pm$ 0,87	3,3
TG (mmol/l)	2,28 $\pm$ 1,12 <sup>***</sup>	1,91	1,2 $\pm$ 0,37	1,08
CRP (mg/l)	6,2 $\pm$ 10,38 <sup>***</sup>	3,4	1,69 $\pm$ 1,63	1,1
( $\mu\text{g/l}$ )	145,38 $\pm$ 113,45 <sup>***</sup>	113,9	45,65 $\pm$ 28,17	39,3
INR	1,07 $\pm$ 0,11	1,06	1,08 $\pm$ 0,08	1,06
FIB (g/l)	4,47 $\pm$ 1,02 <sup>***</sup>	4,27	3,48 $\pm$ 0,86	3,55
TR $\times 10^9/l$	242,69 $\pm$ 66,6	235	253,9 $\pm$ 50,48	261

\* - p&lt;0,05, \*\* - p&lt;0,01, \*\*\* - p&lt;0,001

NAFLD

: AST 40,17 $\pm$ 21,82 U/L, ALT 59,56 $\pm$ 43,94 U/L, GGT 61,62 $\pm$ 67,10 U/L iALP 71,85 $\pm$ 28,67 U/L.

AST

: 20,8 $\pm$ 4,25 U/L, ALT 16,85 $\pm$ 6,23 U/L, GGT 19,45 $\pm$ 14,97 U/L ALP55,50 $\pm$ 16,56 U/L.

NAFLD

AST, ALT, GGT (p&lt;0,001) ALP (p&lt;0,01)

( 16).

16.

NAFLD

	NAFLD	n=55	n=31	
AST (U/l)	40,17 $\pm$ 21,82 <sup>***</sup>	34,8	20,84 $\pm$ 4,25	20,1
ALT (U/l)	59,56 $\pm$ 43,94 <sup>***</sup>	52,5	16,85 $\pm$ 6,23	16,1
ALP (U/l)	71,85 $\pm$ 28,67 <sup>**</sup>	63,1	55,50 $\pm$ 16,56	49,8
GGT (U/l)	61,62 $\pm$ 67,10 <sup>***</sup>	38,4	19,45 $\pm$ 14,97	14,7

\*\* - p&lt;0,01, \*\*\* - p&lt;0,001

AST/ALT

NAFLD

0,79 $\pm$ 0,34,

0,68.

, HOMA-IR  
 NAFLD  
 (p<0,001) ( 17.).

17. , HOMA-IR NAFLD

	NAFLD n=55		n=31	
(mmol/l)	6,56 ± 2,38***	6,00	5,00 ± 0,74	5,00
(mu/l)	39,16 ± 28,88***	4,27	12,41 ± 4,37	13,00
HOMA-IR	13,67 ± 18,88***	7,47	2,77 ± 1,07	2,88

\*\*\* – p<0,001

**6.4. Заступљеност метаболичког синдрома код пацијената NAFLD и контролне групе**

NAFLD 48 (87,27%)  
 ,  
 3 (9,68%) (p<0,001) ( 18.).

18. NAFLD

	NAFLD n=55		n=31	
MS	48	87,27%***	3	9,68%
MS				
0	0	0,00%	14	45,16%
1	1	1,82%	9	29,03%
2	6	10,91%	5	16,13%
3	16	29,09%	3	9,68%
4	16	29,09%	0	0,00%
5	16	29,09%	0	0,00%

\*\*\* – p<0,001

MS (18). NAFLD , 16 (29,09%) 3, 4 5  
 (45,16%) MS, 9 (29,03%) , 14  
 (16,13%) , 3 (9,68%) MS, 5  
 4 5 MS (18).  
 MS NAFLD  
 HDL , p<0,001,  
 HDL ,  
 p<0,01(19).  
 19.  
 NAFLD

MS	NAFLD		n	%
	n	%		
OS (cm)	48	87,27% <sup>***</sup>	0	0,00%
HDL (mmol/l)	33	60,00% <sup>**</sup>	9	29,03%
TG (mmol/l)	36	65,45% <sup>***</sup>	5	16,13%
/ SKP / DKP	50	90,91% <sup>***</sup>	9	29,03%
×5,6 mmol/l/DM	38	69,09% <sup>***</sup>	5	16,13%

\*\* – p<0,01, \*\*\* – p<0,001

MS NAFLD  
 SKP / DKP 50 (90,91%)  
 :  
 87,27%, DM 2 69,09%,  
 TG 65,45% HDL 60,00%.  
 SKP / DKP mmHg, MS NAFLD  
 ,  
 TG, DM  
 (p<0,01), HDL (p<0,001) (20.).

20.

MS

NAFLD

MS	n=55	%	p
OS (cm)	48	87,27%	
HDL (mmol/l)	33	60,00%	
TG (mmol/l)	36	65,45%	
DKP / SKP /	50	90,91%	** vs TG *** vs HDL
×5,6 mmol/l/DM	38	69,09%	×5,6mmol/l/DM, *** vs HDL

\*\* – p<0,01, \*\*\* – p<0,001

### 6.5. Предиктори појаве NAFLD

21.) (

NAFLD ,

, HOMA-IR, , TG, AST, ALT, GGT, CRP, , ,

, MS, MS, SKP, DKP, (p<0,001),

, ALP, OS (p<0,01), , HDL LDL

(p<0,05) ( 21.).

MS (p<0,001)

NAFLD 64 (IP 15,31–267,59), SKP ×

135 mmHg / DKP × 85 mmHg 24,44 (IP

7,34–81,38), DM × 5,6 mmol/l 11,62

(IP 3,81–35,45), × 1,7 mmol/l 9,85 (IP

3,26–29,88), 9,14 (IP 3,26–25,61).

HDL (< 1,03 mmol/l < 1,29 mmol/l )

NAFLD 3,78 (IP

1,43–9,43) (p<0,01) ( 21.).

MS

MS 1, (p<0,001)

NAFLD 8,58 (IP 3,26–25,61) ( 21.).

21. OR

NAFLD,

	OR	95,0% IP		p
( )	1,01	0,97	1,05	0,5869
	0,66	0,26	1,67	0,3826
(mmol/l)	4,09	1,94	8,64	***0,0002
(mu/l)	1,36	1,18	1,56	***0,0000
HOMA-IR	3,55	1,96	6,44	***0,0000
( $\mu\text{mol/l}$ )	1,03	1,01	1,04	***0,0000
UBIL ( $\mu\text{mol/l}$ )	1,14	1,02	1,28	*0,0254
DBIL ( $\mu\text{mol/l}$ )	1,86	0,99	3,47	0,0527
(g/l)	1,1	0,96	1,25	0,1726
HOL (mmol/l)	1,87	1,18	2,97	**0,0076
HDL (mmol/l)	0,13	0,02	0,78	*0,0260
LDL (mmol/l)	1,85	1,1	3,12	*0,0209
TG (mmol/l)	16,02	4,17	61,58	***0,0001
AST (U/l)	1,29	1,15	1,44	***0,0000
ALT (U/l)	1,23	1,1	1,37	***0,0002
ALP (U/l)	1,03	1,01	1,06	**0,0090
GGT (U/l)	1,09	1,04	1,14	***0,0005
CRP (mg/l)	2,23	1,46	3,41	***0,0002
( $\mu\text{g/l}$ )	1,03	1,01	1,04	***0,0001
INR	0,36	0	30,07	0,6519
FIB (g/l)	3,74	1,92	7,31	***0,0001
TR $\times 10^9/l$	1	0,99	1	0,4155
OS (cm)	1,87	1,18	2,98	**0,0079
TT (kg)	1,22	1,12	1,33	***0,0000
BMI ( $\text{kg/m}^2$ )	837,13	0,01	1,01E±08	0,2594
MS	64	15,31	267,586	***0,0000
MS HDL (mmol/l)	3,78	1,43	9,43	**0,0070
MS TG (mmol/l)	9,85	3,26	29,8	***0,0000
MS /SKP / DKP	24,44	7,34	81,38	***0,0000
MS $\geq 5,6\text{mmol/l/DM}$	11,62	3,81	35,45	***0,0000
MS	8,58	3,36	21,93	***0,0000
SKP (mmHg)	1,09	1,05	1,14	***0,0000
DKP (mmHg)	1,11	1,06	1,17	***0,0000
	9,14	3,26	25,61	***0,0000

\* - p&lt;0,05, \*\* - p&lt;0,01, \*\*\* - p&lt;0,001

NAFLD (p&lt;0,001)

: TG 16,02 (IP 4,17–61,58), 4,09 (IP 1,94–8,64),  
HOMA-IR 3,55 (IP 1,96–6,44), 36% (IP 1,18–1,56), AST 29% (IP

1,15–1,44), ALT 23% (IP 1,10–1,37), TT 22% (IP 1,12–1,33), DKP 11% (IP 1,06–1,17), GGT SKP 9% (IP 1,04–1,14/1,17), 3% (IP 1,01–1,04).

OS

NAFLD 87% (IP 1,18–2,97/2,98), ALP 3% (IP 1,01–1,06) (p<0,01).

LDL

NAFLD 85% (IP 1,10–3,12),

HDL

NAFLD 87% (IP

0,02–0,78) (p<0,05) ( 21.).

**6.6. Демографски, антропометријски и биохемијски параметри пацијената NAFLD групе у односу на присуство метаболичког синдрома**

NAFLD 48 (87,27%) S 30 (62,50%) 18 (37,50%), NAFLD MS 5 (71,43%) 2 (28,57%).

MS 50,71±12,26 ,

MS 39,57±14,35.

NAFLD

MS

, BMI (p<0,01),

HOMA-IR

(p<0,05),

NAFLD

MS

HDL (p<0,05).

OS (107,02 ± 8,6) NAFLD MS

MS (101,86±5,9),

( 22.).



22.

NAFLD

	NAFLD MS, n=7		NAFLD MS, n=48	
( )	39,57 ± 14,35	34	50,71 ± 12,26	54
( / )	5 (71,43%) / 2 (28,57%)		18 (37,50%) / 30 (62,50%)	
(mmol/l)	4,99 ± 0,54	4,9	6,79 ± 2,46	6,1**
(mu/l)	23,14 ± 10,95	23	41,49 ± 29,99	29*
HOMA-IR	5,18 ± 2,65	4,78	14,9 ± 19,9	7,61*
Urati (µmol/l)	363,41 ± 76,48	349,8	374,41 ± 97,52	377,65
UBIL (µmol/l)	11,8 ± 3,56	12,9	12,93 ± 5,92	11,65
DBIL (µmol/l)	2,03 ± 0,81	2,1	2,26 ± 1,12	2
(g/l)	46,33 ± 2,72	47,9	44,93 ± 3,12	45,05
HOL (mmol/l)	6,25 ± 1,13	5,83	5,81 ± 1,05	5,82
HDL (mmol/l)	1,32 ± 0,25	1,2*	1,12 ± 0,24	1,12
LDL (mmol/l)	4,03 ± 0,85	4	3,72 ± 0,93	3,8
TG (mmol/l)	2,44 ± 1,67	2,08	2,26 ± 1,04	1,9
AST (U/l)	47,91 ± 26,33	42,1	39,04 ± 21,17	34,8
ALT (U/l)	60,26 ± 20,47	56,9	59,46 ± 46,52	51,2
ALP (U/l)	57,81 ± 19,43	58,1	73,9 ± 29,37	64,1
GGT (U/l)	68,26 ± 45,85	47,8	60,65 ± 69,98	35,6
CRP (mg/l)	6,24 ± 6,25	3,3	6,2 ± 10,9	3,45
(µg/l)	198,37 ± 195,16	142,7	137,65 ± 97,19	111,3
INR	1,04 ± 0,03	1,03	1,08 ± 0,11	1,06
FIB (g/l)	4,25 ± 0,64	4,07	4,5 ± 1,07	4,3
TR x10 <sup>9</sup> /l	237,14 ± 48,43	226	243,5 ± 69,22	235,5
OS (cm)	101,86 ± 5,9	102	107,02 ± 8,6	106
TT (kg)	84,71 ± 10,03	86	93,31 ± 15,17	93,5
BMI (kg/m <sup>2</sup> )	28,65 ± 3,19	28,41	33,44 ± 4	33,46**
SKP (mmHg)	134,29 ± 19,88	140	137,6 ± 18,59	137,5
DKP (mmHg)	81,43 ± 12,15	80	85,21 ± 10,52	90
AST/ALT	0,8 ± 0,32	0,64	0,78 ± 0,35	0,69

\* - p<0,05, \*\* - p<0,01, \*\*\* - p<0,001

NAFLD

MS 11 (22,92%)

, 37 (77,08%)

, 22

(45,83%)

, 12 (25,00%)

3 (6,25%)

( 23.). NAFLD

MS

, 6 (85,71%).

NAFLD MS

NAFLD

MS (p<0,01) (

23.).

23. NAFLD  
BMI

	NAFLD	MS, n=7	NAFLD	MS, n=48
BMI	n	%	n	%
BMI < 18,5kg/m <sup>2</sup>	0	0,00%	0	0,00%
BMI 18,5 kg/m <sup>2</sup> 24,9 kg/m <sup>2</sup>	0	0,00%	0	0,00%
BMI 25 kg/m <sup>2</sup> 29,9 kg/m <sup>2</sup>	6	85,71%	11	22,92% <sup>**</sup>
BMI > 30,0 kg/m <sup>2</sup>	1	14,29%	37	77,08% <sup>**</sup>
BMI d 30 kg/m <sup>2</sup> 34,99 kg/m <sup>2</sup>	0	0,00%	22	45,83% <sup>x**</sup>
BMI 35 kg/m <sup>2</sup> 39,99 kg/m <sup>2</sup>	1	14,29%	12	25,00%
BMI 40 kg/m <sup>2</sup>	0	0,00%	3	6,25%

\*\* – p<0,01

x –

NAFLD S 39 (81,25%) 26  
(54,17%) DM 2. NAFLD MS  
(p<0,01) DM (p<0,05) NAFLD  
MS (T 24), (14,29%),  
DM ( 24.).  
24. DM 2 NAFLD

	NAFLD	MS, n=7	NAFLD	MS, n=48
	1	14,29%	39	81,25% <sup>**</sup>
DM 2	0	0,00%	26	54,17% <sup>*</sup>

\*\* – p<0,01, \* – p<0,05

6.7. Демографски, антропометријски и биохемијски параметри пацијената  
NAFLD групе у односу на BMI

NAFLD 38 (69,09%) , 24 (63,16%)  
14 (36,84%) , 50,32±13,07 .  
, 8 (47,06%) 9 (52,94%) ,

47,00±12,76.

BMI ( 25. 26.).

OS ,

p<0,001 ( 25.).

25.

NAFLD

BMI

	NAFLD, BMI<30 kg/m <sup>2</sup> , n=17		NAFLD, BMI ≥30 kg/m <sup>2</sup> , n=38	
( )	47,00 ± 12,76	47	50,32 ± 13,07	54
(mmol/l)	6,19 ± 1,56	6	6,72 ± 2,67	5,95
(mu/l)	33,76 ± 30,9	27	41,57 ± 28,02	29,5
HOMAIR	10,93 ± 15,55	7,44	14,89 ± 20,26	7,74
(μmol/l)	361,45 ± 74,9	348,2	378,18 ± 102,63	380,35
UBIL (μmol/l)	13,63 ± 4,71	13	12,41 ± 6,06	10,9
DBIL (μmol/l)	2,22 ± 0,77	2,1	2,24 ± 1,2	2
(g/l)	44,61 ± 3,49	45,6	45,32 ± 2,91	45,05
HOL (mmol/l)	6,18 ± 0,98	5,83	5,72 ± 1,08	5,82
HDL (mmol/l)	1,20 ± 0,26	1,16	1,12 ± 0,24	1,13
LDL (mmol/l)	3,96 ± 0,85	3,8	3,66 ± 0,95	3,8
TG (mmol/l)	2,42 ± 1,46	1,87	2,22 ± 0,94	1,93
AST (U/l)	38,72 ± 19,03	34,7	40,82 ± 23,17	34,9
ALT (U/l)	51,91 ± 17,91	49,9	62,98 ± 51,38	55,3
ALP (U/l)	65,08 ± 24,21	59,7	74,88 ± 30,25	65,35
GGT (U/l)	66,29 ± 52,67	56,5	59,53 ± 73,19	35,6
CRP (mg/l)	5,44 ± 8,16	2,7	6,54 ± 11,32	3,55
(μg/l)	176,18 ± 139,11	154	131,60 ± 98,91	106,6
INR	1,06 ± 0,09	1,04	1,08 ± 0,12	1,06
FIB (g/l)	4,20 ± 0,6	4,09	4,59 ± 1,15	4,48
TR ×10 <sup>9</sup> /l	243,29 ± 48,44	240	242,42 ± 73,88	233
OS (cm)	100,18 ± 5,07	102	109,13 ± 8,22	107,50***
TT (kg)	80,76 ± 10,67	76	97,34 ± 13,58	98,75***
SKP (mmHg)	138,24 ± 17,04	140	136,71 ± 19,46	130
DKP (mmHg)	86,47 ± 11,83	90	83,95 ± 10,21	87,5
AST/ALT	0,78 ± 0,33	0,64	0,79 ± 0,35	0,69

\* – p<0,05, \*\* – p<0,01, \*\*\* – p<0,001

NAFLD BMI×30 kg/m<sup>2</sup> ,  
 30 (78,95%), DM 2 21 (55,26%) MS 37 (97,37%),  
 MS, NAFLD

(p<0,01).

NAFLD

HDL

(p<0,05)

NAFLD

3, 4 5

MS (p<0,01) ( 26.).

26.

NAFLD

BMI<30 kg/m<sup>2</sup> BMI≥30 kg/m<sup>2</sup>

	NAFLD, BMI<30 kg/m <sup>2</sup> , n=17		NAFLD, BMI≥30 kg/m <sup>2</sup> , n=38	
	8	47,06%	24	63,16%
	9	52,94%	14	36,84%
	10	58,82%	30	78,95%
DM	5	29,41%	21	55,26%
MS	11	64,71%	37	97,37% **
MS				
MS	12	70,59%	36	94,74% *
MS HDL (mmol/l)	6	35,29%	27	71,05% *
MS TG (mmol/l)	11	64,71%	25	65,79%
MS /SKP / DKP	16	94,12%	34	89,47%
MS ×5,6mmol/l/DM	11	64,71%	27	71,05%
MS				
0	0	0,00%	0	0,00%
1	0	0,00%	1	2,63%
2	6	35,29%	0	0,00%
3	4	23,53%	12	31,58% x**
4	3	17,65%	13	34,22%
5	4	23,53%	12	31,58%

\* – p<0,05, \*\* – p<0,01, \*\*\* – p<0,001

x – 3, 4 ili 5 S

### 6.8. Демографски, антропометријски и биохемијски параметри пацијената NAFLD групе у односу на присуство дијабетес мелитус тип 2

NAFLD 26 (47,27%) DM 2.

NAFLD DM 2 (56,62±8,26 vs. 42,72±12,96)

(p<0,01) ( 27.).

27. ,  
NAFLD DM 2

	NAFLD	DM	n=29	NAFLD	DM	n=26
( )	42,72 ± 12,96		41	56,62 ± 8,26		58,00**
(mmol/l)	5,52 ± 0,81		5,4	7,72 ± 2,98		6,55***
(mu/l)	33,28 ± 17,25		28	45,72 ± 37,2		29
HOMAIR	8,36 ± 4,97		7,35	19,58 ± 25,94		7,88
(µmol/l)	368,19 ± 79,21		354,2	378,39 ± 110,58		377,65
UBIL (µmol/l)	13,44 ± 6,12		12,9	12,05 ± 5,12		10,8
DBIL (µmol/l)	2,23 ± 0,95		2,1	2,23 ± 1,23		1,8
(g/l)	45,68 ± 2,9		45,8	44,46 ± 3,22		44,85
HOL (mmol/l)	6,02 ± 1,07		5,83	5,69 ± 1,05		5,76
HDL (mmol/l)	1,15 ± 0,27		1,12	1,14 ± 0,23		1,15
LDL (mmol/l)	3,98 ± 0,86		3,9	3,50 ± 0,94		3,6
TG (mmol/l)	2,19 ± 1,16		1,87	2,39 ± 1,08		2,02
AST (U/l)	41,03 ± 24,86		33,9	39,21 ± 18,28		35
ALT (U/l)	67,13 ± 50,41		55,3	51,12 ± 34,39		44,15
ALP (U/l)	70,37 ± 24,71		63,1	73,51 ± 32,95		63,25
GGT (U/l)	68,79 ± 81,5		38,4	53,63 ± 46,48		36,5
CRP (mg/l)	4,71 ± 4,5		3,2	7,87 ± 14,31		3,8
(µg/l)	159,30 ± 118,9		154,1	129,85 ± 107,15		103
INR	1,06 ± 0,08		1,04	1,09 ± 0,13		1,06
FIB (g/l)	4,29 ± 0,82		4,25	4,67 ± 1,2		4,42
TR x10 <sup>9</sup> /l	246,38 ± 69,65		231	238,58 ± 64,14		237,5
OS (cm)	105,31 ± 8,44		103	107,54 ± 8,46		106,5
TT (kg)	93,90 ± 15,81		92	90,35 ± 13,72		90,5
TV (m)	1,72 ± 0,12		1,72**	1,63 ± 0,1		1,61
BMI (kg/m <sup>2</sup> )	31,83 ± 4,13		32,43	33,93 ± 4,07		34,01
SKP (mmHg)	134,48 ± 15,6		135	140,19 ± 21,38		140
DKP (mmHg)	86,55 ± 9,92		90	82,69 ± 11,33		82,5
AST/ALT	0,67 ± 0,22		0,61	0,91 ± 0,4		0,78**

\* - p<0,05, \*\* - p<0,01, \*\*\* - p<0,001

DM 2 5 (19,23%) 21 (80,77%)  
DM 11 (37,93%) 18 (62,07%)  
NAFLD DM 2 (p<0,01).

NAFLD DM

(p<0,001)

AST/ALT (p<0,01) ( 27.).

28.

NAFLD

DM 2

	NAFLD	DM, n=29	NAFLD	DM, n=26
	11	37,93%	21	80,77% **
	18	62,07%	5	19,23%
BMI < 18,5kg/m <sup>2</sup>	0	0,00%	0	0,00%
BMI 18,5 kg/m <sup>2</sup> 24,9 kg/m <sup>2</sup>	0	0,00%	0	0,00%
BMI 25 kg/m <sup>2</sup> 29,9 kg/m <sup>2</sup>	12	41,38%	5	19,23%
BMI ≥ 30,0 kg/m <sup>2</sup>	17	58,62%	21	80,77%
	12	41,38%	5	19,23%
BMI 30 kg/m <sup>2</sup> 34,99 kg/m <sup>2</sup>	11	37,93%	11	42,31% x**
BMI 35 kg/m <sup>2</sup> 39,99 kg/m <sup>2</sup>	5	17,24%	8	30,77%
BMI 40 kg/m <sup>2</sup>	1	3,45%	2	7,69%
	15	51,72%	25	96,15% ***
MS	22	75,86%	26	100,00% *
MS				
(cm)	23	79,31%	25	96,15%
MS HDL (mmol/l)	15	51,72%	18	69,23%
MS TG (mmol/l)	20	68,97%	16	61,54%
MS / SKP i/ ili DKP	24	82,76%	26	100,00%
MS ×5,6 mmol/l/DM	12	41,38%	26	100,00% ***
MS				
0	0	0,00%	0	0,00%
1	1	3,45%	0	0,00%
2	6	20,69%	0	0,00%
3	10	34,48%	6	23,08% y*
4	9	31,03%	7	26,92%
5	3	10,35%	13	50,00% **
BMI ≥30	17	58,62%	21	80,77%

\* – p<0,05, \*\* – p<0,01, \*\*\* – p<0,001

x –

y –

3, 4 5 MS

NAFLD DM 2, 5 (19,23%)

21 (80,77%)

DM 2

12 (41,38%)

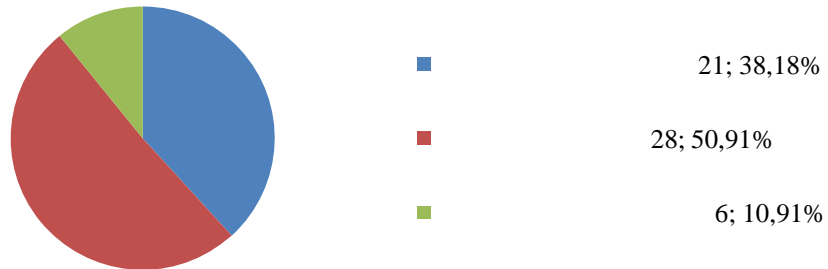
17 (58,62%)

( 28.).

DM 2 (p<0,01). NAFLD (p<0,001) MS (p<0,05). DM 2, NAFLD 3 MS 5, DM (p<0,05) (28.).

**6.9. Демографски, антропометријски и биохемијски параметри пацијената NAFLD групе у односу на вредност NAFLD фибриног скорa**

NAFLD ( NAFLD -1,45), ( NAFLD 0,675) ( NAFLD je , 28 (50,91%), 21 (38,18%) 6 (10,91%) ( 1).



1. NAFLD NAFLD

Kruskal-Wallis ANOVA

(p<0,001),

AST/ALT (p<0,01),

NAFLD

, TR, OS, BMI, SKP, (p<0,05).

(p<0,01)

(p<0,05) ( 29.).

(64,50±5,24)

(57,19±5,13)

(40,11±11,11) (p<0,001),

(p<0,01) ( 29.).

(p<0,05), (p<0,01).

(p<0,05). ALT

ALT (p<0,05).

(p<0,05).

(p<0,001) (p<0,05).

OS BMI

(p<0,001) (p<0,05) ( 29.).



29.

NAFLD

NAFLD

	n=28		n=21		n=6		
( )***	40,11±11,11	38,50	57,19±5,13	a***58,00	64,50±5,24	a***b*65,00	
*** (a vs b±c)	18 (64,29%)	10 (35,71%)	b**c*	4 (19,05%)	17 (80,95%)	1 (16,67%)	5 (83,33%)
(mmol/l)**	5,76±1,19	5,45	7,10±2,38	a**6,20	8,37±4,72	a*6,40	
(mu/l)	36,05±20,03	29,95	44,64±36,14	29,00	34,43±37,54	20,80	
HOMAIR	9,71±7,21	7,47	17,40±23,85	7,63	19,07±33,33	6,07	
Urati (μmol/l)	375,62±87,11	388,40	352,96±67,87	354,20	431,03±177,15	398,30	
UBIL (μmol)	13,31±6,08	12,40	11,55±4,91	11,20	14,62±6,20	13,50	
DBIL (μmol)*	2,13±1,02	1,85	2,07±0,60	2,00	3,30±1,99	2,85	
(g/l)*	46,27±2,85	bc*46,60	44,15±2,71	43,70	43,02±3,62	43,30	
HOL (mmol/l)	6,02±1,09	5,83	5,86±1,03	6,25	5,1±0,91	5,14	
HDL (mmol/l)	1,12±0,26	1,10	1,21±0,22	1,22	1,07±0,29	1,07	
LDL (mmol/l)	3,91±0,86	3,85	3,65±0,95	3,80	3,38±1,20	3,30	
TG (mmol/l)	2,37±1,32	1,9	2,28±0,89	2,04	1,87±0,85	1,55	
AST (U/l)	39,05±25,67	30,30	42,35±19,10	38,60	37,80±9,31	39,80	
ALT (U/l)	65,10±52,36	51,20	59,22±34,64	c*55,30	34,87±18,50	30,35	
ALP (U/l)	66,84±24,73	59,75	73,63±28,17	65,90	89,00±43,48	87,00	
GGT (U/l)	67,34±82,97	37,90	49,70±32,54	41,40	76,70±78,55	55,95	
CRP (mg/l)	4,45±3,47	3,50	5,89± 8,06	3,10	15,45±26,83	4,30	
(μg/l)	154,27±125,48	148,40	127,29± 94,96	101,00	167,20±124,54	129,55	
INR	1,06±0,08	1,03	1,06±0,10	1,06	1,18±0,20	1,10	
FIB (g/l)	4,23±0,88	4,16	4,53±0,80	4,27	5,41±1,77	a*4,93	
TR x10 <sup>9</sup> /l **	275,39±72,41	***bc*263,00	207,81±39,00	212,00	212,17±35,89	230,50	
OS (cm) **	104,14±5,55	102,50	106,24±9,56	107,00	117,17±8,40	a***b*117,50	
TT (kg)	94,63±14,68	92,50	87,35±15,84	83,00	98,00±6,00	b*99,00	
TV (m)***	1,73± 0,10	bc**1,74	1,62±0,11	1,60	1,61±0,04	1,60	
BMI (kg/m <sup>2</sup> )**	31,47±3,50	31,84	33,18±4,35	32,04	37,91±2,51	a***b*37,84	
SKP (mmHg)**	130,54±15,95	130,00	141,43±13,24	a*140,00	153,33±32,04	15,50	
DKP (mmHg)	83,21±11,32	80,00	87,38±6,25	90,00	82,50±18,37	80,00	
AST/ALT**	0,67±0,21	0,62	0,80±0,31	0,70	1,27±0,51	a**b*1,17	

\* - p<0,05, \*\* - p<0,01, \*\*\* - p<0,001

a - vs , b - vs , c - vs

TT,

(p<0,05). SKP

SKP (p<0,05). AST/ALT

(p<0,01) (p<0,05)

( 29.).

NAFLD 11 (39,29%)

17 (60,71%)

6 (28,57%) 15 (71,43%)

4 (66,67%)

NAFLD ( 30.).

30. NAFLD

NAFLD

	n=28		n=21		n=6	
BMI < 18,5kg/m <sup>2</sup>	0	0,00%	0	0,00%	0	0,00%
BMI 18,5 kg/m <sup>2</sup> 24,9 kg/m <sup>2</sup>	0	0,00%	0	0,00%	0	0,00%
BMI 25 kg/m <sup>2</sup> 29,9 kg/m <sup>2</sup>	11	39,29%	6	28,57%	0	0,00%
BMI × 30,0 kg/m <sup>2</sup>	17	60,71%	15	71,43%	6	100,00%
	11	39,29%	6	28,57%	0	0,00%
BMI 30 kg/m <sup>2</sup> 34,99 kg/m <sup>2</sup>	12	42,86%	9	42,86%	1	16,67% xa*
BMI 35 kg/m <sup>2</sup> 39,99 kg/m <sup>2</sup>	5	17,86%	4	19,05%	4	66,67%
BMI 40 kg/m <sup>2</sup>	0	0,00%	2	9,52%	1	16,67%

\*\* – p<0,01

a – vs

x –

(p<0,05) ( 30.).

NAFLD

DM 2.

NAFLD

NAFLD

(p<0,01),

(p<0,05).

DM 2

(p<0,001) ( 31.).

31.

DM 2

NAFLD

NAFLD

	n=28		n=21		n=6	
	15	53,57%	19	90,48% <sup>a**</sup>	6	100% <sup>a*</sup>
DM	5	17,86%	15	71,43% <sup>a***</sup>	6	100% <sup>a***</sup>

\* - p<0,05, \*\* - p<0,01, \*\*\* - p<0,001

a - vs

MS

NAFLD

(100,00%)

(78,57%),

MS,

MS:

SKP / DKP

DM 2.

(p<0,05).

TG

(p<0,05) ( 32.).

32.

NAFLD

NAFLD

	n=28		n=21		n=6	
MS	22	78,57%	20	95,24%	6	100,00%
MS						
MS (cm)	22	78,57%	20	95,24%	6	100,00%
MS HDL (mmol/l)	16	57,14%	14	66,67%	4	66,67%
MS TG (mmol/l)	20	71,43% <sup>c*</sup>	15	71,43%	1	16,67%
MS /SKP /DKP	23	82,14%	21	100,00%	6	100,00%
MS ×5,6 mmol/l/DM	14	50,00%	18	85,71% <sup>a*</sup>	6	100,00% <sup>a*</sup>
MS						
0						
1	1	3,57%	0	0,00%	0	0,00%
2	5	17,86%	1	4,76%	0	0,00%
3	9	32,14%	5	23,81%	2	33,33%
4	8	28,57%	5	23,81%	3	50,00%
5	5	17,86%	10	47,62%	1	16,67%

\* – p<0.05

a – vs

, c – vs

MS

NAFLD

### 6.10. Резултати ултразвучног прегледа јетре

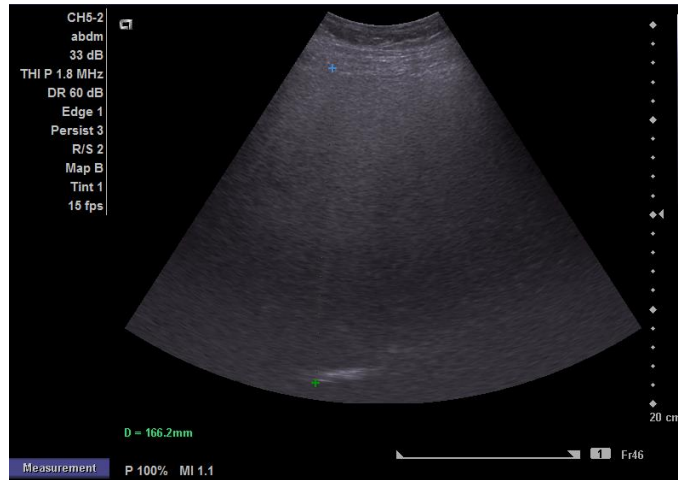
UZ  
I  
UZ  
II  
(C 4.), III,  
UZ (C 5.).



3. I.



4. II.



5. , III.

NAFLD , 23 (41,82%),  
 III , 20 (36,36%) UZ  
 II 12 (21,82%) I .  
 Kruskal-Wallis ANOVA ,  
 , LDL , OS, BMI ( $p < 0,05$ ), HOMA-IR TT ( $p < 0,01$ )  
 ( 33.).  
 - Mann-Whitney ,  
 , NAFLD  
 II BMI  
 I , I  
 ,  $33,26 \pm 4,16$  (33,29) vs.  $29,85 \pm 3,11$  (33,26)  $\text{kg/m}^2$  ( $p < 0,05$ ). ,  
 UZ III , UZ  
 I , OS ( $109,26 \pm 7,76$   
 vs.  $100,75 \pm 6,15$  cm) BMI ( $34,01 \pm 4,12$  vs.  $29,85 \pm 3,11$   $\text{kg/m}^2$ ) ( $p < 0,01$ ).  
 UZ  
 III , UZ  
 II ( $p < 0,05$ ) UZ I ( $p < 0,001$ ).  
 UZ I  
 HOMA-IR

UZ II (p<0,01) III (p<0,05). UZ I (p<0,05).  
 II III I  
 , ALP, GGT, , CRP,  
 ( 33.).  
 33.,  
 NAFLD UZ

	NAFLD UZ I	n=12	NAFLD UZ II	n=20	NAFLD UZ III	n=23
( )	48,00 ± 15,18	53	50,80 ± 12,74	54	48,65 ± 12,36	52
(mmol/l)	5,49 ± 0,93	5,35	7,10 ± 2,97	<sup>a*</sup> 6,00	6,64 ± 2,24	<sup>a*</sup> 6,10
( $\mu$ mol/l) <sup>a*</sup>	22,92 ± 8,16	22	48,03 ± 33,13	<sup>a**</sup> 35,40	39,92 ± 29,15	<sup>a*</sup> 30,00
HOMA-IR <sup>**</sup>	5,61 ± 2,12	5,16	18,11 ± 21,99	<sup>a**</sup> 8,50	14,01 ± 20,03	<sup>a*</sup> 7,92
( $\mu$ mol/l)	350,86 ± 95,67	336,65	382,27 ± 106,38	375,25	376,52 ± 85,07	381,3
UBIL ( $\mu$ mol/l)	11,15 ± 2,7	11,6	14,23 ± 7,15	12,1	12,38 ± 5,23	12,2
DBIL ( $\mu$ mol/l)	1,78 ± 0,47	1,8	2,45 ± 1,44	2,1	2,28 ± 0,89	2,1
(g/l)	45,06 ± 2,57	44,85	44,87 ± 3,29	44,85	45,33 ± 3,26	46
HOL (mmol/l)	6,27 ± 0,94	5,83	5,99 ± 0,98	6,17	5,54 ± 1,13	5,28
HDL (mmol/l)	1,25 ± 0,24	1,18	1,12 ± 0,22	1,08	1,12 ± 0,27	1,12
LDL (mmol/l)	4,15 ± 0,83	<sup>c*</sup> 4,05	3,92 ± 0,9	3,95	3,41 ± 0,9	3,5
TG (mmol/l)	2,24 ± 1,25	1,83	2,32 ± 0,94	1,87	2,27 ± 1,23	1,96
AST (U/l)	38,51 ± 23,19	33,2	43,32 ± 26,89	35	38,30 ± 16,14	34,8
ALT (U/l)	50,04 ± 21,91	46,45	67,36 ± 61,87	54,55	57,74 ± 32,93	55,3
ALP (U/l)	72,26 ± 26,44	65,55	71,88 ± 28,34	61,8	71,61 ± 31,21	65,9
GGT (U/l)	84,10 ± 113,11	39,7	50,68 ± 50,56	35,1	59,41 ± 45,37	41,7
CRP (mg/l)	5,69 ± 4,9	4,15	7,11 ± 14,95	3,65	5,68 ± 7,65	3,2
( $\mu$ g/l)	151,88 ± 161,38	111,05	137,57 ± 100,73	129,95	148,78 ± 98,56	142,7
INR	1,02 ± 0,05	1,03	1,09 ± 0,08	<sup>a*</sup> 1,08	1,08 ± 0,14	1,03
FIB (g/l)	4,46 ± 0,7	4,29	4,60 ± 1,31	4,28	4,36 ± 0,91	4,2
TR x10 <sup>9</sup> /l	245,17 ± 58,12	245,5	256,45 ± 79,25	237,5	229,43 ± 58,44	226
OS (cm) <sup>*</sup>	100,75 ± 6,15	101	106,40 ± 9	103,5	109,26 ± 7,76	<sup>a**</sup> 107,00
TT(kg) <sup>**</sup>	82,10 ± 9,22	79,1	89,77 ± 13,59	91,5	99,63 ± 14,8	<sup>a***b*</sup> 100,00
TV (m)	1,66 ± 0,12	1,66	1,64 ± 0,1	1,61	1,71 ± 0,12	<sup>b*</sup> 1,72
BMI (kg/m <sup>2</sup> ) <sup>*</sup>	29,85 ± 3,11	29,27	33,26 ± 4,16	<sup>a*</sup> 33,29	34,01 ± 4,12	<sup>a**</sup> 34,22
SKP (mmHg)	132,92 ± 13,22	140	132,50 ± 15,6	130	143,48 ± 21,92	140
DKP (mmHg)	82,08 ± 10,33	80	83,00 ± 9,51	80	87,61 ± 11,57	90
AST/ALT	0,78 ± 0,26	0,69	0,80 ± 0,34	0,74	0,78 ± 0,39	0,63

a - vs UZ I, b - vs UZ II, c - vs UZ III,  
 \* - p<0,05, \*\* - p<0,01, \*\*\* - p<0,001

UZ II III  
 UZ I (p<0,05),  
 3x2. ,  
 UZ II UZ  
 I (p<0,05), ( 34.).  
 34. BMI UZ

	NAFLD UZ I, n=12		NAFLD UZ II, n=20		NAFLD UZ III, n=23	
	Broj	%	Broj	%	Broj	%
BMI (kg/m <sup>2</sup> )						
BMI < 18,5 kg/m <sup>2</sup>	0	0,00%	0	0,00%	0	0,00%
BMI o 18,5 kg/m <sup>2</sup> 24,9 kg/m <sup>2</sup>	0	0,00%	0	0,00%	0	0,00%
BMI o 25 kg/m <sup>2</sup> 29,9 kg/m <sup>2</sup>	8	66,67%	4	20,00%	5	21,74%
BMI x 30,0 kg/m <sup>2</sup> *	4	33,33%	16	80% <sup>a*</sup>	18	78,26% <sup>a*</sup>
BMI (kg/m <sup>2</sup> )		%		%		%
BMI o 30 kg/m <sup>2</sup> 34,99 kg/m <sup>2</sup>	3	25,00%	10	50,00% <sup>ax*</sup>	9	39,13% <sup>ax*</sup>
BMI o 35 kg/m <sup>2</sup> 39,99 kg/m <sup>2</sup>	1	8,33%	5	25,00%	7	30,43%
BMI 40 kg/m <sup>2</sup>	0	0,00%	1	5,00%	2	8,70%

\* – p<0,05

a ó vs.

I, xó

BMI ≥ 30 kg/m<sup>2</sup>

3x2

DM 2

NAFLD

UZ

(p<0,05) ( 35.).

35.

DM 2

NAFLD

UZ

	NAFLD UZ I, n=12		NAFLD UZ II, n=20		NAFLD UZ III, n=23	
*	5	41,56%	16	80,00% <sup>a*</sup>	19	82,61% <sup>a*</sup>
DM*	2	16,67%	10	50,00%	14	60,87% <sup>a</sup>

\* – p<0,05, a ó vs. UZ

I



UZ II III (p<0,05).  
 , DM 2 UZ  
 III ,  
 UZ I (p<0,05) ( 35.).  
 NAFLD UZ II III p<0,05.  
 NAFLD UZ III  
 UZ II ( 36.).  
 36. NAFLD UZ

	NAFLD UZ I, n=12		NAFLD UZ II, n=20		NAFLD UZ III, n=23	
	7	58,33%	15	75,00%	10	43,48%
	5	41,67%	5	25,00%	13	56,52% <sup>b*</sup>

\* – p<0,05, b ó vs.

II

UZ II III (p<0,01) UZ  
 I ( 37.).  
 HDL-  
 UZ I  
 II (p<0,01) III UZ  
 (p<0,05). DM 2  
 III UZ ,  
 UZ I (p<0,05) (T 37.)  
 NAFLD UZ II III  
 4 5  
 UZ I (p<0,05) ( 37.).

37. NAFLD  
UZ

	NAFLD UZ I, n=12		NAFLD UZ II, n=20		NAFLD UZ III, n=23	
MS	6	50,00%	20	100,00% <sup>a**</sup>	22	95,65% <sup>a**</sup>
MS						
MS (cm)	9	75,00%	18	90,00%	21	91,30%
MS HDL (mmol/l)	3	25,00%	15	75,00% <sup>a**</sup>	15	65,22% <sup>a*</sup>
MS TG (mmol/l)	7	58,33%	13	65,00%	16	69,57%
MS /SKP / DKP	10	83,33%	18	90,00%	22	95,65%
MS ×5,6 mmol/l/DM	5	41,67%	15	75,00%	18	78,26% <sup>a*</sup>
MS						
0	0	0,00%	0	0,00%	0	0,00%
1	1	8,33%	0	0,00%	0	0,00%
2	5	41,67%	0	0,00%	1	4,35%
3	3	25,00%	6	30,00%	7	30,43%
4	1	8,33%	9	45,00% <sup>ax*</sup>	6	26,09% <sup>ax*</sup>
5	2	16,67%	5	25,00%	9	39,13%

\* – p<0,05, \*\* – p<0,01,  
a – vs UZ I, x ó

4 i 5

MS

6.10.1. Предиктори ултразвучног налаза масне јетре

6.10.1.1. Резултати униваријантне логистичке регресионе анализе

NAFLD (UZ II III) : BMI, MS, MS, MS HDL (p<0,01), , HOMA-IR, OS, TT, , DM 2 MS DM 2 (p<0,05). MS UZ 42 (IP 4,28–411,97), MS HDL 6,92 (IP 1,61–29,80), 7,56 (IP 1,85–30,86), 5,63 (IP 1,20–26,41), 10,67 (IP 1,12–101,34), DM 2 6,32 (1,23–32,34), 6,12 (IP

1,54–24,37), MS DM 2  
 4,62 (IP 1,20–17,79) ( 38.).

38. OR

	OR	95% IP		p
( )	1,01	0,96	1,06	0,6939
	1,01	0,28	3,69	0,9904
(mmol/l)	2,23	0,98	5,07	0,0558
(mu/l)	1,08	1,01	1,16	*0,0248
HOMAIR	1,39	1,04	1,86	*0,0250
(μmol/l)	1,00	1,00	1,01	0,3567
UBIL (μmol/l)	1,08	0,95	1,23	0,2612
DBIL (μmol/l)	2,12	0,86	5,19	0,1021
(g/l)	1,01	0,82	1,24	0,9537
HOL (mmol/l)	0,61	0,32	1,17	0,1386
HDL (mmol/l)	0,12	0,01	1,80	0,1233
LDL (mmol/l)	0,52	0,24	1,13	0,1002
TG (mmol/l)	1,04	0,58	1,88	0,8868
AST (U/l)	1,00	0,97	1,04	0,7637
ALT (U/l)	1,01	0,99	1,03	0,4031
ALP (U/l)	1,00	0,98	1,02	0,9552
GGT (U/l)	0,99	0,99	1,00	0,2247
CRP (mg/l)	1,01	0,94	1,08	0,8467
(μg/l)	1,00	0,99	1,00	0,8208
FIB (g/l)	1,02	0,54	1,92	0,9569
TR x10 <sup>9</sup> /l	1,00	0,99	1,01	0,8832
OS (cm)	1,16	1,03	1,31	*0,0150
TT (kg)	1,08	1,02	1,14	*0,0115
BMI (kg/m <sup>2</sup> )	1,34	1,07	1,67	***0,0094
	5,63	1,20	26,41	*0,0285
	10,67	1,12	101,34	*0,0393
	7,56	1,85	30,86	0,0049
SKP (mmHg)	1,02	0,98	1,06	0,3675
DKP (mmHg)	1,03	0,97	1,09	0,3326
	6,12	1,54	24,37	*0,0101
DM	6,32	1,23	32,34	*0,0270
MS OS (cm)	3,25	0,62	17,15	0,1648
MS HDL (mmol/l)	6,92	1,61	29,80	***0,0094
MS TG (mmol/l)	1,48	0,40	5,50	0,5587
MS /SKP / DKP	2,67	0,39	18,17	0,3164
MS ×5,6 mmol/l/DM	4,62	1,20	17,79	*0,0261
MS	3,27	1,47	7,29	***0,0037
MS	42,00	4,28	411,97	***0,0013

\* – p<0,05, \*\* – p<0,01, \*\*\* – p<0,001

MS 3,27 (IP 1,47–7,29), HOMA-IR 39% (IP 1,04–1,86),  
 BMI 34% (IP 1,07–1,67), S 16% (IP 1,03–1,31), 8% (IP 1,01–1,16),  
 TT 1kg UZ 8% (IP 1,02–1,14) ( 38.).

39.).

HDL UZ MS

39. OR

	OR	95% IP		p
TT (kg)	1,12	1,02	1,22	*0,0180
	15,25	1,97	118,25	**0,0091
MS HDL (mmol/l)	7,25	1,21	43,30	*0,0298
Constant	0,00			0,0126

\* – p<0,05, \*\* – p<0,01, R<sup>2</sup> = 0,5319

53,19% UZ  
 (R<sup>2</sup> = 0,5319). R  
 HDL  
 MS, IP  
 ( 39.).

6.11. Патохистолошка анализа биопсијских узорака пацијената  
NAFLD групе

16 (29,09%)

Brunt [144].

NAFLD, 4 (25%)

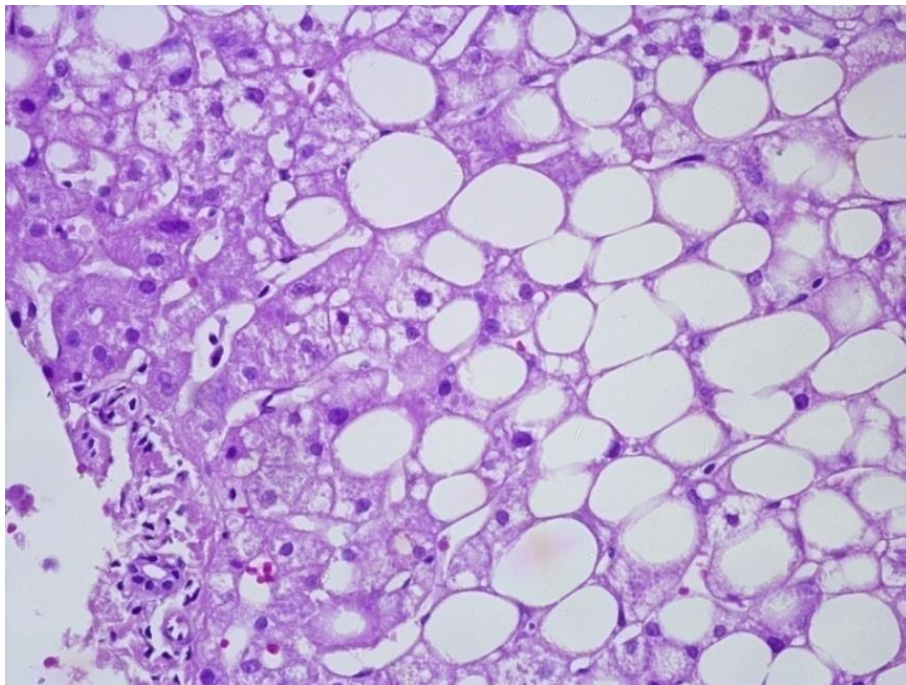
( 6.),

(NASH)

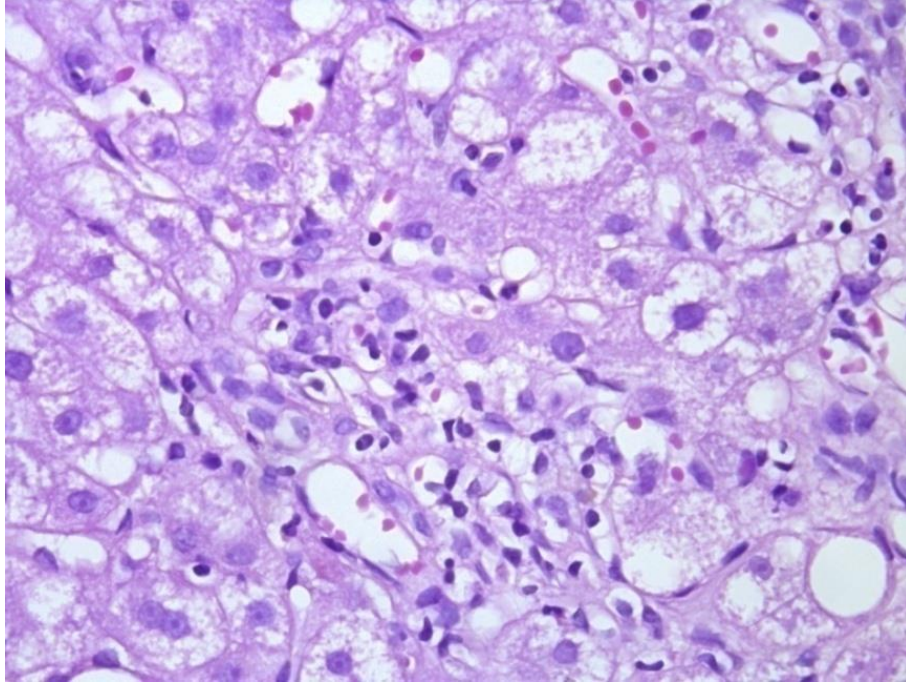
( ,  
)

75 %

( 7. 8.).

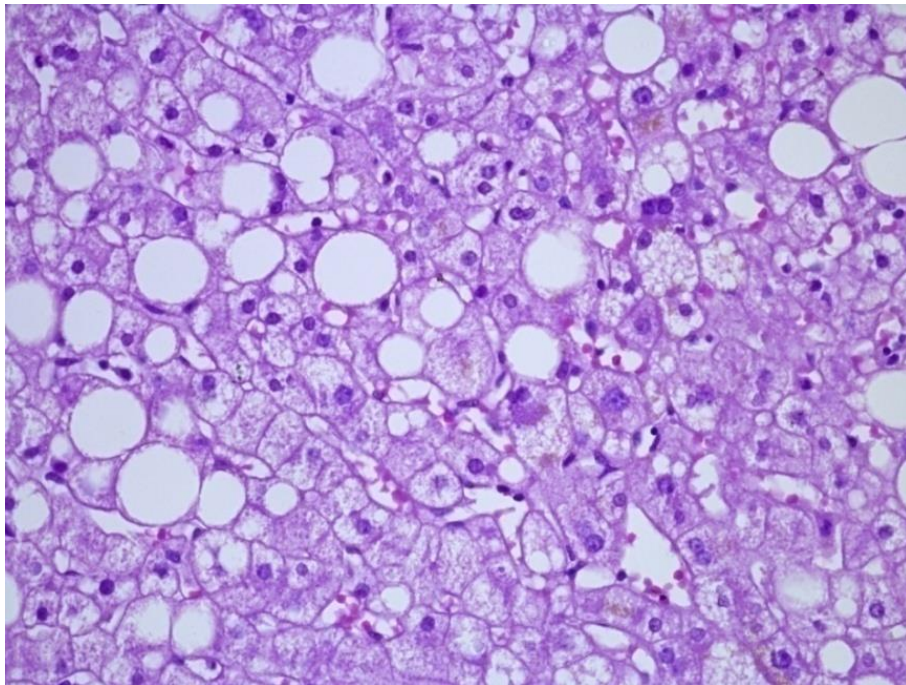


6. Steatosis hepatis. HE, x 40



7. Steatohepatitis.  
x 40

. HE,



8. o i Mallory hijalin. HE, objektiv x 10

, 56,25%  
 ( 1), 12,5%  
 ( 2) (6,25%)  
 ( 3).  
 (šbridgingō) (T 40.).

40.

NAFLD

Brunt .

	n=16	n %
1, 5% - 33%	7	43,75%
2, 33% - 66%	7	43,75%
3, >66%	2	12,5%
	3	18,75%
	6	37,5%
	7	43,75%
200x) (		
	3	18,75%
1=1	9	56,25%
2=2-4	3	18,75%
3=>4	1	6,25%
	6	37,5%
	7	43,75%
	3	18,75%
	0	0
0	4	25%
1,	9	56,25%
2,	2	12,5%
3,	1	6,25%
0	13	81,25%
/	0	0%
	2	12,5%
	1	6,25%
	0	0%

NASH  
 , HOMA-IR, , AST, ALT,  
 ALP, GGT, CRP, , OS, TT, BMI, SKP, DKP (p<0,001),  
 LDL (p<0,01), ,  
 (p<0,05) . NASH  
 HOMA-IR  
 (p<0,05) (T 41).

41. ,  
 , NASH

	, n=31		( . ), n=4		NASH, n=12	
( )	47,84 ± 10,08	49	48 ± 15,3	48,5	48,75 ± 11,76	49
(mmol/l)	5 ± 0,74	5	5,5 ± 1,07	5,6	6,12 ± 0,84	a*** 5,90
(mu/l)	12,41 ± 4,37	13	20 ± 5,29	a** 21,00	33,45 ± 17,28	a*** 28,50
HOMAIR	2,77 ± 1,07	2,88	4,72 ± 0,68	a** 4,89	9,31 ± 5,58	a*** b* 7,52
(µmol/l)	239,98 ± 56,57	237,4	373,1 ± 89,55	a** 373,05	353,21 ± 73,07	a*** 338,90
UBIL (µmol/l)	10,17 ± 2,91	9,9	9,3 ± 3,24	9,6	15,68 ± 5,38	a** b* 13,90
DBIL (µmol/l)	1,81 ± 0,54	1,6	1,55 ± 0,54	1,65	2,59 ± 0,92	a* 2,35
(g/l)	44,05 ± 3,84	44,9	43,2 ± 2,72	43,45	44,69 ± 2,45	44,75
HOL (mmol/l)	5,16 ± 1,08	5,12	5,98 ± 0,8	5,76	5,91 ± 0,78	a* 6,23
HDL (mmol/l)	1,28 ± 0,28	1,34	1,29 ± 0,21	1,21	1,13 ± 0,25	1,22
LDL (mmol/l)	3,26 ± 0,87	3,3	4,08 ± 0,82	4,05	4,05 ± 0,55	a** 4,00
TG (mmol/l)	1,2 ± 0,37	1,08	2,24 ± 1,39	1,91	1,75 ± 0,33	a*** 1,79
AST (U/l)	20,84 ± 4,25	20,1	45,1 ± 39,33	a* 28,15	49,48 ± 31,92	a*** 39,20
ALT (U/l)	16,85 ± 6,23	16,1	45,23 ± 24,37	a** 36,75	81,59 ± 74,38	a*** 51,40
ALP (U/l)	55,5 ± 16,56	49,8	72,2 ± 40,28	58,65	85,54 ± 30,69	a*** 74,10
GGT (U/l)	19,45 ± 14,97	14,7	173 ± 173,2	a** 116,25	71,58 ± 55,02	a*** 62,15
CRP (mg/l)	1,69 ± 1,63	1,1	8,53 ± 7,89	a* 6,95	8,12 ± 10,06	a*** 3,75
(µg/l)	45,65 ± 28,17	39,3	181,8 ± 291,6	46,45	126,46 ± 77,84	a*** 108,90
INR	1,08 ± 0,08	1,06	1,09 ± 0,1	1,05	1,11 ± 0,14	1,1
FIB (g/l)	3,48 ± 0,86	3,55	4,77 ± 0,92	a** 4,58	4,27 ± 0,99	a* 4,17
TR x10 <sup>9</sup> /l	c* 253,90 ± 50,48	261	215 ± 39,87	219	219,33 ± 32,54	220,5
OS (cm)	78,87 ± 7,18	79	102,5 ± 7,05	a*** 101,50	104,33 ± 9,07	a*** 103,50
TT (kg)	65 ± 8,9	62	84,75 ± 12,53	a** 85,00	85,95 ± 13,99	a*** 85,70
TV (m)	1,7 ± 0,09	1,68	1,67 ± 0,13	1,64	1,64 ± 0,11	1,6
BMI (kg/m <sup>2</sup> )	22,52 ± 2,08	22,77	30,4 ± 4,25	a** 30,11	31,85 ± 4,7	a*** 30,17
SKP (mmHg)	116,45 ± 13,86	120	137,5 ± 17,08	a* 135,00	145,83 ± 23,53	a*** 140,00
DKP (mmHg)	72,9 ± 9,98	70	87,5 ± 5	a** 90,00	85,83 ± 8,75	a*** 90,00
AST/ALT	/ ± /	/	0,92 ± 0,33	0,89	0,75 ± 0,37	0,62

\* - p<0,05, \*\* - p<0,01, \*\*\* - p<0,001

a - vs , b - vs , c - vs NASH



OS ( $p < 0,001$ ), HOMA-IR, L, GGT, BMI, DKP ( $p < 0,01$ ), SKP, AST CRP ( $p < 0,05$ ) NASH ( $p < 0,05$ ) (41.).

NASH ( $p < 0,001$ ). NASH ( $p < 0,05$ ) NASH ( $p < 0,001$ ) (42.).

NASH MS (91,67% vs. 9,68%) ( $p < 0,001$ ). SKP / DKP DM NASH ( $p < 0,001$ ). NASH DM 2 MS (p<0,01) MS HDL (p<0,05). NASH MS, 4 5 MS (p<0,001) (42.). 50% (p<0,001) (p<0,05) (42.).

42.  
, NASH

	, n=31		( . ), n=4		NASH, n=12	
	21	67,74%	3	75,00%	8	66,67%
	10	32,36%	1	25,00%	4	33,33%
BMI < 18,5kg/m <sup>2</sup>	1	3,23%	0	0,00%	0	0,00%
BMI 18,5 kg/m <sup>2</sup> 24,9 kg/m <sup>2</sup>	29	93,55%	0	0,00%	0	0,00%
BMI 25 kg/m <sup>2</sup> 29,9 kg/m <sup>2</sup>	1	3,23%	2	50,00% <sup>ax***</sup>	6	50,00% <sup>ax***</sup>
BMI × 30,0 kg/m <sup>2</sup>	0	0,00%	2	50,00%	6	50,00%
	31	100,00%	2	50,00%	6	50,00%
BMI 30 kg/m <sup>2</sup> 34,99 kg/m <sup>2</sup>	0	0,00%	1	25,00% <sup>ay*</sup>	4	33,33% <sup>ay***</sup>
BMI 35 kg/m <sup>2</sup> 39,99 kg/m <sup>2</sup>	0	0,00%	1	25,00%	1	8,33%
BMI 40 kg/m <sup>2</sup>	0	0,00%	0	0,00%	1	8,33%
	4	12,90%	2	50,0%	7	58,33% <sup>az**</sup>
DM	0	0,00%	1	25,00%	4	33,33% <sup>az**</sup>
MS	3	9,68%	2	50,00%	11	91,67% <sup>az***</sup>
MS						
MS (cm)	0	0,00%	3	75,00% <sup>az***</sup>	10	83,33% <sup>az***</sup>
MS HDL (mmol/l)	9	29,03%	2	50,00%	8	66,67% <sup>az*</sup>
S TG (mmol/l)	5	16,13%	3	75,00% <sup>az*</sup>	7	58,33% <sup>az**</sup>
MS /SKP / DKP	9	29,03%	3	75,00%	11	91,67% <sup>az***</sup>
MS ×5,6 mmol/l/DM	5	16,13%	2	50,00%	9	75,00% <sup>az***</sup>
MS						
0	14	45,16%	0	0,00%	0	0,00%
1	9	32,26%	1	25,00%	0	0,00%
2	5	12,90%	1	25,00%	1	8,33%
3	3	9,68%	0	0,00%	3	25,00% <sup>az***</sup>
4	0	0,00%	0	50,00%	6	50,00% <sup>aw***</sup>
5	0	0,00%	2	16,67%	2	16,67%

\* – p<0,05, \*\* – p<0,01, \*\*\* – p<0,001

a – vs

x –

y –

z –

w –

3, 4 5 S

4 5 S

6.12. Квантитативно мерење цитокератина-18 у крвној плазми.

18

NAFLD

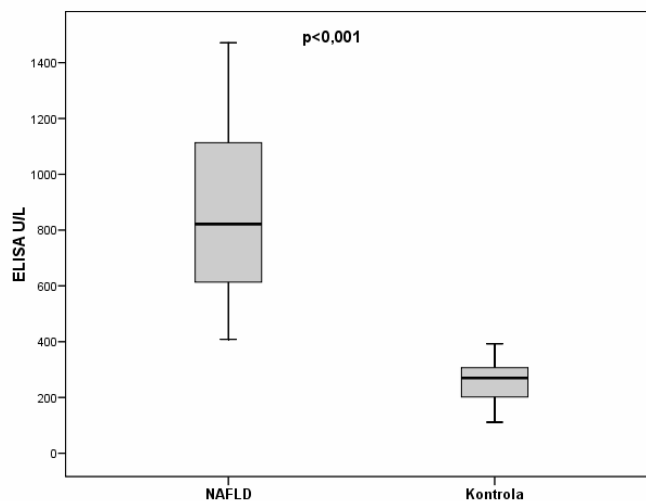
43. 1.

43. CK-18  
NAFLD

	, n=31		NAFLD, n=55	
CK-18 (U/L)	258,58 ± 79,39	270	879,81 ± 248,50	***964,50

\*\*\* – p<0,001

-18 NAFLD  
(879,81±248,50 vs. 258,58±79,39) (p<0,001) ( 43. 1.).



1. Box-plot

CK-18 NAFLD

44. CK-18  
NAFLD

	CK-18 (U/L)	
NAFLD , n=39	859,10 ± 351,70	741,50
, n=4	716,38 ± 213,62	651,00
NASH, n=12	998,29 ± 223,80	*1007,50

\* – p<0,05

-18

NASH

(998,29±223,80 vs. 716,38±213,62) (p<0,05)

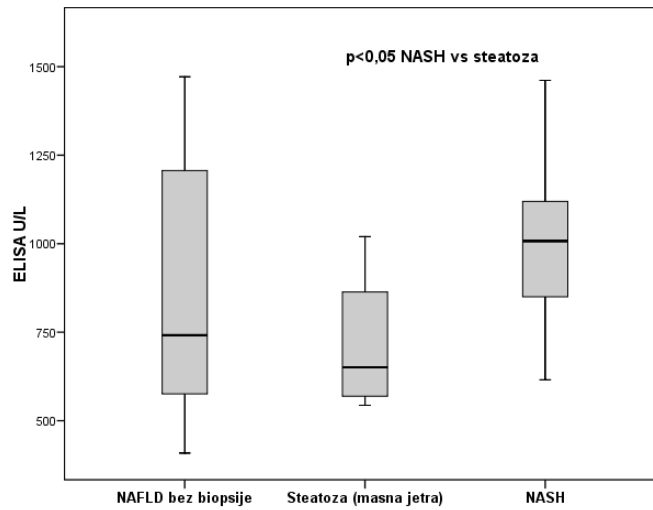
NAFLD

-18 NAFLD

859,10±351,70. Kruskal-Wallis

CK-18

( 44. 2.).



2. Box-plot

CK-18

NAFLD

45.

CK-18

NASH

NAFLD

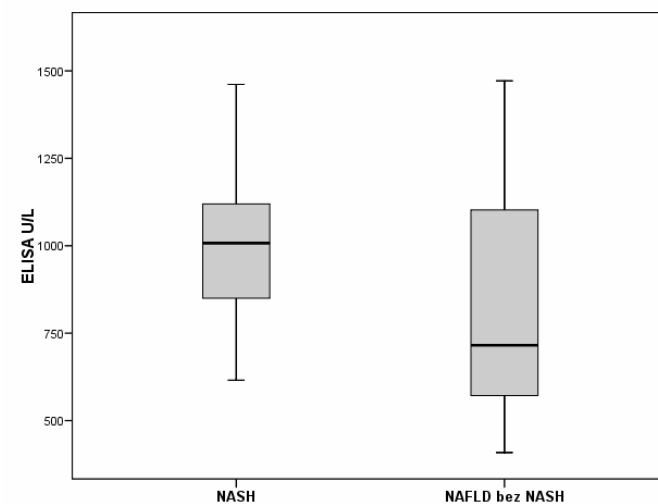
	NAFLD	NASH, n=43	NASH, n=12	
CK-18 (U/L)	845,83 ± 341,95	715,5	998,29 ± 223,80	*1007,50

NASH

-18

NAFLD

0,05 (p=0,0622) ( 45. 3.).

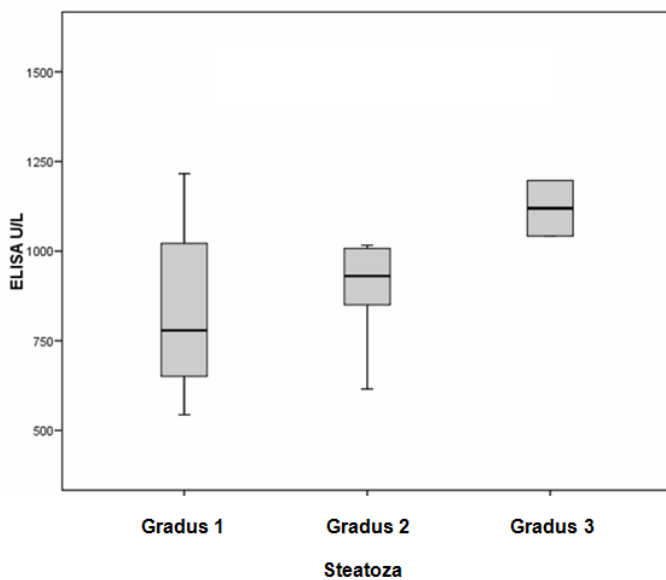


3. Box-plot ELISA NASH non-NASH  
NAFLD

46. CK-18 NAFLD

	. 1, n=7		. 2, n=7		.3, n=2	
CK-18 (U/L)	840,50 ± 250,54	779,5	960,36 ± 259,29	930,40	1119,50 ± 109,6	1119,5

. Kruskal Wallis (p<0,05), Mann-Whitney (46. -18 CK-18 4.).



4. Box-plot

CK-18

NAFLD

47.

CK-18

NAFLD

	. 0, n=3	. 1, n=9	. 2, n=3
CK-18 (U/L)	615,17 ± 83,6	900,94 ± 143,3	1143,17 ± 110,11
	595	<sup>a*</sup> 930,50	<sup>b*a**</sup> 1197,00

\* - p<0,05, \*\* - p<0,01

- vs. 0, - vs. 1

CK-18

, Kruskal Wallis

CK-18

(p<0,05).

-

CK-18

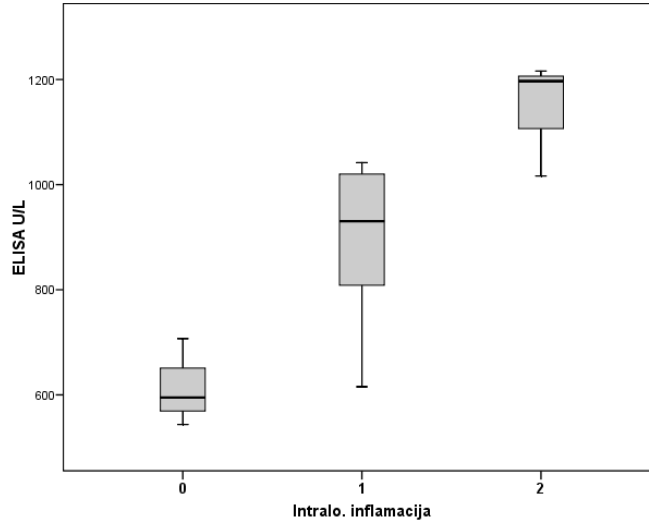
(p<0,05),

(p<0,01).

CK-18

( $p < 0,05$ )

( 47. 5.).



5. Box-plot

CK-18

NAFLD

48.

CK-18

NAFLD

	0, n=3		, n=6		, n=7				
CK-18 (U/L)	615,17	± 83,6	595	884,7	± 157,1	<sup>a*</sup> 911,00	1098,8	± 215,9	<sup>a**</sup> 1023,00

\* -  $p < 0,05$ , \*\* -  $p < 0,01$  a - vs. 0

CK-18

. ANOVOM

CK-18 ( $p < 0,01$ ).

-

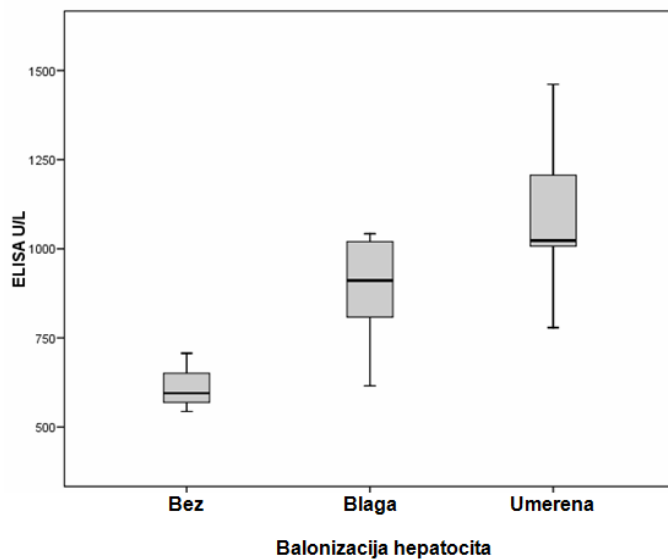
CK-18

( $p < 0,05$ ),

( $p < 0,01$ ) (

48.

6.).



6. Box-plot

CK-18

NAFLD

49.

CK-18

NAFLD

	0, n=13		2, n=2	
CK-18 (U/L)	855,81 ± 199,57	891,5	1129,00 ± 123,04	*1129,00

\* – p<0,05,

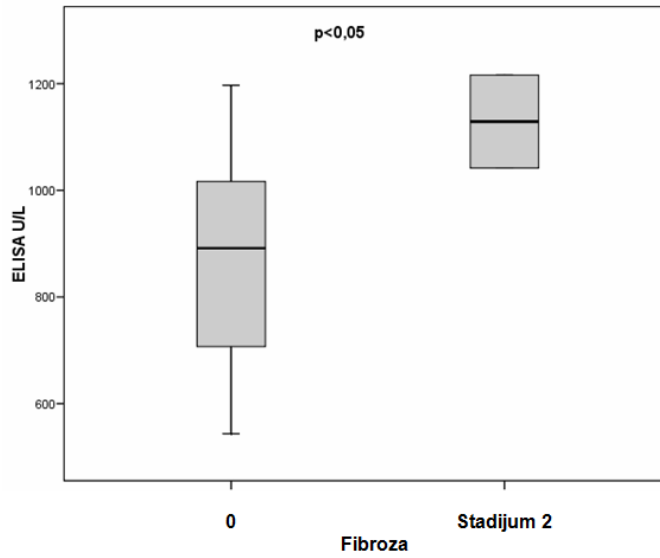
Mann-Whitney

CK-18

(1129,00±123,00 vs. 855,81±199,57) (p<0,05) ( 49.

7.).





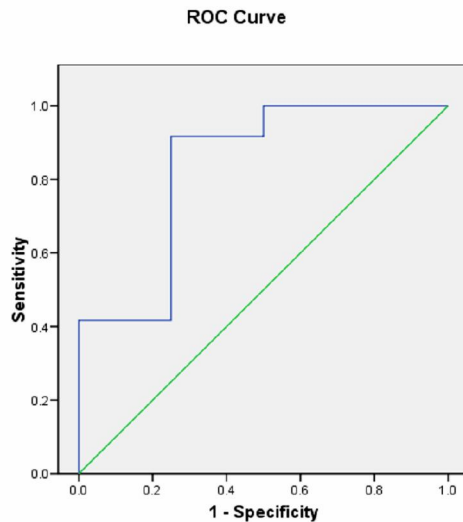
7. Box-plot

CK-18

**6.12.1. ROC анализа предиктивних вредности CK-18 у процени присуства NASH у NAFLD групи биопсираних пацијената**

9. ROC ( . receiver operating characteristic)

CK-18	NASH	
NAFLD.	0,83	0,13
	(p=0,0523)	95%
	(0.57 1.10)	.
	66,67%,	75%, 50%
	91,67%	.
ROC		
CK-18.	CK-18 743	92%,
	75% ( 50.).	



9. ROC  
NAFLD

NASH  
CK-18

50.  
NASH

CK-18

ELISA			±
542,50	1,0000	0,0000	1,000
569,25	1,0000	0,2500	1,250
605,25	1,0000	0,5000	1,500
661,25	0,9167	0,5000	1,417
<b>743,00</b>	<b>0,9167</b>	<b>0,7500</b>	<b>1,667</b>
793,75	0,8333	0,7500	1,583
850,00	0,7500	0,7500	1,500
911,00	0,6667	1,0000	1,417
964,50	0,5833	1,0000	1,333
1007,50	0,5000	1,0000	1,250
1018,25	0,4167	1,0000	1,167
1021,50	0,4167	1,0000	1,417
1032,50	0,3333	1,0000	1,333
1119,50	0,2500	1,0000	1,250
1206,50	0,1667	1,0000	1,167
1338,75	0,0833	1,0000	1,083
1462,50	0,0000	1,0000	1,000

18

(p&lt;0,01),

СК-

SKP (p&lt;0,05)

( 51.).

51.

СК-18

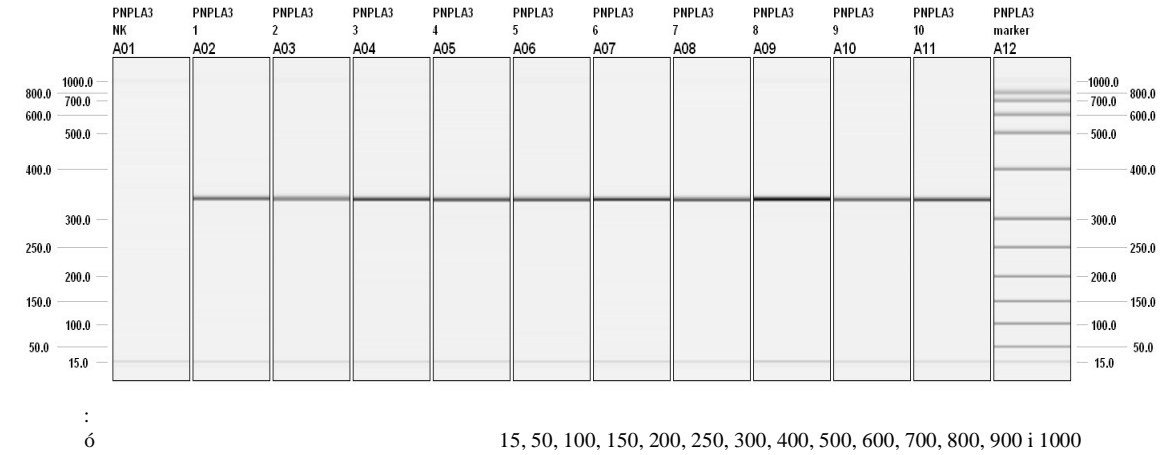
NAFLD

	r
( )	0,37**
(mmol/l)	0,36**
(mu/l)	0,23
HOMAIR	0,24
(μmol/l)	0,15
UBIL (μmol/l)	-0,04
DBIL (μmol/l)	0,05
(g/l)	-0,11
HOL (mmol/l)	-0,13
HDL (mmol/l)	-0,15
LDL (mmol/l)	-0,11
TG (mmol/l)	-0,05
AST (U/l)	0,11
ALT (U/l)	-0,01
ALP (U/l)	0,18
GGT (U/l)	-0,12
CRP (mg/l)	0,09
(μg/l)	-0,03
FIB (g/l)	0,28*
TR x10 <sup>9</sup> /l	-0,16
OS (cm)	0,23
TT (kg)	0,15
TV (m)	-0,14
BMI (kg/m <sup>2</sup> )	0,25
SKP (mmHg)	0,29*
DKP (mmHg)	0,23
AST/ALT	0,08

\* – p&lt;0,05, \*\* – p&lt;0,01

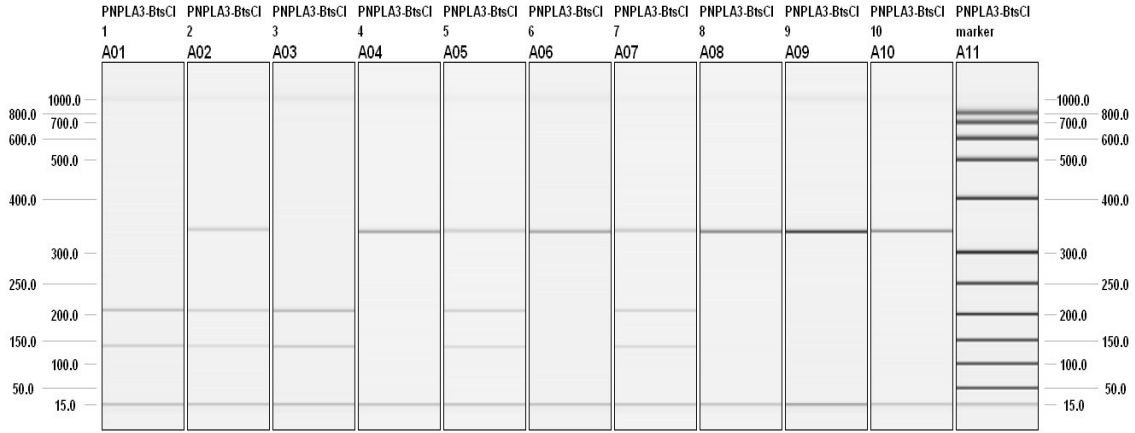
6.13. Резултати молекуларног испитивања, доказ полиморфизма  
**PNPLA3 rs738409 (C10109G)**

DNK 86 PCR ,  
 PCR 333 bp,  
 ( 10.).



1610 PCR . PCR DNK 333 bp.  
 10. DNK ( 1. 10.),  
 333 bp

PCR  
 BtsCI (New England Biolabs)  
 (C10109C), (C10109G)  
 (G10109G). DNK  
 333 bp 200 bp 133 bp,  
 333 bp, 200 bp 133 bp,  
 333 bp. PNPLA3 rs738409  
 ( 11.).



:  
 ó 15, 50, 100, 150, 200, 250, 300, 400, 500, 600, 700, 800, 900 i 1000

NK ó  
 : 1 i 3, (C10109C),  
 : 2, 5 i 7, (C10109G) i  
 : 4, 6, 8, 9 i 10, (G10109G).

11. PNPLA3 rs738409,  
 ( 1. 10.), BtsCI, PCR-RFLP  
 23 (26,74%)  
 (CC), 25 (29,07%) (CG) 38 (44,19%)  
 (GG) ( 52.).

52. NAFLD

	, n=31		NAFLD, n=55		, n=86	
C/C	10	32,26%	13	23,64%	23	26,74%
C/G	9	29,03%	16	29,09%	25	29,07%
G/G	12	38,71%	26	47,27%	38	44,19%

13 (23,64%) NAFLD CC , 16  
 (29,09%) , CG 26 (47,27%)  
 , GG. 10 (32,26%) CC  
 , 9 (29,03%) CG 12 GG  
 (38,71%). (GG)

NAFLD ( $\chi^2=0,58, p=0,4453$ ),

NAFLD ( 52.).

NAFLD 42 (76,36%)  
21(67,74%) .

G ,  
G NAFLD ,  
G

NAFLD ( $\chi^2=1,20, p=0,2732, OR=1,42; 0,72<OR<2,80$ ) ( 53.).

53. G ( C/G G/G)

NAFLD

		n=31	NAFLD	n=55
C/C	10	32,26%	13	23,64%
C/G ili G/G	21	67,74%	42	76,36%

NAFLD ( NAFLD ,

) (GG)  
(75%), NASH (58,33%),  
( ) (41,03%), (38,71%).

(C/C) NAFLD

NAFLD ( $\chi^2=4,99, p=0,5452$ ) ( 54.).

54. NAFLD

	, n=31		NAFLD, bb. n=39		, n=4		NASH, n=12	
C/C	10	32,26%	12	30,77%	0	0,00%	1	8,33%
C/G	9	29,03%	11	28,21%	1	25,00%	4	33,33%
G/G	12	38,71%	16	41,03%	3	75,00%	7	58,33%

NAFLD (100%) G , 1 C/G 3 G/G  
 . NASH 11(91,67%) G , 4 (33,33%)  
 C/G , 7 (58,33%) G/G ,  
 (C/C). (C/C)  
 , NASH ,  
 NAFLD  
 ( $\chi^2=4,34, p=0,2270$ ) ( 55.).

55. G ( C/G G/G)  
 NAFLD

	, n=31		NAFLD, bb. n=39		, n=4		NASH, n=12	
C/C	10	32,26%	12	30,77%	0	0,00%	1	8,33%
C/G ili G/G	21	67,74%	27	69,23%	4	100,00%	11	91,67%

G/G  
 S (44,51±26,18), S  
 C/G (41,83±18,65).  
 S  
 C/C (29,46±10,51) ( $p<0,05$ ).  
 L G/G (69,07±53,69)  
 C/C  
 (41,14±27,06) ( $p<0,05$ ).  
 C/G ,  
 C/C ( $p<0,05$ ) ( 56.).  
 -18 NAFLD  
 C/G , C/C  
 ,  
 CK-18 ( 56.).

56.  
NAFLD

	C/C, n=13		C/G, n=16		G/G, n=26	
( )	48,23 ± 12,92	51	50,88 ± 13,9	55,5	48,85 ± 12,8	52
(mmol/l)	5,95 ± 1,15	5,5	6,08 ± 1,2	5,65	7,15 ± 3,17	6,15
(mu/l)	28,12 ± 12,2	28	36,88 ± 18,1	30,4	46,08 ± 37,64	28
HOMAIR	7,7 ± 4,12	6,6	10,18 ± 5,93	7,42	18,79 ± 26,2	7,72
(µmol/l)	382,76 ± 132,15	377	398,6 ± 71,19	381,5	352,4 ± 83,51	363,7
UBIL (µmol/l)	12,67 ± 6,77	10,7	12,09 ± 5,63	10,2	13,27 ± 5,25	12,7
DBIL (µmol/l)	2,22 ± 1,58	1,7	2,19 ± 0,91	2	2,26 ± 0,91	2,15
(g/l)	44,45 ± 3,26	44,8	45,32 ± 2,89	45,05	45,3 ± 3,19	45,7
HOL (mmol/l)	5,96 ± 1,25	5,81	5,71 ± 0,94	5,48	5,91 ± 1,07	5,93
HDL (mmol/l)	1,1 ± 0,24	1,1	1,09 ± 0,27	1,13	1,21 ± 0,23	1,18
LDL (mmol/l)	3,84 ± 0,99	3,7	3,65 ± 0,8	3,75	3,78 ± 0,99	3,9
TG (mmol/l)	2,21 ± 1,26	1,88	2,17 ± 0,72	1,97	2,39 ± 1,27	1,86
AST (U/l)	29,46 ± 10,51	28	41,83 ± 18,65	<sup>a*</sup> 34,90	44,51 ± 26,18	<sup>a*</sup> 36,50
ALT (U/l)	41,14 ± 27,06	29,1	59,08 ± 33,29	52,85	69,07 ± 53,69	<sup>a*</sup> 56,40
ALP (U/l)	71,07 ± 25,87	65,9	62,54 ± 14,48	62,85	77,97 ± 35,12	63,25
GGT (U/l)	40,92 ± 30,28	30,6	51,34 ± 36,03	35,55	78,3 ± 89,04	44,75
CRP (mg/l)	12,25 ± 19,52	5,9	3,39 ± 2,04	3,15	4,91 ± 4,65	3,65
(µg/l)	113,86 ± 75,25	108,2	164,1 ± 111,3	132	149,6 ± 129,9	128,3
INR	1,06 ± 0,09	1,06	1,09 ± 0,13	1,06	1,07 ± 0,1	1,04
FIB (g/l)	4,7 ± 1,53	4,52	4,61 ± 0,63	4,68	4,27 ± 0,9	4,16
TR x10 <sup>9</sup> l <sup>-1</sup> *	279,08 ± 77,47	<sup>bc*</sup> 257,00	225,9 ± 46,19	215,5	234,9 ± 66,98	228,5
OS (cm)	105,46 ± 6,77	105	108,7 ± 8,62	109	105,4 ± 9,09	102,5
TT (kg)	87,82 ± 11,51	84	98,71 ± 18,04	99,5	90,42 ± 13,26	90,5
TV (m) *	1,6 ± 0,08	1,57	1,71 ± 0,13	<sup>a*</sup> 1,70	1,69 ± 0,1	<sup>a*</sup> 1,68
BMI (kg/m <sup>2</sup> )	34,24 ± 4,01	33,3	33,63 ± 3,81	34,01	31,62 ± 4,32	31,14
SKP (mmHg)	131,15 ± 10,83	130	144,7 ± 23,56	140	135,6 ± 17,34	135
DKP (mmHg)	83,08 ± 6,3	80	88,75 ± 11,03	<sup>a*</sup> 90,00	83,08 ± 11,84	85
CK-18 U/L	751,58 ± 338,99	615,50	980,4 ± 330,3	950,8	880,5 ± 302,6	882,3
AST/ALT	0,86 ± 0,34	0,78	0,78 ± 0,3	0,68	0,75 ± 0,37	0,63

\* - p<0,05, \*\* - p<0,01, \*\*\* - p<0,001  
a - vs C/C, b - vs C/G, c - vs G/G

DM 2, NAFLD, BMI, ( 57.).



57.

NAFLD

	C/C, n=13		C/G, n=16		G/G, n=26	
	10	76,92%	8	50,00%	14	53,85%
	3	23,08%	8	50,00%	12	46,15%
BMI < 18,5kg/m <sup>2</sup>	0	0,00%	0	0,00%	0	0,00%
BMI 18,5 kg/m <sup>2</sup> 24,9 kg/m <sup>2</sup>	0	0,00%	0	0,00%	0	0,00%
BMI 25 kg/m <sup>2</sup> 29,9 kg/m <sup>2</sup>	2	15,38%	4	25,00%	11	42,31%
BMI > 30,0 kg/m <sup>2</sup>	11	84,62%	12	75,00%	15	57,69%
	C/C, n=13		C/G, n=16		G/G, n=26	
	2	15,38%	4	25,00%	11	42,31%
BMI 30 kg/m <sup>2</sup> 34,99 kg/m <sup>2</sup>	6	46,15%	6	37,50%	10	38,46%
BMI 35 kg/m <sup>2</sup> 39,99 kg/m <sup>2</sup>	3	23,08%	6	37,50%	4	15,38%
BMI 40 kg/m <sup>2</sup>	2	15,38%	0	0,00%	1	3,85%
	9	69,23%	12	75,00%	19	73,08%
DM	8	61,54%	7	43,75%	11	42,31%
MS	12	92,31%	15	93,75%	21	80,77%
MS						
MS (cm)	12	92,31%	15	93,75%	21	80,77%
MS HDL (mmol/l)	9	69,23%	12	75,00%	12	46,15%
MS TG (mmol/l)	7	53,85%	11	68,75%	18	69,23%
MS /SKP / DKP	12	92,31%	15	93,75%	23	88,46%
MS ≥5,6 mmol/l/DM	9	69,23%	10	62,50%	19	73,08%
MS						
0	0	0,00%	0	0,00%	0	0,00%
1	0	0,00%	0	0,00%	1	3,85%
2	1	7,69%	1	6,25%	4	15,38%
3	5	38,46%	4	25,00%	7	26,92%
4	3	23,08%	6	37,50%	7	26,92%
5	4	30,77%	5	31,25%	7	26,92%

\* – p<0,05, \*\* – p<0,01, \*\*\* – p<0,001

C/C

, 10 GG 5

CG .

G , CG 3 GG .

NASH 11(91,67%) G , 4 (33,33%) CG

, 7 (58,33%) GG ,

CC.

NASH

G

GG

,  
CG,  
(bridging)

CG.

( 58).

58.

	C/C, n=1		C/G, n=5		G/G, n=10	
I, 5% - 33%	0	0,00%	3	60,00%	4	40,00%
II, 33% - 66%	1	100,00%	2	40,00%	4	40,00%
III, >66%	0	0,00%	0	0,00%	2	20,00%
	0	0,00%	1	20,00%	2	20,00%
	1	100,00%	0	0,00%	5	50,00%
	0	0,00%	4	80,00%	3	30,00%
	0	0,00%	1	20,00%	2	20,00%
1	1	100,00%	1	20,00%	7	70,00%
2-4	0	0,00%	2	40,00%	1	10,00%
>4	0	0,00%	1	20,00%	0	0,00%
0	1	100,00%	3	60,00%	9	90,00%
/	0	0,00%	0	0,00%	0	0,00%
	0	0,00%	1	20,00%	1	10,00%
	0	0,00%	1	20,00%	0	0,00%

\* - p<0,05, \*\* - p<0,01, \*\*\* - p<0,001

## 7. ДИСКУСИЈА

, ,

,

NAFLD

DM 2 ,

[184]

NAFLD

10-20%,

50% 90% BMI 35 kg/m<sup>2</sup>.

NAFLD 2 DM 50%.

HDL

NAFLD

[2,7,8, 27, 185]

NAFLD

PNPLA3 ,

NAFLD/NASH [22,108,109,186, 187]

HCC [33,152,156,157,158,159]

NAFLD

[7, 38, 58, 59]

ALT

§      ð [8, 188].      80%      NAFLD

NASH [17, 116, 117]      ALT,

NASH      ,      NAFLD

NASH      [189].

NAFLD

NASH,      ,      HCC

[184].

NAFLD

R,      c a      RS      ,

NAFLD

-18

NASH      [102, 136, 137, 138, 139],

52      ,      55      NAFLD,

§      ð.      31      ,

49      .      16      ,

6

. NAFLD 23  
 (41,82%) 32 (58,18%). 10  
 (32,26%) 21 (67,74%).  
 NAFLD . NAFLD  
 17 (30,91%) 38 (69,09%) .  
 , 22 (40,00%)  
 , 13 (23,64%) 3 (5,45%)  
 . , 29  
 . ,  
 NAFLD (p<0,001).  
 BMI (32,83±4,20 vs. 22,87±7,18 kg/m<sup>2</sup>) OS (106,36±8,44 vs. 78,87±7,18 cm)  
 NAFLD  
 (p<0,001).  
 Leite . NAFLD  
 BMI, OS (p<0,001)  
 [20] Williams . 45,4%  
 BMI (32,40±5,30 vs. 27,6±4,94 kg/m<sup>2</sup>)  
 [16] . Rocha . 53% NAFLD  
 , 40% , 30% 10 %  
 [190] . Kirovski .  
 BMI (28,7±5,9 vs. 24,8±3,6 kg/m<sup>2</sup>) OS (102,2±13,4  
 vs. 86,9±13,1 cm) NAFLD (p<0,001) [191],  
 .  
 26 (47,27%) NAFLD DM  
 2.  
 NAFLD 18%  
 45%. NAFLD  
 , ,  
 , ,  
 - . DM 2

157, 192, 193] NAFLD DM 2 , [42, NAFLD [39,154] .

AST/ALT MS, ,

NAFLD DM 2, NASH [38, 41,43] .

NAFLD (72,73% vs. 12,90%),

(137,18±18,60 vs. 116,45±13,86 mmHg) (84,73±10,69 vs. 72,90±9,98 mmHg)

(p<0,001). Hamaguchi . (123,7±15,9 mmHg)

(77,8±9,7 mmHg) NAFLD (p<0,001) [194]

Williams . 68,2 % NAFLD [16] .

NAFLD [195] .

NAFLD LDL , (p<0,05), ALP, (p<0,01), AST, ALT, GGT, , ,

, CRP, , HOMA-IR (p<0,001), HDL (p<0,05).

INR, .

NAFLD: , HOMA-IR, , TG, S , ALT,

GGT, CRP, , FIB, HOL, HDL , LDL , TT, MS, MS, SKP, DKP, OS.

NAFLD

[20, 42, 196, 197, 198]

NAFLD

42%-72% [199, 200]

NAFLD

, LDL

HDL

Lee [201] Kirovski [191]

NAFLD 16,02 , HOL 87%, LDL 85%, HDL NAFLD 87%.

NAFLD,

[202]

NAFLD

HOMA-IR

Salgado [203]

Önnerhag [204]

HOMA-IR

3,55

NAFLD.

(AST, ALT, GGT ALP),

ALT

NASH,

NAFLD

ALT

[117, 205]

AST/ALT

1

[38]

ALT

(p<0,001), GGT, S ALP (p<0,01).

S /ALT 0,68. NAFLD 0,79±0,34,

Hu . BMI, S, , G,

HDL , HOL, LDL ,

( , , , 2 DM)

NAFLD, [206]

NAFLD Leite .

ALT, TG OS ,

NAFLD 5 [20]. HDL

BMI

NAFLD Kirovski . [191].

Miyake .

, BMI, SKP DKP, S , ALT, GGT, ALP, HOL, TG, HDL

, LDL ,

NAFLD [207],

Bedogni . BMI, OS,

TG, , ALT HDL

NAFLD [5].

NAFLD 48 (87,27%)

MS. NAFLD

, MS (p<0,001).

NAFLD , 16 (29,09%) 3, 4 5 MS.

:

SKP / DKP 90,91%, 87,27%,

DM 69,9%, TG 65,45% HDL

60,00% ,

:

(p<0,01) HDL- DM 2 (p<0,001).



MS  
 NAFLD 64 , MS,  
 : SKP / DKP 24,44 ,  
 DM 11,62 TG 9,85  
 (p<0,001). HDL  
 NAFLD 3,78  
 (p<0,01). OS NAFLD  
 87% (p<0,01). , 1,  
 NAFLD 8,58 (p<0,001).  
 Pinidiyapathirage .  
 BMI×25 kg/m<sup>2</sup>, OS×90 cm OS×80 cm , SKP×130 mmHg,  
 DKP×85mmHg, ×5,6 mmol/l,  
 HOMA TG×1,7 mmol/l NAFLD.  
 , BMI OS NAFLD 5  
 [208].  
 Chituri .  
 87% NAFLD MS, 94%  
 , 82% , 50% [53]  
 98% Dvorak  
 . 98% NAFLD [19].  
 Radu .  
 : 88,41%,  
 68,87%, 62,58%,  
 55,79 % HDL 39,90 % [209]. Kotronen .  
 90% NAFLD  
 , 33% MS [210].  
 Hu .  
 NAFLD.  
 NAFLD 1,5 3,8  
 , SKP / DKP, ,

× 5,6 mmol/l

[206]

, DM,

TG NAFLD

Cheah 1,2

NAFLD [196]

Wang 3,6 NAFLD,

MS.

NAFLD

NAFLD [52]

Hamaguchi 3147 NAFLD

MS 4-11 NAFLD

[211]

MS NASH, AASLD,

NAFLD MS

[9]

, 29,09 % 5

90% NAFLD

, 33% [210]

212, 213]

MS NAFLD,

MS, 4

5

(p<0,001).

[59, 214], MS

MS NAFLD

, ÷ ÷

NASH

BMI, DM 2 MS.

NAFLD

MS

BMI, (p<0,01),

HOMA-IR (p<0,05)

MS.

NAFLD MS

HDL (p<0,05). NAFLD MS

(p<0,01) DM

2 (p<0,05) NAFLD MS.

NAFLD MS

11 (22,92%) , 37 (77,08%) , 22

(45,83%) , 12 (45,83%) 3

(6,25%) , NAFLD MS

NAFLD MS

NAFLD MS (p<0,01).

MS (97,37% vs.

64,71%), 3, 4 5 MS (p<0,01)

Kang

NAFLD MS

OS, HDL

HOMA [214]

Marchesini . MS

NAFLD BMI, 18% 67%

3 MS BMI,

[59]. Rocha .

BMI OS. 12%

56% [190]

20%-30% UZ

84,8% 93,6%

[215]

Nedleman

UZ 88% [181]

NAFLD , 23 (41,82%)

III , 20 (36,36%)

UZ II 12 (21,82%) UZ I

UZ II III

BMI,

HOMA-IR UZ

I , UZ III ,

OS.

, ALP, GGT,

, CRP,

(p<0,05)

(p<0,01)

UZ II III UZ

I , DM 2 UZ

III ,

UZ I (p<0,05).

HDL

UZ  
 4 5  
 I (p<0,05). MS DM  
 III ,  
 UZ I (p<0,05). UZ

: BMI, MS, MS, MS HDL  
 (p<0,01), , HOMA-IR, OS, ,  
 , DM MS  
 DM (p<0,05). MS  
 UZ 42 , MS  
 HDL 6,92 , 7,56 , 5,63 ,  
 10,67 , DM 6,32 , 6,12  
 MS DM 4,62 .

UZ : ,  
 HDL MS.  
 53,19% UZ .  
 Eguchi

OS, BMI,  
 HOMA-IR <sup>[216]</sup> Abanhag .  
 NAFLD II,  
 BMI  
 [197].  
 Ghamar-Chehreh .  
 , HOMA-IR,  
 , TG TT

[217]. Razavizade  
HDL- , TG ALT  
[218]  
, NAFLD  
,  
,  
MS UZ  
NAFLD UZ II III  
MS,  
[58, 219]  
UZ  
NAFLD [124],  
BMI×30 kg/m<sup>2</sup>.  
30% [125].  
[115, 126],  
UZ  
NAFLD,  
NASH  
HCC

HCC,  
NAFLD  
NAFLD.  
ngulo  
NAFLD  
(bridging  
NAFLD [141]. NAFLD  
NAFLD [220, 221]  
Angulo  
NAFLD, NAFLD,  
[222]  
AASLD NAFLD  
NAFLD, [9]  
NAFLD  
6 (10,91%)  
NAFLD 0,675  
28 (50,91%) NAFLD -1,45  
28 (50,91%)  
(p<0,001),

( $p < 0,01$ ).

,  
( $p < 0,05$ ),

S /ALT ( $p < 0,01$ ), BMI OS ( $p < 0,001$ ).

( $p < 0,05$ ).

DM 2.

NAFLD

( $p < 0,01$ )

( $p < 0,05$ ).

DM 2

( $p < 0,001$ ).

MS

NAFLD

(100,00%)

(78,57%),

MS,

ALT

ALT

( $p < 0,05$ ).

NAFLD

0,675,



S /ALT [38] 1 (1,27±0,51),

16 NAFLD

6 ,

(bridging )

0,675.

NAFLD

NAFLD

ALT

NAFLD

Brunt [144]

( , )

12

75 % . 4 (25%)

, 56,25%

, 12,5%

(6,25%)

(bridging)

NASH

, HOMA-IR, , TG,

S , ALT, ALP, GGT, CRP, , OS, , BMI, SKP, DKP (p<0,001),

, LDL (p<0,01), ,

(p<0,05). NASH

HOMA-IR

( $p < 0,05$ ).

OS ( $p < 0,001$ ), HOMA-IR, ALT, GGT, BMI, DKP ( $p < 0,01$ ), SKP, S CRP ( $p < 0,05$ ).

NASH (50% vs. 0,00%), NASH MS (91,67% vs. 9,68%) MS: (83,33% vs. 0,00%), SKP / DKP (91,67% vs. 29,03%),  $\times 5,6$  mmol/l DM (75% vs. 16,13%) ( $p < 0,001$ ), G (58,33% vs. 16,13%) ( $p < 0,01$ ) HDL (66,67% vs. 29,03%).

, NASH 4 5 MS ( $p < 0,001$ ), (58,33% vs. 12,90%) (33,33%). 50% G

Sobhonslidsuk . NASH BMI (27,7 vs. 23,9) OS (89,1 vs. 76,4) (86,7% vs. 33,3%), (50% vs. 13,3%), (63,3% vs. 6,7%) ( $p < 0,001$ ) . NASH S , ALT, , HOMA-IR, TG ( $p < 0,001$ ) ( $p < 0,01$ ) . HOMA NASH, [223]. Wasfy . , NASH , BMI, HOMA-IR , NASH TG ALT, . S S /ALT

NASH , ,  
HOMA-IR

NASH ,

[224]

Bookman .

NASH

NASH,

[254]

NASH,

Marchesini

. 88 %

[135]

NASH

MS

67%

NASH

[59]

, ð

ö.

[226]

NASH

-18,

[227].

,

,

,

-18, CK-18,

,

NASH,

,

[102, 136, 137, 138, 228, 229, 230].

Chen . 800

10 , Yang . -18,

-18,

NASH [231, 232].

AASLD NAFLD 2012.

-18 ,

CK-18

[9].

CK-18 NAFLD NASH

NASH

.

-

18 NAFLD

(p<0,001). CK-18

NASH

(p<0,05).

CK-18

, Kruskal Wallis

CK-18 ( $p < 0,05$ ).  
-  
CK-18  
( $p < 0,05$ ).  
CK-18  
-  
CK-18 ( $p < 0,01$ ).  
NASH  
CK-18  
( $p < 0,05$ ).  
CK-18  
SKP ( $p < 0,05$ ).  
Shen [137].  
CK-18 [227, 233].  
ROC  
CK-18 N SH NAFLD.  
0,83 0,13,  
( $p = 0,0523$ ), 95%  
(0,57 1,10). (*cut-off*) CK-18 743 U/L  
92%, 75%.  
CK-18  
NAFLD ( NASH )

NASH,

NAFLD,

[22, 109, 234] . Romeo .

, Dallas Heart ,

rs738409 (I148M) PNPLA3

MRS. G

(0,49),

(0,23) -

(0,17) [22].

I148M

PNPLA3 (

22 ,

NAFLD,

HCC [110, 111, 112, 113].

148.

PNPLA3 ,

[235, 236, 237] .

NAFLD

[238] ,

NAFLD.

PNPLA3 I148M

NASH,

, IR, C

[239].

PNPLA3

I148M

,  
 NAFLD [187, 240, 241, 242, 243] .  
 PNPLA3 I148M a  
 NAFLD,  
 BMI, , , TG, HDL-  
 LDL- [110, 111, 243, 244] .  
 PNPLA3 I148M  
 HOMA ,  
 HOMA-IR PNPLA3 I148M  
 , I148M PNPLA3  
 IR [110, 242, 243, 245] .  
 NAFLD .  
 PNPLA3 rs738409 , CC, CG GG  
 32,26%, 29,03% 38,71%,  
 NAFLD 23,64%, 29,09% 47,27%.  
 , NAFLD,  
 (GG)  
 S ALT ,  
 CC (p<0,05), PNPLA3 I148M  
 NAFLD. I148M  
 PNPLA3 BMI, , MS,  
 TG, HOL, HDL , LDL ,  
 HOMA-IR.  
 Romea .  
 HOMA-IR, , BMI,  
 LDL HDL [22] . Kotronen . , TG, HOL,  
 rs738409 S ALT,  
 , TG [242] .

Speliotes . PNPLA3 I148M  
 BMI, OS, TG, HDL , LDL , MS  
 HOMA-IR <sup>[110]</sup> .

Sookoian . PNPLA3 I148M  
 NAFLD , , BMI IR  
 HOMA. rs738409 G  
 S ALT, , BMI, HOMA-IR  
<sup>[243]</sup> .

rs738409  
 NAFLD  
 GG CC  
 ALT 28%.  
 rs738409

NAFLD  
 ,  
 HOMA-IR,  
 BMI <sup>[112]</sup> .  
 , rs738409  
 NAFLD  
 , rs738409  
 ,  
 [110, 111, 241, 243, 246] .  
 16 .  
 G , GG  
 , (GG 3,24  
 3,2  
 CC  
 I148M PNPLA3 ).



G

G [112]

, 15 G , 10 GG

, 5 CG 1

CC. (100%)

G , 1 CG 3 GG . NASH 11 (91,67%)

G , 4 (33,33%) CG , 7 (58,33%) GG

CC. NASH

G ,

CG, GG

(bridging) CG.

G

G

## 8. ЗАКЉУЧАК

:

1.

87,27 % NAFLD, 50%  
 NAFL 91,67% NASH.  
 , 29,09% 5  
 S  
 NAFLD NASH

2.

MS ,  
 NAFLD:  
 / × 130 mmHg /  
 × 85 mmHg 24,44 , DM 2  
 × 5,6 mmol/l 11,62 , × 1,7  
 mmol/l 9,85 , HDL  
 3,78 .  
 1,  
 NAFLD 8,58 .

3.

NAFLD  
 , ,  
 , DM 2  
 NAFLD ,  
 NAFLD .

MS

4. NAFLD

NAFLD (NAFL NASH)

HOMA-IR

NASH

NAFLD.

HOMA-IR

3,55

NAFLD.

5.

NAFLD.

NAFLD/NASH

LDL

HDL

NAFLD 16,02 , HOL 87%

LDL

85%,

HDL

NAFLD 87%.

6.

NAFLD (NAFL NASH)

OS

NAFLD

7.

NAFLD NASH

, DM 2,

8. DM 2 NAFLD , S /ALT,
- NAFLD ,
- DM 2 .
9. ALT , GGT, S ALP.
- NASH,
- NAFLD
- CRP, ,
10. NAFLD ,
11. NAFLD 0,675,
- DM 2, ,
- S /ALT 1.
12. NAFLD

13. II III  
BMI, OS, ,  
, DM 2,  
, 4 5

I .  
14. UZ,

15. ,  
: HDL 6,92 ,  
× 5,6 mmol/l DM 2 4,62 ,  
6,12 , 7,66 , 5,63  
10,67 . MS  
UZ  
3,27 .

16. , HDL  
53,19%  
NAFLD .

17. NAFLD  
CK-18 . NAFLD  
, CK-18  
NASH .

18. , CK-18 ,

19. NASH  
CK-18  
NASH .
20. CK-18  
NAFLD  
NASH ,
21. NASH NAFLD. š õ
22. I148M PNPLA3 NAFLD  
NAFLD,  
G S  
ALT,  
PNPLA3 I148M , CC ,  
NAFLD
23. I148M PNPLA3 BMI,  
, , , HDL  
, LDL ,  
, HOMA-IR,  
NAFLD,
24. G  
NAFLD,  
,

G

,

.

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## СКРАЋЕНИЦЕ

AASLD	( . <i>American Association for The Study of Liver Diseases</i> )
ALP	
ALT	
apo B	
AST	
ATP	
Bax	
BMI	( . <i>body mass index</i> )
bp	
CK-18	-18
CoA	Koenzim A
CRN	Clinical Research Network
CRP	C
CT	
DBIL	
DKP	
DM tip 2	2
FIB	
GGT	-
HCC	
HDL	( . <i>High Density Lipoprotein</i> )
HNE	
HOL	
HOMA-IR	( . <i>Homeostasis Model Insulin Resistance Assessment Index</i> )
hs-CRP	C (engl. <i>High sensitive-C reactive protein</i> )
Hus	
IDF	(engl. <i>International Diabetes Federation</i> )
IKK-	<i>kappa B</i>
IL	
INR	
IP	(engl. <i>confidence interval</i> )
IR	
KVB	

LDL	( . <i>Low Density Lipoprotein</i> )
MDA	
MR	
MRS	
MS	
MTP	
NAFL	( . <i>Non-alcoholic Fatty Liver</i> )
NAFLD	( . <i>Non-alcoholic Fatty Liver Disease</i> )
NAS	NAFLD <i>activity score</i>
NASH	( . <i>Non-alcoholic Steatohepatitis</i> )
NCEP-ATP III	<i>The National Cholesterol Educational Programm Adult Treatment Panel III</i>
NF-kB	<i>kappa B</i>
NHANES	<i>National Helth and Nutrition Examination Survey</i>
OR	( . <i>Odds Ratio</i> )
OS	
PCR	( . <i>Polymerase chain reaction</i> )
PNPLA3	<i>Patatin like phospholipase domain conteining-3</i>
PPAR	( . <i>Peroxisome proliferator-activated receptor gamma</i> )
SAD	
SKP	
SNP	( . <i>single nucleotide polymorphism</i> )
SREBP-1c	-1c ( . <i>Sterol regulatory element binding protein-1c</i> )
TE	
TG	
TGF	
TNF-	
TR	
TT	
TV	
UBIL	
UZ	
VLDL	( . <i>Very Low Density Lipoprotein</i> )
vs.	( . <i>versus</i> )
SZO	

## Биографија аутора

1972.

" - ", -

1999.

9,05 10

28.08.2000.

" "

26.12.2000.

01.01.2001.

2007.

2008/2009.

∅ -

∅ 28.06.2012.

2012.

2014. š

∅ -

2014.

## ИЗЈАВА О АУТОРСТВУ

Изјављујем да је докторска дисертација, под насловом

### **Клиничко-биохемијске карактеристике неалкохолне масне болести јетре као манифестације метаболичког синдрома**

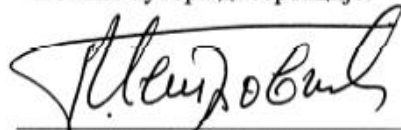
која је одбрањена на Медицинском факултету Универзитета у Нишу:

- резултат сопственог истраживачког рада;
- да ову дисертацију, ни у целини, нити у деловима, нисам пријављивала на другим факултетима, нити универзитетима;
- да нисам повредила ауторска права, нити злоупотребила интелектуалну својину других лица.

Дозвољавам да се објаве моји лични подаци, који су у вези са ауторством и добијањем академског звања доктора наука, као што су име и презиме, година и место рођења и датум одбране рада, и то у каталогу Библиотеке, Дигиталном репозиторијуму Универзитета у Нишу, као и у публикацијама Универзитета у Нишу.

У Нишу, \_\_\_\_\_.

Потпис аутора дисертације:



Др Гордана (Д) Петровић

**ИЗЈАВА О ИСТОВЕТНОСТИ ШТАМПАНОГ И ЕЛЕКТРОНСКОГ ОБЛИКА  
ДОКТОРСКЕ ДИСЕРТАЦИЈЕ**

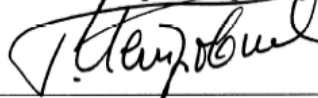
Наслов дисертације:

**Клиничко-биохемијске карактеристике неалкохолне масне  
болести јетре као манифестације метаболичког синдрома**

Изјављујем да је електронски облик моје докторске дисертације, коју сам предала за уношење у **Дигитални репозиторијум Универзитета у Нишу**, истоветан штампаном облику.

У Нишу, \_\_\_\_\_.

Потпис аутора дисертације:



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Др Гордана (Д) Петровић

## ИЗЈАВА О КОРИШЋЕЊУ

Овлашћујем Универзитетску библиотеку „Никола Тесла“ да у Дигитални репозиторијум Универзитета у Нишу унесе моју докторску дисертацију, под насловом:

### **Клиничко-биохемијске карактеристике неалкохолне масне болести јетре као манифестације метаболичког синдрома**

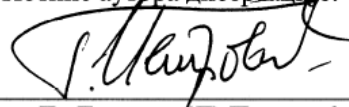
Дисертацију са свим прилозима предала сам у електронском облику, погодном за трајно архивирање.

Моју докторску дисертацију, унету у Дигитални репозиторијум Универзитета у Нишу, могу користити сви који поштују одредбе садржане у одабраном типу лиценце Креативне заједнице (Creative Commons), за коју сам се одлучио/ла.

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6. Ауторство – делити под истим условима (CC BY-SA)

У Нишу, \_\_\_\_\_.

Потпис аутора дисертације:



Др Гордана (Д) Петровић