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ORIGINAL ARTICLE

Reduced glutathione ameliorates liver function, oxidative stress and inflammation after interventional therapy for hepatocellular carcinoma

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Summary

Purpose: *To investigate the influence of reduced glutathione (GSH) in liver function, oxidative stress, inflammatory response, immune function and quality of life of patients after an interventional therapy for hepatocellular carcinoma.*

Methods: *96 hepatocellular carcinoma patients undergoing hepatic arterial intervention chemotherapy were selected and randomly divided into the control group (n=48) and the observation group (n=48). The patients in the control group were given conventional treatment after operation, while those in the observation group were treated with GSH based on the treatment in the control group. The liver function, oxidative stress, inflammation, quality of life and adverse reactions were compared before and after treatment between the two groups.*

Results: *The levels of superoxide dismutase (SOD), cluster of differentiation (CD)3+, CD4+ and CD4+/CD8+ as well as physical, emotion and social function scores after treatment were higher in the observation group than in the control group. The observation group had lower levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBiL), malondialdehyde (MDA), advanced oxidation protein product (AOPP), C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a) and CD8+ as well as pain score than the control group ($p<0.05$). The total effective rate in the observation group was remarkably higher than in the control group ($p<0.05$), while there were no significant differences in disease control rate and clinical adverse reactions between the two groups ($p>0.05$).*

Conclusions: *GSH can evidently ameliorate the liver function and immune function, reduce oxidative stress and inflammatory response and improve the postoperative quality of life of the patients after the interventional therapy for hepatocellular carcinoma, with satisfactory clinical therapeutic effects, so it is worthy of further application and generalization.*

Key words: *reduced glutathione, primary hepatocellular carcinoma, liver function, oxidative stress, inflammatory response*

Introduction

Primary hepatocellular carcinoma, a common malignant tumor in the clinic, is an important cause of cancer-related death. The morbidity rate ranks fifth, and the mortality rate ranks third among the malignant tumors according to clinical statistics. China has a high incidence of hepatocellular carcinoma, with the number of people affected accounting for over 50% of the total in the

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world, and the morbidity and mortality rates show constantly rising trends [1,2]. With the development of interventional radiology in recent years, transcatheter arterial infusion (TAI) and transcatheter arterial chemoembolization (TACE) have become the major non-radical therapies for primary hepatocellular carcinoma in clinical practice [3,4]. However, it has been reported in clinical studies that the liver function of the patients is impaired seriously, the content of reduced glutathione (GSH) in the body is decreased, and the oxidative stress and inflammation are aggravated after treatment with TAI and TACE, which can lower the quality of life in mild cases and even cause liver failure and death of patients in severe cases [5]. As a kind of antidote, GSH is capable of protecting the hepatocytes and ameliorating the hepatic microcirculation and function. In this research, the hepatocellular carcinoma patients receiving interventional therapy were supplemented with exogenous GSH after operation, so as to investigate the influences of GSH on the patient liver function, oxidative stress, inflammatory response, immune function and quality of life after the interventional therapy for hepatocellular carcinoma.

Methods

General data

A total of 96 patients with primary hepatocellular carcinoma admitted to and treated in our hospital from December 2017 to October 2018 were selected as the study subjects. The Ethics Committee of The Second Affiliated Hospital of Kunming Medical University approved this project and all patients signed the informed consent. Then, they were divided into the control group (n=48) and the observation group (n=48) using a random number table and double-blind method. There were 29 males and 19 females aged 45-75 years (mean 66.67 ± 4.63) in the control group. The course of disease was 6 months-4 years, with 2.44 ± 0.57 years on average. The Karnofsky performance status (KPS) score was 73.68±2.24, the tumor diameter was 5.47±1.21 cm, and the pathological stage included 21 cases in stage IIIb and 27 cases in stage IV. The observation group consisted of 27 males and 21 females aged 45-75 years (mean 66.35±4.57), with a course of disease of 6 months-4 years, (mean 2.51 ± 0.62 years), the KPS score of 74.11±2.30 and the tumor diameter was 5.54±1.23 cm. In terms of pathological stage, there were 20 cases in stage IIIb and 28 cases in stage IV. The general data, such as gender, age, course of disease, KPS score, tumor diameter and pathological stage had no statistically significant differences between the two groups (p>0.05), which were comparable.

Inclusion and exclusion criteria

All the patients who were definitely diagnosed through imaging, pathology and clinical symptoms and signs and met the related diagnostic criteria of primary hepatocellular carcinoma [6], and those with a KPS score>70, a Child-Pugh liver function classification of grade A or grade B, normal blood routine test results, leukocytes ≥ 3.5×10^9/L, platelets ≥ 70.0×10^9/L, hemoglobin ≥ 90.0×10^9/L and a Child-Pugh life expectancy of more than 6 months were enrolled. This research was approved by the Ethics Committee of our hospital, and the patients and their families were informed and signed the informed consent. Exclusion criteria: patients complicated with alcohol liver dysfunction, fatty liver or other serious liver conditions, those complicated with brain injury, systemic infection, hematologic disease, biliary calculi, acute pancreatitis, cholangiitis or other severe diseases, those who had tumor metastasis confirmed *via* computed tomography, those who had contraindications to chemotherapy, pregnant or lactating women, or those unwilling to participate in this research.

Therapeutic methods

All the patients underwent hepatic arterial intervention chemotherapy and completed various examinations before operation. Routine preparation for the operation was performed. With the patients in supine position, the right inguinal region was disinfected and draped, and the right femoral artery was punctured after local anesthesia with 2% lidocaine was satisfactory. The arterial sheath was implanted using a 4F guidewire to establish the femoral arterial channel, through which the catheter was sent to the celiac trunk for angiography. Digital subtraction angiography device was used to examine and define the lesion site, supplying vessels and complication of arteriovenous fistula. Then, under the guidance of the guidewire, the catheter was inserted into the hepatic artery or common hepatic artery through the arterial sheath. After the catheter was confirmed to be well inserted again, it was fixed, and the interventional therapy was performed. Next, 50 mg of oxaliplatin, 15 mg of epirubicin, 30 mg of epirubicin, 500 mg of tegafur and 2 mL of lipiodol were perfused until no deposition of lipiodol was visible at the lesion site. The next treatment was conducted after an interval of 40 days, and a total of 4 treatments were administered. After the operation, the patients received conventional treatments, such as gastric mucosal protection, antiemesis and analgesia according to the disease conditions. The patients in the control group were administered with 60 g of vitamin B, 2 g of vitamin C, 250 mL of branched-chain amino acid and 20 g of inosine for 7 consecutive days (once a day) after the operation. On the basis of the treatment in the control group, the patients in the observation group were given GSH (Shanghai Fudan Forward Science and Technology Co., Ltd., Shanghai, China. NMPN: H20031265, specification: 0.6 g*6 pcs). 1.8 g of GSH were dissolved in 250 mL of 5% glucose solution and then infused intravenously (once a day) for 21 days.

Evaluation indexes

About 3-5 mL of peripheral venous blood was collected before and after treatment and then centrifuged to harvest the supernatant, which was stored in a cryogenic refrigerator for later use (1): Changes in liver function

indexes before and after treatment included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin (TBiL), among which ALT and AST were measured *via* enzyme coupling method, ALP was detected by continuous monitoring assay, and TBiL was determined using diazonium salt method. (2): Changes in inflammatory indexes before and after treatment involved malondialdehyde (MDA), superoxide dismutase (SOD), advanced oxidation protein product (AOPP), interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α), among which MDA was measured by thiosulfate barbital condensation method, SOD by xanthine oxidase method, and AOPP, IL-6, CRP and TNF-α by enzyme-linked immunosorbent assay. (3): The changes in T-lymphocyte subsets [cluster of differentiation (CD)3+, CD4+, CD8+ and CD4+/CD8+] were determined before and after treatment. Peripheral venous blood (3 mL) was drawn from the elbow before and after treatment and then anticoagulated with heparin, and the T-lymphocyte subsets in the peripheral blood were detected using a full-automatic flow cytometer (Roche, Basel, Switzerland). All the relevant kits were purchased from Thermo Fisher Scientific (Waltham, MA, USA) in this research except for the SOD kit bought from Nanjing Jiancheng Bioengineering Institute (Nanjing, China), and the operations were performed in strict accordance with the instructions. (4): As for the quality of life before and after treatment, the Quality of Life Questionnaire Core 30 (QLQ-C30) [7] was utilized to score on the patients' quality of life (physical, emotional, pain and social functions) before and after treatment. Among them, the lower pain score indicates milder pain symptoms, while the higher scores of physical, emotional and social functions represent better quality of life of the patients.

Response evaluation

At 3 months after treatment, the therapeutic effect was evaluated according to the internationally used Response Evaluation Criteria in Solid Tumors [8], including complete response (CR) (The target lesion disappears completely for over 4 weeks based on the color Doppler ultrasonography or magnetic resonance imaging examination after treatment), partial response (PR) (After treatment, the target lesion is decreased by more than 30% for over 4 weeks), stable disease (SD) (The target lesion is decreased by less than 30% or increased by less than 20% after treatment) and progressive disease (PD) (After treatment, the target lesion is increased by more than 20%, or new lesion occurs). The effective rate= (CR+PR)/total cases ×100%, and disease control rate= (CR+PR+SD)/total cases ×100%.

Statistics

SPSS 22.0 software (SPSS Inc., Chicago, IL, USA) was used for data processing. The measurement data were expressed by mean±standard deviation (x±s), and evaluated by t-test. The enumeration data were presented as cases (n) or ratios (%), and x^2 was applied. P<0.05 suggested that the difference was statistically significant.

Results

Changes in liver function indexes before and after treatment in the two groups

The levels of ALT, AST, ALP and TBiL were elevated in both groups after treatment, but the observation group had lower levels of ALT, AST, ALP and TBiL than the control group after treatment (p<0.05) (Table 1).

Table 1. Comparisons of changes in liver function indexes before and after treatment between the two groups (x±s)

Group	*Time*	*ALT (U/L)*	*AST (U/L)*	*ALP (U/L)*	*TBiL (mmol/L)*
Control group (n=48)					
	Before treatment	56.78±21.44	74.44±18.79	121.45±11.33	38.45±8.87
	After treatment	102.12±24.11▲	126.32±21.35▲	137.27±10.89▲	56.68±9.46▲
Observation group (n=48)					
	Before treatment	57.45±19.56	72.79±19.47	122.23±12.45	38.77±9.11
	After treatment	77.36±19.67▲#	104.66±20.58▲#	166.27±11.63▲#	47.79±8.66▲#

▲p<0.05 *vs.* before treatment, #p<0.05 *vs.* control group

Table 2. Comparisons of changes in stress indexes before and after treatment between the two groups (x±s)

Group	*Time*	*MDA (nmo/L)*	*SOD (U/mL)*	*AOPP (μmol/L)*
Control group (n=48)				
	Before treatment	4.52±0.63	63.47±15.13	44.52±4.36
	After treatment	4.04±0.45▲	75.26±12.57▲	41.44±3.85▲
Observation group (n=48)				
	Before treatment	4.44±0.57	62.72±14.45	44.74±4.42
	After treatment	3.67±0.39▲#	84.68±10.51▲#	38.65±3.67▲#

▲p<0.05 *vs.* before treatment, #p<0.05 *vs.* control group

Changes in stress indexes before and after treatment in the two groups

After treatment, the MDA and AOPP levels declined, while the SOD level rose in both groups. However, the levels of MDA and AOPP were lower, and that of SOD was higher in the observation group than those in the control group, displaying statistically significant differences (p<0.05) (Table 2).

Changes in inflammatory indexes before and after treatment in the two groups

The levels of CRP, IL-6 and TNF-α were reduced after treatment in the two groups, and these levels were lowered in the observation group compared with those in the control group, with statistically significant differences (p<0.05) (Table 3).

Changes in T-lymphocyte subsets in the peripheral blood before and after treatment in the two groups

After treatment, both groups exhibited raised content of CD3+, CD4+ and CD4+/CD8+ and decreased CD8+ (p<0.05), and the observation group had higher content of CD3+, CD4+ and CD4+/CD8+ but lower CD8+ after treatment in comparison with the control group (p<0.05) (Table 4).

QLQ-C30 scores before and after treatment in the two groups

The scores of physical, emotional and social functions were increased, while the pain score was decreased in both groups after treatment (p<0.05). Moreover, the scores of physical, emotional and social functions were higher, but the pain score was lower in the observation group than those in the control group after treatment (p<0.05) (Table 5).

Clinical efficacy in the two groups

The observation group had a remarkably higher total effective rate than the control group

Table 3. Comparisons of changes in inflammatory indexes before and after treatment between the two groups (x±s)

Group	*Time*	*CRP (ng/L)*	*IL-6 (ng/L)*	*TNF-a (ng/L)*
Control group (n=48)				
	Before treatment	21.44±3.45	114.56±14.64	56.44±11.23
	After treatment	14.57±2.35▲	91.22±13.56▲	41.57±10.12▲
Observation group (n=48)				
	Before treatment	22.21±3.34	115.33±15.22	57.27±11.36
	After treatment	11.13±1.79▲#	75.67±12.45▲#	32.45±9.76▲#

▲p<0.05 *vs.* before treatment, #p<0.05 *vs.* control group

Table 4. Comparisons of changes in T-lymphocyte subsets in the peripheral blood before and after treatment between the two groups (x±s)

Group	*Time*	*CD3+ (%)*	*CD4+ (%)*	*CD8+ (%)*	*CD4+/CD8+*
Control group (n=48)					
	Before treatment	53.65±4.22	25.42±3.02	26.45±2.37	0.96±0.15
	After treatment	57.43±4.17▲	29.54±2.58▲	24.56±2.12▲	1.20±0.21▲
Observation group (n=48)					
	Before treatment	52.88±4.15	25.26±2.63	26.34±2.26	0.96±0.17
	After treatment	62.37±4.21▲#	32.14±2.44▲#	22.15±1.76▲#	1.45±0.23▲#

▲p<0.05 *vs.* before treatment, #p<0.05 *vs.* control group

Table 5. Comparisons of QLQ-C30 scores before and after treatment between the two groups (x±s, points)

Group	*Time*	*Physical function*	*Emotional function*	*Pain function*	*Social function*
Control group (n=48)					
	Before treatment	61.71±5.44	53.56±5.64	23.68±4.33	48.77±5.58
	After treatment	69.33±5.25▲	60.29±5.37▲	20.25±4.09▲	53.42±5.11▲
Observation group (n=48)					
	Before treatment	61.42±5.53	53.74±5.57	24.02±4.44	47.89±6.02
	After treatment	74.68±5.34▲#	65.78±4.86▲#	16.37±3.54▲#	58.77±5.45▲#

▲p<0.05 *vs.* before treatment, #p<0.05 *vs.* control group

Table 6. Comparison of clinical efficacy between the two groups

Group	*CR* *n*	*PR* *n*	*SD* *n*	*PD* *n*	*Total effective rate* *n (%)*	*Disease control rate* *n (%)*
Control group (n=48)	13	20	13	2	33 (68.75)	46 (95.83)
Observation group (n=48)	28	14	6	0	42 (87.50)#	48 (100.00)

#p<0.05 *vs.* control group

Table 7. Comparisons of clinical adverse reactions between the two groups [n (%)]

Group	*Nausea and vomiting*	*Thrombocytopenia*	*Leucopenia*	*Anemia*	*Mild bone marrow depression*
Control group (n=48)	15 (31.25)	13 (27.08)	10 (20.83)	11 (22.92)	18 (37.50)
Observation group (n=48)	14 (29.17)	15 (31.25)	9 (18.75)	9 (18.75)	17 (35.41)

(97.50% *vs.* 68.75%), and the difference was statistically significant (p<0.05). However, there was no statistically significant difference in the disease control rate between the two groups (100.00% *vs.* 95.83%) (p>0.05) (Table 6).

Clinical adverse reactions in the two groups

The incidence rates of adverse reactions such as nausea and vomiting, thrombocytopenia, leucopenia, anemia and mild bone marrow supression during treatment had no statistically significant differences between the two groups (p>0.05) (Table 7).

Discussion

Hepatocellular carcinoma, one of the most serious chronic liver diseases, has fairly high clinical morbidity and mortality rates, and most of the patients have had progressed and deteriorated carcinoma when definitely diagnosed because there are no apparent symptoms in the early stage of primary hepatocellular carcinoma, thus missing the best timing for operation and causing enormous difficulty to the clinical treatment of the disease [9]. With the application of TAI and TACE in the clinical treatment of hepatocellular carcinoma in recent years, increasingly more authors have noticed that the chemical drugs or embolic agents can kill the hepatocellular carcinoma cells and damage the normal hepatic tissue cells at the same time, and the postoperative liver function indexes such as ALT and AST in the patients are increased stepwise [10,11]. It has been reported in a relevant study [12] that the patients have severe liver function damage and markedly raised ALT and ALP after TACE. According to the results in this research, the levels of ALT, AST, ALP and TBiL were elevated in both groups, but the observation group had smaller increases in ALT, AST, ALP and TBiL than the control group after treatment (p<0.05), which are basically consistent with the above reports. However, the postoperative supplement of exogenous GSH can evidently weaken the increase in liver function indexes in the patients, suggesting that GSH has prominent protective effects on the liver function.

GSH is a tripeptide containing γ-amide bond and active sulfhydryl, which is composed of glutamic acid, cystine and glycine and exists widely in cells, and it can activate the redox system and sulfhedryl protease in the body. In addition, GSH plays crucial roles in maintaining the normal immune system function, resisting oxidation and integrating detoxication [13]. As a vital organ with metabolic functions in human body, the liver possesses multiple functions and roles such as deoxidation, storage of hepatic glycogen, secretion and synthesis of proteins as well as detoxication. The direct toxicity of anticancer drugs stimulates the liver to produce massive electrophilic groups, free radicals and other toxic substances, further attacking the hepatic tissues and cells, inducing peroxidation damage to the lipids in liver organelles or liver cell membrane, thus improving the oxidative stress level in the hepatic tissues, aggravating inflammatory responses and ultimately resulting in the hepatocyte necrosis [14,15]. MDA is the end product of lipid peroxidation under the action of free radicals *in vivo*, which can trigger the crosslinking polymerization of biomacromolecules including proteins and nucleic acids and possesses relatively strong cytotoxicity. The expression level of AOPP, a product of saccharification/oxidative modification of proteins, is closely associated with the oxidative stress level in the body, and AOPP has been proven to be an important clinical marker of oxidative stress so far [16]. As a vital antioxidant enzyme in organisms, SOD is able to eliminate the harmful substances generated during the metabolism

in vivo. In the process of peroxidation damage to the hepatic tissues, the exacerbated oxidative stress can increase the levels of MDA and AOPP, and a large amount of SOD is activated in the body for the purpose of maintaining normal metabolic functions. Therefore, the changes in the MDA, AOPP and SOD levels can effectively reflect the degree of tissue injury caused by the stress response [17]. The results in this research indicated that the levels of MDA and AOPP were lower, and that of SOD was higher in the observation group after treatment than those in the control group ($p<0.05$), implying that GSH protects the hepatocyte from injury by inhibiting the stress response in the hepatic tissues.

For the hepatocellular carcinoma patients receiving chemotherapy, the oxidative stress and high inflammatory response are triggered simultaneously, in which the oxidative stress can stimulate the occurrence of inflammatory response, and the inflammatory response can also aggravate the oxidative stress [18]. IL-6 is one of the common pro-inflammatory cytokines in the clinic, which participates in the whole process of inflammatory response in the body on the one hand and directly reflects the severity of oxidative stress on the other hand. When the organism is in a stress status, the IL-6 level rises consistently, further induces CRP synthesis, promotes TNF-α secretion, affects the defense ability of the body and obviously alters the T-lymphocyte subsets in the peripheral blood of the patients, thereby influencing the efficacy of chemotherapy [19,20]. In this research it was revealed that the levels of CRP, IL-6 and TNF-α were reduced after treatment in the observation group compared with those in the control group ($p<0.05$), and the levels of T-lymphocyte subsets in the peripheral blood were ameliorated notably. All the results in this research indicate that GSH can reduce the inflammatory response level after operation, enhance the immune function and improve the postoperative quality of life through directly or indirectly removing the peroxide free radicals in the body.

Conclusions

In conclusion, GSH can prominently ameliorate the liver function and immune function, reduce oxidative stress and inflammatory response and improve the postoperative quality of life of the patients after the interventional therapy for hepatocellular carcinoma, with satisfactory clinical therapeutic effects, so it is worthy of further application and generalization.

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Conflict of interests

The authors declare no conflict of interests.

References

1. Liu B, Yang XF, Liang XP et al. Expressions of MiR-132 in patients with chronic hepatitis B, posthepatitic cirrhosis and hepatitis B virus-related hepatocellular carcinoma. Eur Rev Med Pharmacol Sci 2018;22:8431-7.
2. Zheng C, Zheng L, Yoo JK et al. Landscape of Infiltrating T Cells in Liver Cancer Revealed by Single-Cell Sequencing. Cell 2017;169:1342-56.
3. Kobayashi T, Kawai H, Nakano O et al. Rapidly declining skeletal muscle mass predicts poor prognosis of hepatocellular carcinoma treated with transcatheter intra-arterial therapies. BMC Cancer 2018;18:756.
4. Liu X, Wang Z, Chen Z et al. Efficacy and Safety of Transcatheter Arterial Chemoembolization and Transcatheter Arterial Chemotherapy Infusion in Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. Oncol Res 2018;26:231-9.
5. Morisco F, Camera S, Guarino M et al. Laser ablation is superior to TACE in large-sized hepatocellular carcinoma: a pilot case-control study. Oncotarget 2018;9:17483-90.

6. Ringelhan M, McKeating JA, Protzer U. Viral hepatitis and liver cancer. Philos Trans R Soc Lond B Biol Sci 2017;372.
7. King MT, Bell ML, Costa D, Butow P, Oh B. The Quality of Life Questionnaire Core 30 (QLQ-C30) and Functional Assessment of Cancer-General (FACT-G) differ in responsiveness, relative efficiency, and therefore required sample size. J Clin Epidemiol 2014;67:100-7.
8. Ma B, King AD, Leung L et al. Identifying an early indicator of drug efficacy in patients with metastatic colorectal cancer-a prospective evaluation of circulating tumor cells, 18F-fluorodeoxyglucose positron-emission tomography and the RECIST criteria. Ann Oncol 2017;28:1576-81.
9. Liu ZH, Zhang YF, Xu ZD. UNC119 promoted cell growth and migration by Wnt/beta-catenin signal and TGF-beta/EMT signal pathway in hepatocellular carcinoma. JBUON 2018;23:1717-24.
10. Jiang Q, Song X, Chen Z, Wang C, Luo H. Effects of remifentanil on hemodynamics, liver function and ICAM-1 expression in liver cancer patients undergoing surgery. Oncol Lett 2017;14:872-6.
11. Ji W, Chen J, Mi Y, Wang G, Xu X, Wang W. Role of natural killer cells in liver transplantation treatment of liver cancer. Exp Ther Med 2017;14:2380-4.
12. Khan F, Khan TJ, Kalamegam G et al. Anti-cancer effects of Ajwa dates (Phoenix dactylifera L.) in diethylnitrosamine induced hepatocellular carcinoma in Wistar rats. BMC Complement Altern Med 2017;17:418.
13. Ohta Y, Yashiro K, Ohashi K, Horikoshi Y, Kusumoto C, Matsura T. Compound 48/80, a mast cell degranulator, causes oxidative damage by enhancing vitamin C synthesis via reduced glutathione depletion and lipid peroxidation through neutrophil infiltration in rat livers. J Clin Biochem Nutr 2017;60:187-98.
14. Li CC, Yu HF, Chang CH, Liu YT, Yao HT. Effects of lemongrass oil and citral on hepatic drug-metabolizing enzymes, oxidative stress, and acetaminophen toxicity in rats. J Food Drug Anal 2018;26:432-8.
15. Kocahan S, Dogan Z, Erdemli E, Taskin E. Protective Effect of Quercetin Against Oxidative Stress-induced Toxicity Associated With Doxorubicin and Cyclophosphamide in Rat Kidney and Liver Tissue. Iran J Kidney Dis 2017;11:124-31.
16. Ozbay I, Kucur C, Kocak FE, Savran B, Oghan F. Advanced oxidation protein product levels as a marker of oxidative stress in paediatric patients with chronic tonsillitis. Acta Otorhinolaryngol Ital 2016;36:381-5.
17. Yahya RS, Ghanem OH, Foyouh AA, Atwa M, Enany SA. Role of interleukin-8 and oxidative stress in patients with hepatocellular carcinoma. Clin Lab 2013;59:969-76.
18. Bergmann J, Muller M, Baumann N et al. IL-6 trans-signaling is essential for the development of hepatocellular carcinoma in mice. Hepatology 2017;65:89-103.
19. Da SM, Julien P, Bilodeau JF, Barbier O, Rudkowska I. Trans Fatty Acids Suppress TNF-alpha-Induced Inflammatory Gene Expression in Endothelial (HUVEC) and Hepatocellular Carcinoma (HepG2) Cells. Lipids 2017;52:315-25.
20. Rekik S, Guyot E, Bhais M et al. The CRP level and STATE score predict survival in cirrhotic patients with hepatocellular carcinoma treated by transarterial embolization. Dig Liver Dis 2016;48:1088-92.