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Original Article

Significance of MIF, MMP-9 and coagulation and fibrinolytic factors levels in patients with pulmonary infection after intervention

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Abstract: Objective: To investigate the expression and significance of macrophage migration inhibitory factor (MIF), matrix metalloproteinase-9 (MMP-9) and coagulation and fibrinolysis system in patients with pulmonary infection after hepatocellular carcinoma intervention. Methods: Retrospective analysis was performed on 128 patients with hepatocellular carcinoma underwent interventional surgery and they were divided into the infected group (n=33) and non-infected group (n=95) according to infection condition. The levels of MIF, MMP-9 and coagulation and fibrinolysis factors were detected, and correlation between their levels and the occurrence of postoperative pulmonary infection were analyzed. Results: The MIF and MMP-9 levels in plasma were decreased two weeks after operation in both groups, which were significantly higher in the infection group than those in the non-infected group (P<0.01). Compared with those before operation, activated partial thromboplastin time (APTT) and serum levels of FIB (fibrinogen), D-D (D-dimer) and FDP (fibrin degradation products) were significantly increased. However, the levels of antithrombin-III, coagulation factor II, coagulation factor V and coagulation factor VII were significantly decreased after two weeks of operation (P<0.05). The changes in the infected group were more obvious than those in the non-infection group (P<0.05). The serum levels of C-reactive protein, interleukin-8, tumor necrosis factor-alpha in infected group were significantly higher than those in the non-infected group after two weeks of operation (P<0.001). The plasma levels of MIF, MMP-9 and FIB, D-D and FDP after two weeks of operation were positively correlated with the incidence of postoperative pulmonary infection (r=0.364, 0.663, 0.275, 0.187, 0.564, respectively, P<0.05). The mortality in infected group was 6.06%. Conclusion: MIF and MMP-9 are highly expressed in patients with pulmonary infection after hepatocellular carcinoma intervention, and the dysfunction of coagulation and fibrinolytic system is obvious, which can be used to predict the risk of pulmonary infection in patients underwent hepatocellular carcinoma intervention.

Keywords: Hepatocellular carcinoma intervention, pulmonary infection, macrophage migration inhibitory factor, matrix metalloproteinase-9, coagulation and fibrinolysis system

Introduction

Primary hepatocellular carcinoma is common in digestive system and its incidence ranks 8th in male and ranks 12th in female in China among 183 countries [1]. Interventional surgery is widely used in clinical practice because of its advantages in small trauma and less postoperative adverse reactions [2-4]. After the interventional operation, patients with hepatocellular carcinoma need to stay in bed, and are complicated with chronic consumption in body, decreased organ function, hard sputum excretion, etc., leading to an increase of the risk of lung infection [5]. Some report [6, 7] showed that the lung infection incidence of postoperative cancer patients was about 10%, seriously affecting the prognosis of patients.

Macrophage migration inhibitory factor (MIF), which is secreted by T cells, is closely related to the proliferation, angiogenesis and tumorigenesis of cells [8]. Matrix metalloproteinase-9 (MMP-9) can effectively degrade extracellular matrices and plays an important role in the invasion and metastasis of tumor cells [9]. The

coagulation and fibrinolysis system plays a key role in human inflammatory response, which can reflect viscosity of blood and the risk of thrombosis. Gabazza and colleagues [10] have also reported that patients with lung disease were complicated with abnormalities in coagulation and fibrinolysis system. Therefore, this study detected the expression of MIF, MMP-9 and coagulation and fibrinolysis factors in patients with pulmonary infection after hepatocellular carcinoma intervention to explore the clinical significance of these factors.

Materials and methods

Patients

This retrospective analysis collected data of 128 patients with hepatocellular carcinoma who received interventional surgery in Shandong Cancer Hospital and Institute from April 2016 to March 2019. All of them met the diagnostic criteria of liver cancer in the "practical guide for pathological diagnosis of primary hepatocellular carcinoma (2015)" [11]. Patients were divided into infected group (n=33) and non-infected group (n=95) according to whether pulmonary infection occurred after intervention. This study was approved by the Medical Ethics Committee of Shandong Cancer Hospital and Institute.

Inclusion criteria: patients aged 20-65 years; patients confirmed by postoperative pathological biopsy; patients without distant liver metastasis; patients' preoperative Child-Pugh grade were A and B; patients signed informed consent.

Exclusion criteria: patients with abnormal preoperative pulmonary imaging findings or abnormal value of white blood cells; patients with liver or kidney failure; patients who have history of glucocorticoids or adrenocortical hormone treatment in the past one month; patients combined with endocrine system or blood system diseases; patients who had withdrawn from the study halfway; pregnant or lactating women.

Methods

Surgical method: All hepatocellular carcinoma patients received blood routine, liver and kidney function, function of blood coagulation, electrocardiogram and other examinations preoperatively. After fasting for 6~8 h, percutaneous femoral arterial puncture was performed to place 5F catheter and then selective celiac artery angiography was performed to identify the artery that supplied the tumor and its direction. After the position determination of catheter, the patients were injected with 20 to 40 mg of pirarubicin (Shenzhen Main Luck pharmaceuticals Inc.) and 500~1000 mg of 5-fluorouracil (Hainan Choitec pharmaceuticals Co., Ltd.) through it. Then 10 mL of iodized oil (Shanghai Xudong Haipu pharmaceutical co., Ltd.) and 20 mg of mitomycin (Hanhui pharmaceutical co., Ltd.) were mixed and injected, and the proximal end of the artery was embolized with gelatin sponge. Routine anti-infective treatment was performed after surgery.

The collection and detection of blood sample

Fasting venous blood (5 mL) was collected before and after the surgery and the plasma and the serum were obtained. First, the expression of MIF and MMP-9 in plasma of patients was detected by double-antibody sandwich enzyme-linked immunosorbent (ELISA; Shenzhen Kangtai Biological Products Co., Ltd.). Second, automatic blood coagulation analyzer was used to detect indicators of blood coagulation including prothrombin time (PT), activated partial thromboplastin time (APTT), FIB (fibrinogen), D-D (D-dimer), and indicators about the activity of fibrinolytic system such as FDP (fibrin degradation products), AT-III (antithrombin-III) and blood coagulation factor including FII (coagulation factor II), FV (coagulation factor V) and FVII (coagulation factor VII). Lastly, ELISA was used to detect the expression of CRP (C-reactive protein), IL-8 (interleukin-8), TNF-α (tumor necrosis factor-alpha) in serum of patients with hepatocellular carcinoma. The kits were purchased from Shanghai enzyme link biotechnology Co., Ltd. and all experimental procedures were strictly carried out according to the instructions.

After correcting the sex, age and Child-Pugh grade, partial correlation analysis was used to analyze the correlation between the expression of MIF, MMP-9 in plasma and indexes of coagulation and fibrinolytic system and the incidence of postoperative pulmonary infection in 128 hepatocellular carcinoma patients after 2 weeks of surgery.

Table 1. Comparison of baseline data between the two groups

Groups	Infected group (n=33)	Non-infected group (n=95)	t/χ^2 value	*P* value
Sex	15/18	45/50	0.036	0.849
Male				
Female				
Age (year)	45.5±5.2	46.3±5.7	0.710	0.479
Child-Pugh Grade			0.821	0.365
A grade	14	49		
B grade	19	46		
AFP			1.695	0.193
Positive	24	79		
Negative	9	16		
Pathologic classification			0.671	0.413
Massive type	18	58		
Nodular type	12	27		
Diffuse type	3	10		

Note: AFP: alpha fetoprotein.

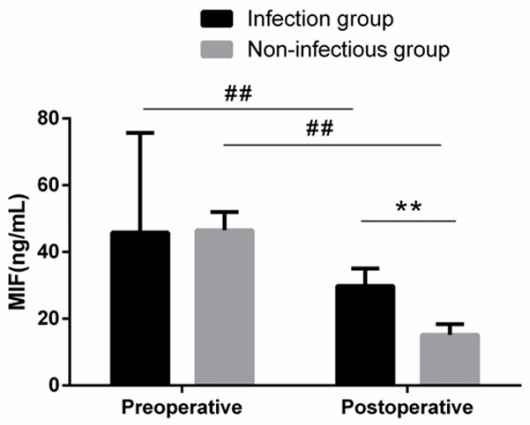

Figure 1. Comparison of the plasma level of MIF between the two groups. MIF: macrophage migration inhibitory factor; compared with preoperative group, ##P<0.01; compared with non-infected group, **P<0.01.

Statistical analysis

All analyses were performed using SPSS 25.0. The counting data was expressed as a percentage (%), and comparison between groups was conducted by chi-square test; the quantitative data were expressed as mean ± standard deviation ($\bar{x}$ ± sd), and paired-t test was used for preoperative and postoperative comparison, while independent t test was used for comparison between the two groups. Partial correlation analysis was used to analyze the correlation between the expression of MIF, MMP-9 in plasma and indexes of coagulation and fibrinolysis system and the incidence of postoperative pulmonary infection. P<0.05 was considered statistically significant.

Results

Comparison of baseline data between the two groups

There were no significant differences in the baseline data including gender, age, Child-Pugh grade, alpha-fetoprotein (AFP) and pathological type between the two groups (P>0.05, **Table 1**).

Comparison of the expression of MIF in plasma between the two groups

The expressions of MIF in plasma of preoperative patients in the infected group and the non-infected group were 45.85±29.85 ng/mL and 46.51±5.44 ng/mL, respectively, which were significantly decreased to 29.85±5.17 ng/mL and 15.17±3.22 ng/mL after two weeks of operation. The post-operative level of MIF in infected group was significantly higher than that in the non-infected group, see **Figure 1**.

Comparison of the plasma level of MMP-9 between the two groups

The expressions of MMP-9 in plasma of preoperative patients in the infected group and the non-infected group were 0.77±0.18 ng/mL and 0.80±0.16 ng/mL, respectively, which were significantly decreased to 0.56±0.12 ng/mL and 0.33±0.07 ng/mL after operation, with obvious differences between the two groups. See **Figure 2**.

Comparison of coagulation function between the two groups

Before the operation, there were no significant differences in coagulation function between infected group and non-infected group (P> 0.05). After two weeks of operation, APTT was significantly prolonged, and the expressions of FIB and D-D in plasma were significantly

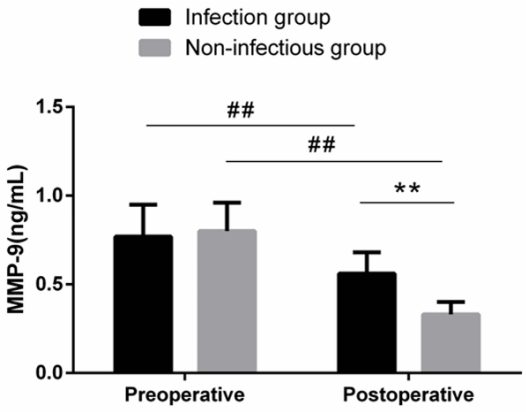

Figure 2. Comparison of the plasma level of MMP-9 between the two groups. MMP-9: matrix metalloproteinase-9; compared with preoperative group, ##P<0.01; compared with non-infected group, **P<0.01.

increased when compared with those of preoperation, and the changes in the infected group were more obvious (P<0.05, **Table 2**).

Comparison of fibrinolytic system function between the two groups

There were no significant differences in fibrinolytic system function between two groups before the operation (P>0.05). The expression of FDP in serum was significantly increased, and the expression of AT-III, FII, FV and FVII were significantly decreased after two weeks of operation when compared with those before operation, with changes more obvious in the infected group (P<0.05, **Table 3**).

Comparison of serum level of inflammatory factors between the two groups

There were no significant differences in the serum levels of CRP, IL-8 and TNF-α between two groups before operation (P>0.05). The serum levels of CRP, IL-8 and TNF-α in infection group after two weeks of operation were significantly increased (P<0.001) and higher than those in the non-infected group (P<0.001, **Table 4**).

The correlation between the plasma levels of MIF, MMP-9 and indexes of coagulation and fibrinolysis system and the incidence of postoperative pulmonary infection

Partial correlation analysis results showed that the plasma levels of MIF, MMP-9 and serum levels of FIB, D-D and FDP in patients after two weeks of operation were positively correlated with postoperative pulmonary infection incidence (P<0.05, **Table 5**).

The mortality in infected group

Two patients (6.06%) died from multiple organ dysfunction syndrome in the infection group.

Discussion

Interventional therapy has been recognized as the first choice for unresectable middle and advanced liver cancer at present. However, postoperative pulmonary infection is one of the most common complications. Patients have sticky sputum and difficulty in breathing, which may induce bronchial obstruction and lung distension. Moreover, the sputum may be stuck in the throat and cause asphyxia, which worsens prognosis of the patients and even endangers the patents' life [12].

CRP, interleukins and TNF-α are common indicators of the inflammatory state of the body [13]. This study found that the serum levels of CRP, IL-8, and TNF-α in the infected group were significantly higher than those in the non-infected group after two weeks of operation, suggesting that patients with pulmonary infection after hepatoma carcinoma intervention had more severe inflammatory reactions. The results about the plasma level of MIF suggested a high expression of MIF in the patients complicated with pulmonary infection after hepatoma carcinoma intervention. It was originally believed that MIF was only involved in the occurrence and development of inflammatory response, but it was also found that it had a dual role in the occurrence and development of malignant tumors in recent years. MIF is highly expressed in various solid tumors such as liver cancer, esophageal cancer and gastric cancer. Studies have shown that the plasma level of MIF has a certain relationship with the prognosis of patients with hepatoma carcinoma [14].

In addition, MIF can participate in tumor suppression of inflammatory cells through the autocrine pathway. Huang [15] found that MIF is a key cytokine linking chronic inflammation and malignant tumors, which can maintain the activity of ERK2 MAP-kinase and ERKl and promote cell proliferation and carcinogenesis by

Table 2. Comparison of coagulation function between the two groups ($\bar{x}$ ± sd)

Group	Time	PT (s)	APTT (s)	FIB (g/L)	D-D (μg/L)
Infected group (n=33)	Before operation	14.29±3.10	35.49±2.14	2.54±0.78	0.75±0.21
	Two weeks after operation	14.10±2.11	37.89±4.17#	3.11±0.69##	1.32±0.31##
	t	0.291	2.941	3.144	8.745
	P	0.772	0.005	0.003	<0.001
non-infected group (n=95)	Before operation	14.49±2.44	35.10±2.31	2.46±0.61	0.77±0.26
	Two weeks after operation	14.23±2.37	36.18±4.29	2.64±0.55	0.85±0.19
	t	0.745	2.360	2.136	2.421
	P	0.457	0.019	0.034	0.016

Note: PT: prothrombin time, APTT: activated partial thromboplastin time, FIB: fibrinogen, D-D: D-dimer; compared with non-infected group, #P<0.05, ##P<0.01.

Table 3. Comparison of function of fibrinolytic system between groups ($\bar{x}$ ± sd)

Group	Time	FDP (mg/L)	AT-III (%)	FII (%)	FV (%)	FVII (%)
Infected group (n=33)	Before operation	0.60±0.17	102.29±8.88	96.19±8.37	99.09±10.60	95.46±16.58
	Two weeks after operation	0.99±0.18##	88.47±10.19##	78.86±10.05##	90.47±11.27#	82.68±14.28#
	t	9.049	5.874	7.612	3.201	3.355
	P	<0.001	<0.001	<0.001	0.002	0.001
non-infected group (n=95)	Before operation	0.59±0.12	104.10±10.05	95.58±9.34	100.58±10.05	96.11±15.89
	Two weeks after operation	0.72±0.09	97.04±13.17	91.05±12.28	97.03±14.29	89.96±14.36
	t	8.447	4.143	2.862	1.981	2.799
	P	<0.001	<0.001	0.005	0.049	0.006

Note: FDP: fibrin degradation products; AT-III: antithrombin-III; FII: coagulation factor II; FV: coagulation factor V; FVII: coagulation factor VII; compared with non-infected group, #P<0.05, ##P<0.01.

Table 4. Comparison of serum level of inflammatory factor between the two groups ($\bar{x}$ ± sd)

Group	Time	CRP (mg/L)	IL-8 (ng/L)	TNF-α (pg/mL)
Infected group (n=33)	Before operation	17.84±3.29	0.22±0.10	16.41±4.25
	Two weeks after operation	29.57±5.10##	0.63±0.10##	28.85±4.44##
	t	11.103	16.654	11.627
	P	<0.001	<0.001	<0.001
non-infected group (n=95)	Before operation	19.14±3.55	0.21±0.09	15.53±4.10
	Two weeks after operation	18.88±3.39	0.22±0.08	15.94±3.39
	t	0.516	0.809	0.751
	P	0.606	0.419	0.453

Note: CRP: C-reaction protein; IL-8: interleukin-8; TNF-α: tumor necrosis factor-α; Compared with the non-infected group, ##P<0.01.

inhibiting p53-dependent apoptosis. The body can directly stimulate the release of MIF into the blood after infection, and the release of MIF can in turn further activate the inflammatory response to stimulate macrophages and T cells to release a large amount of MIF, thus forming a vicious circle. High levels of MIF are sufficient to stimulate the expression of interleukin-like inflammatory factors and further aggravate the inflammatory response, which may also be one of the factors leading to the obvious inflammatory response and poor prognosis of postoperative hepatoma carcinoma patients in this study. Our research also confirmed that there was a correlation between the expression of MIF and the postoperative infections incidence in HCC patients, but it could not explain whether inflammation caused an increase in MIF or MIF-induced activation of the inflammatory response, which requires further

Table 5. The correlation between the plasma level of MIF, MMP-9 and indexes of coagulation and fibrinolysis system and the incidence of postoperative pulmonary infection

Indexes	r	P
MIF	0.364	0.033
MMP-9	0.663	0.045
FIB	0.275	0.029
D-D	0.187	0.047
FDP	0.564	0.031

Note: MIF: macrophage migration inhibitory factor; MMP-9: matrix metalloproteinase-9; FIB: fibrinogen; D-D: D-dimer; FDP: fibrin degradation product.

basic experiments to verify, and may provide new insights for inhibiting infection after surgery.

MMP-9 belongs to the gelatinase in the MMP family. It can produce type IV collagenase when activated to degrade the extracellular matrix and type IV collagen in the basement membrane, and its overexpression can decrease intercellular adhesion force and promote the production and migration of endothelial cells as well as formation of blood vessels. Cells need to generate tumor blood vessels in the process of carcinogenesis, so cancer cells promote the synthesis and secretion of MMP-9 in large quantities to promote angiogenesis and further accelerate the growth and development of tumors [16]. Studies [17, 18] have shown that MMP-9 is highly expressed in cancer tissues at the gastric and esophageal junction, and its expression is closely related to lymph node metastasis and clinical stage. In our study, we also found that MMP-9 was highly expressed in patients complicated with pulmonary infection after hepatoma carcinoma intervention, which may be one of the reasons for the obvious postoperative inflammatory response of patients with HCC. This study also confirmed that there was a certain correlation between the expression of MMP-9 and the postoperative infection incidence in patients with hepatoma carcinoma. However, it could not explain whether the high expression of MMP-9 was caused by inflammation or the activation of inflammatory response was caused by high level of MMP-9, which also requires further basic experiments to verify.

Coagulation and fibrinolysis system are important components of the body's inflammatory response. After infection, the body releases a large amount of inflammatory cytokines such as CRP and TNF-α to activate the coagulation system, inhibit the fibrinolytic system, and decrease the production and activity of anticoagulant substances [19, 20]. Different degrees of infection can cause different degrees of activation. When the anticoagulant function is decreased, the activity of fibrinolytic system would enhance, which is even more obvious in patients severely infected, and they are prone to be in high blood coagulation state, which significantly increases the risk of abnormity of coagulation and fibrinolysis system. As the illness is aggravating, it can lead to a large number of fibrin depositions in the vascular bed, inducing extensive capillary hemorrhage or thrombosis, causing the disorder in coagulation and fibrinolytic function, and even appearing diffuse intravascular coagulation [21, 22]. In this study, we found that the dysfunction of coagulation and fibrinolytic system in patients complicated with lung infection after hepatoma carcinoma intervention was more obvious than that without infection. However, we have not proved the causal relationship between them, which needs to be verified by basic research. In addition, it was found that two patients in the infected group died of MODS in this study, which was speculated to be caused by severe disorder of coagulation and fibrinolysis system in patients with pulmonary infection.

This study did not elaborate the mechanism between the expression of MIF, MMP-9 and function of coagulation system and occurrence of postoperative infection, which was also the deficiency of this study. In the later stage, animal experiments are needed for more detailed and in-depth research, which may provide more solutions to reduce the occurrence of postoperative infections.

In conclusion, compared with patients without pulmonary infection after hepatoma carcinoma intervention, patients with infection showed significantly higher plasma level of MIF and MMP-9 and more obvious dysfunction of coagulation and fibrinolysis system. Therefore, the expression of MIF, MMP-9 and indexes of coagulation and fibrinolysis system in our study could be used to evaluate the risk of pulmonary infection after hepatoma carcinoma intervention.

Disclosure of conflict of interest

None.

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