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Research Article

Evaluation of impact of tall like receptor 4 and liposaccharide in pathogenesis of hepatic cancer

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Abstract:

Functional TLR4 expression has been linked to HCC development. TLR4 may serve an important role in HCC development by promoting the malignant transformation of epithelial cells and tumor growth. The consequences might be dependent on the complex signaling networks triggered by TLR4 activation and the tumor microenvironment.

The study included 90 consecutive subjects classified into 3 group their age from 40 to 70 years old.

Group (I): HCC patients on top of chronic HCV infection. they were 45 patients 30 male and 15 females, their age ranged from 45 to 55 who were subdivided into 3 subgroups according to Barcelona clinic liver cancer (BCLC):
Group (Ia): included 8 HCC patients in early stage. (stage A).
Group (Ib): included 12 HCC patients in intermediate stage (stage B).
Group (Ic): included 25 HCC patients in advanced stage. (stage C).

- Group (II): 30 Cirrhotic patients with chronic HCV, 21 male and 9 females, their age ranged from 50 to 60. This group was subdivided into 2 subgroups according to Child–Pugh score

Group (IIa): included 8 Child–Pugh A.
Group (IIb): included 22 Child–Pugh B and C.

- Group (III): controlled group included 15 normal subjects. 10 male and 5 females, their age ranged from 45 to 60. They were selected to match patients' groups in demographic and socioeconomic standards.

In our study where 15 persons are control showed lower level in TLR4 with mean 1.0±0.2, however 30 patients with HCV and other 45 patients with HCC showed higher level in TLR with mean 2.27±0.6 and 4.2±1.06 respectively.

In our study there is statistically significant difference in serum TLR4 level between group (Ia) (2.25±0.5) and other subgroups which shows more increase in serum level of TLR4 in Group IB (3.2-1.06) than Group IA. Also shows more increase in serum level of TLR4 in Group IC (4.0±2.0) than Group IA and IB

In our study HCC group showed higher level of LPS with mean 4.5±1.26 however lower in HCV group with mean 2.9-1.0 and least in control group with mean 1.1±0.4

In our study there is statistically significant difference in serum LPS level between group (IA) with mean 3.0±0.5 and other subgroups which shows more increase in serum level of LPS in Group IB with mean 4.4-1.0 than Group IA. Also shows more increase in serum level of LPS in Group IC with mean 4.0±1.76 than Group IA and IB

In our study there is statistically significant difference in serum LPS level between group (IIB) and group (IIA) which shows more increase in serum level of TLR4 in Group IIB with mean 2.7±1.1 than Group IIA with mean 2.20±0.2

In our study there is statistically insignificant difference of the mean value ± SD of sex as regard to LPS and TLR expression (t = 1.2, p = 0.22). (t = 0.16, p = 0.87) respectively.In our study there is statistically significant positive correlation between ALT, AST, Platelets, alpha fetoprotein and LPS as regard to TLR4 expression in group II more in IIB,C than IA . but insignificant of the mean value ± SD of other parameters.

In our study there is statistically significant difference of the mean value ± SD of ALT, AST, Platelets, alpha fetoprotein and TLR4 as regard to LPS expression in group I more in IB, C than IA. but insignificant of the mean value ± SD of other parameters.In our study there is statistically significant difference of the mean value ± SD of ALT, AST, Platelets and TLR4 as regard to LPS expression in group II more in IIB than IIA. but insignificant of the mean value ± SD of other parameters.

Conclusion: TLR4 and LPS measurement should be carried for all patient with HCV Who are at risk for HCC with close monitoring. Conduct a study on a Gut microbiota as therapeutic targets for HCC.

Keywords: liposaccharide

Introduction:

Hepatocellular carcinoma (HCC)is a common malignancy in developed countries and its incidence is on the rise in the developing world. Most HCC cases (80%) occur in either sub-Saharan Africa or in Eastern Asia. North and South America, Northern Europe, and Oceania are low-rate (5.0/100,000) areas for liver cancer among most populations. (**1**).

In Egypt, hepatocellular carcinoma (HCC) is the second most common cancer in men and the 6th most common cancers in women. It has been recognized that the most important clinical risk factor for the development of HCC is cirrhosis. Approximately 80% of HCCs develop in cirrhotic livers (**2**).

Increasing evidence indicates that the gut-liver axis is involved in HCC. Endotoxemia produced by gut microbiota may contribute to hepato-carcinogenesis and may serve as a target to the prevention or treatment of HCC. (3).

Toll-like receptors (TLRs) , are important in immune response that detect conserved pathogen associated molecular patterns (PAMPs) of intestinal microbes components, They are expressed by B lymphocytes, T lymphocytes, and fibroblast**.** TLRs mediate the production of pro-inflammatory cytokines and chemokine resulting in inflammation. **(4)**

TLR4 is an important member of TLRs, which could sense endotoxin and activate transcription factors that initiate innate immunity. TLR4 was also expressed on T lymphocyte, playing a vital role in adaptive immunity. **(5)**

Functional TLR4 expression has been linked to HCC development. TLR4 may serve an important role in HCC development by promoting the malignant transformation of epithelial cells and tumor growth. The consequences might be dependent on the complex signaling networks triggered by TLR4 activation and the tumor microenvironment**. (6)**

TLR4 is associated with cancer in several ways. Diverse cell lines and tissue samples derived from patients with head and neck, esophageal, gastric, colorectal, liver, pancreatic, skin, ovarian, cervical, and breast cancer have been shown to express increased amounts of TLR4.

Constitutive expression of some TLR4 genetic variants has also been linked to cancer. These characteristics are therefore being considered for their prognostic value in cancer treatment. In these scenarios of established cancer, TLR4 facilitates an environment that is suitable for continued cancer cell proliferation. Pro-cancer mechanisms could include the evasion of cancer cells from immune surveillance. **(7)**

Persistent activation of TLR4-induced inflammatory signaling in chronic inflammatory conditions can also contribute to carcinogenesis. Experimental evidence suggests that cancer cell migration and invasion are induced by triggering of TLR4-NF-κB under inflammatory conditions. LPS-induced TLR4-signaling also promotes cancer cell survival and proliferation in hepatocellular carcinoma. **(8)**.

Aim of the study:

1. To assess the association between Toll like receptor 4 and HCC
2. To study association between lipopolysaccharides and HCC.

Patients and Methods

A) Patients

This cross–section study was carried out in University Hospital, from September 2017 to September 2020. The study included **90** consecutive subjects classified into 3group their age from 40 to 70 years old

- **Group (I):** HCC patients on top of chronic HCV infection. they were 45 patients 30 male and 15 females, their age ranged from 45 to 55 who were subdivided into 3 subgroups according to Barcelona clinic liver cancer (BCLC):

Group (Ia): included 8 HCC patients in early stage. (stage A).
Group (Ib): included 12 HCC patients in intermediate stage (stage B).
Group (Ic): included 25 HCC patients in advanced stage. (stage C).

- **Group (II):** 30 Cirrhotic patients with chronic HCV, 21 male and 9 female, their age ranged from 50 to 60 .This group was subdivided into 2 subgroups according to Child–Pugh score

Group (IIa): included 8 Child–Pugh A.
Group (IIb): included 22 Child–Pugh B and C.
These patients were HCV and PCR positive, Diagnosis of chronic HCV infection. Diagnosis of cirrhosis was based on clinical, laboratory and sonography. Diagnosis of HCC was based on clinical, laboratory and Radiological finding

European Association for the Study of the Liver (EASL) guideline

On clinical management of HCC in 2000:
1. Radiological criteria: two coincident imaging technique
- Focal lesion >2 cm with arterial hypervascularization
2. Combined criteria: one imaging technique associated with AFP
- Focal lesion >2 cm with arterial hypervascularization
- AFP levels >400 ng/mL
• Four techniques considered: US, spiral CT, MRI and angiography

- **Group (III):** controlled group included 15 normal subjects. 10 male and 5 females, their age ranged from 45 to 60. They were selected to match patients' groups in demographic and socioeconomic standards.

Consent was obtained from all subjects to participate in this study. The study was approved by IRB Faculty of Medicine, Zagazig university.

Exclusion criteria:

Patients with hepatitis B coinfection, autoimmune diseases, bilharzial infection, Diabetes, chronic diseases (Ischemic heart disease–cerebrovascular stroke –chronic renal failure). Metabolic liver diseases. (Wilson disease, hemochromatosis and iron overload disorders, alpha-1 antitrypsin disease), abnormal thyroid function, Pregnant female, recent Hepatic encephalopathy, recent upper gastrointestinal bleeding, portal vein thrombosis, Patients who started antiviral medicine or immunosuppressive medications. and patients who received specific treatment for HCC.

B) Methods:

All patients were subjected to the following:
1-Complete history and physical examination.
2-Routine laboratory investigations including:

- Complete blood picture.
- Liver function tests. (ALT, AST, S.Albumin and S.Bilirubim)

(All patients were tested for ALT, AST, S.Bilirubin and S.Albumin)

- Blood urea and serum creatinine.
- Random blood sugar.
- Hepatitis markers that include:

- HBsAg, HBc Ab., HCV Ab.
- PCR for HCV.
- Anti-schistosoma Ab.
- Serum cupper, cerioplasmin and serum iron.
- Free t3, t4 and TSH.
- ANA and anti-liver, kidney microsomal Ab
- Alpha –fetoprotein.

3-specific laboratory investigations including:

- Blood sample for analysis of TLR4 and LPS Ab. Expression by using an enzyme-linked immunosorbent assay.

Serum TLR4 (Toll-Like Receptor 4) and LPS was measured by ELISA as following:

1. Add 100µL standard or sample to each well. Incubate 90 minutes at 37℃

- 2. Add 100µL Biotinylated Detection Ab. Incubate 1 hour at 37℃
- 3. Aspirate and wash 3 times
- 4. Add 100µL HRP Conjugate. Incubate 30 minutes at 37℃
- 5. Aspirate and wash 5 times
- 6. Add 90µL Substrate Reagent. Incubate 15 minutes at 37℃
- 7. Add 50µL Stop Solution. Read at 450nm immediately.
- 8. Calculation of results.

4–Radiological studies:

- Pelvi abdominal sonar and Tri- phasic C.T.

Statistical Analysis:

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered, and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0)

Results:

The mean value ± SD of different laboratory parameters of the three groups of the study. Application of ANOVA test revealed statistically significant difference in hemoglobin level between group (I) and other studied groups ($f = 16.2$, $p < 0.001$), also statistically significant difference in serum creatinine between group (I) and other studied groups ($f = 3.54$, $p < 0.05$), ($k = 56.07$, $p < 0.005$) respectively, also statistically significant difference in ALT and AST level between group (I) and other studied groups (KW= 9.01, p =0.008), (KW = 18.8, $p < 0.001$). respectively, also significant difference in INR level between group (I) and other studied groups ($f = 3.54$, $p < 0.018$), But shows insignificant difference in serum albumin and total serum protein between group (I) and other studied groups ($f = 0.16$, $p < 0.95$ NS) and ($f = 0.69$, $p < 0.56$ NS) respectively (table 2,3).
Shows demographic data among the three studied groups of the study.

	I N = 45	II N = 30	III N = 15	F	P
Hb $\bar{X}$±SD	ab 10.3±2.3	a 10.2±1.81	12.78±1.5	16.2	0.005
S. albumin $\bar{X}$±SD	2.6±0.6	2.8±0.5	3.9±0.4	0.16	NS
Total prot. $\bar{X}$±SD	6.76±0.66	6.87±0.5	6.97±0.4	0.69	NS
S. cr $\bar{X}$±SD	a 1.25±0.7	a 1.06±0.64	0.65±0.11	3.54	0.018*
ALT $\bar{X}$±SD	b 37.2±19	a 43.7±59.1	37.2±19	9.01	0.008*
AST $\bar{X}$±SD	ab 82.3±69.6	a 72.8±109	38.7±24	18.8	<0.001
INR X±SD	a 1.6±0.2	a 1.5±0.10	*0.9±0.11	3.54	0.018*

Table (2): *Comparison of Some laboratory Parameters of the Three studied groups.*

(a) Significant results when compared to Group III.
(b) Significant results when compared to Group II.

	Group I N =45	**Group II N=30**	**Group III N =30 N=15**
Age (years) $\bar{X}$+SD	**50±5.0**	**55.0±5.0**	**60.0±10.0**
Gender: Male Female	**30 66.67%** **15 33.33%**	**21 70 %** **9 30 %**	**10 66.7% 5 33.3%**

Occupation Farmer profesional **Occupation** Farmer Worker	**33 73.33%** **12 26.67 %** **33 73.33%** **12 26.67 %**	**22 73.33%** **8 26.67%** **22 73.33%** **8 26.67%**	**10 66.7%** **5 33.3%** **10 66.7%** **5 33.3%**
Education High Low	**33 73.33%** **12 26.67 %**	**22 73.33%** **8 26.67%**	**10 66.7%** **5 33.3%**
Marital status Single Married	**0 0%** **45 100**	**0 0%** **30 100%**	**0 0%** **15 100%**
Income Level High Low	**33 73.33%** **12 26.67 %**	**22 73.33%** **8 26.67%**	**10 66.7%** **5 33.3%**

Table (3): *Comparison of the mean value ± SD of the serum TLR4 Level among 3 studied groups, among three subgroups in group I and among 2 subgroups in group II*

TLR4	Group I N = 45	Group II N = 30	Group III N = 15	F	P
$\bar{X}$±SD	ab 4.2±1.06	a 2.27-0.6	*1.0±0.2	153	<0.001*

TLR4	Group I			F	P
	IA N = 8	IB N = 12	IC N = 25		
$\bar{X}$±SD	2.25±0.5	a 3.2-1.06	ab *4.0±2.0	145	<0.001

TLR4	Group II		T	P
	IIA N = 8	IIB N = 22		
$\bar{X}$±SD	2.00±0.2	2.67±0.6	0.9	<0.001

KW (Kruskal Wallis Test). statistically significant difference in serum TLR4 level between group (III) and other studied groups which shows increase in serum level of TLR4 in Group I and Group II In comparison to Group III. + P < 0.001 when compare HCV Groups vs HCC Groups (table 4).

Table (4): *Comparison of the mean value ± SD of the serum LPS Level among 3 studied groups, among 3 subgroups in group I and among 2 subgroups in group II*

	I N = 45	II N = 30	III N = 15	F	P
LPS $\bar{X}$±SD Range	ab 4.5±1.26 2.5-5.76	a 2.9-1.0 2.0-3.8	 1.1±0.4 0.6-1.5	135	<0.001*

LPS	Group I			F	P
	IA N = 8	IB N = 12	IC N = 25		
	ab	a			

$\bar{X}$±SD	3.0±0.5	4.4-1.0	*4.0±1.76	149	<0.001*
Range	2.5.-3.5	3.4-5.4	2.24-5.76		

LPS	Group II		T	P
	IIA N = 8	IIB N = 22		
$\bar{X}$±SD	2.20±0.2	2.7±1.1	0.07	<0.001*

a) Significant results when compared to Group III.
(b) Significant results when compared to Group II.

Table (5):*Comparison of mean value ± SD between LPS expression and Gender in group I:*

Statistically significant difference in serum TLR4 level between group (Ia) and other subgroups which shows more increase in serum level of TLR4 in Group IB than Group IA. Also shows more increase in serum level of TLR4 in Group IC than Group IA and IB. statistically significant difference in serum TLC4 level between group (IIB) and group (IIA) which shows more increase in serum level of TLR4 in Group IIB than Group IIA. statistically significant difference in serum LPS level between group (III) and other studied groups. which shows increase in serum level of LPS in Group I and Group II In comparison to Group III + P < 0.001 when compare HCV Groups vs HCC Groups. A statistically significant difference in serum LPS level between group (IA) and other subgroups which shows more increase in serum level of LPS in Group IB than Group IA. Also shows more increase in serum level of LPS in Group IC than Group IA and IB.

	No	LPS expression $\bar{X}$±SD	T	p
Male	30	2.62±2.0	1.2	0.22
Female	15	3.2±2.0	NS	

(a) Significant results when compared to Group III.
(b) Significant results when compared to Group II.
Shows a statistically insignificant difference of the mean value ± SD of sex as regard to LPS expression (t = 1.2, p = 0.22).

Table (6): *Comparison of mean value ± SD between TOL4 expression and Gender in group I:*

	No	TOL4 expression X±SD (Range)	T	p
Male	30	2.53±1.6	0.16	0.87 NS
Female	15	2.48±1.4		

Shows a statistically insignificant difference of the mean value ± SD of sex as regard to TOL4 expression (t = 0.16, p = 0.87).
A statistically significant difference in serum LPS level between group (IIB) and group (IIA) which shows more increase in serum level of TLR4 in Group IIB than Group IIA (table 7).

Table (7): *Correlation between TLR and other parameters in groupI:*

	Group IA	Group IB	Group IC
	R	R	R
ALT	0.61*	0.55*	0.51*
AST	-0.51*	0.50*	0.48*
	0.11	0.12	0.10
	0.19	0.20	0.17
WBCS	0.13	0.16	0.15
HB	---0.22	0.25	0.28
ETS	---0.40*	0.41*	0.44*
	0.16	0.17	0.19
Urea	0.1	0.2	0.3

LPS	---0.72*	0.73*	0.75*
Alpha fetoprotein	0.44*	0.55*	0.66*

A statistically significant positive correlation between ALT, AST, Platelets, alpha fetoprotein and LPS as regard to TLR4 expression in group II more in IIB, C than IA. but insignificant of the mean value ± SD of other parameters. A statistically significant difference of the mean value ± SD of ALT, AST, Platelets and LPS as regard to TLR4 expression in group II more in IIB than IIA. but insignificant of the mean value ± SD of other parameters (table 8).

Table (8): *Correlation between TLR and other parameters in group II:*

	Group IIA	Group IIB
	R	R
ALT	0.44 *	0.42*
AST	-0.43*	0.41*
Age	0.13	0.12
	0.2	0.19
WBCS	0.11	0.12
HB	---0.16	--0.15
	0.15	0.17
	0.16	0.15
Urea	0.1	0.1
LPS	---0.51*	--0.53*

A statistically significant difference of the mean value ± SD of ALT, AST, Platelets, alpha fetoprotein and TLR4 as regard to LPS expression in group I more in IB, C than IA. but insignificant of the mean value ± SD of other parameters. A statistically significant difference of the mean value ± SD of ALT, AST, Platelets and TLR4 as regard to LPS expression in group II more in IIB than IIA. but insignificant of the mean value ± SD of other parameters. (table 9)

Tabl (9): *Correlation between LPS and other parameters in group I:*

	Group IA	Group IB	Group IC
	R	R	R
ALT	0.55 *	0.59*	0.58*
AST	-0.56*	0.51*	0.49*
	0.12	0.13	0.10
umin	0.18	0.21	0.18
S	0.14	0.15	0.17
	---0.45	0.43	0.41
TLETS	---0.41*	0.43*	0.45*
	0.17	0.18	0.19
	0.2	0.26	0.28
LPS	---0.70*	0.72*	0.73*
Alpha fetoprotein	0.41*	0.51*	0.63*

Table (10): *Correlation between LPS and other parameters in group II:*

	Group IIB	Group IIB

	r	R
ALT	0.442*	0.49*
	-0.60*	0.5*
	0.12	0.14
Albumin	0.22	0.26
WBCS	0.24	0.27
	0.23	0.25
PLATLETS	---0.48*	0.50*
Creatinine	0.23	0.25
a	0.19	0.20
TLR	--0.47*	0.55*

Decision:

HCC is the sixth most common cancer worldwide and the third most common cause of cancer death. In Egypt, liver cancer forms 1.68% of the total malignancies. HCC constitutes 70.48% of all liver tumors among Egyptians. (**9).**

Cirrhosis is a primary risk factor for HCC. Independently of the presence of cirrhosis, HBV infection increases the danger, whereas liver cancer against the background of HCV infection is almost exclusively seen in those with advanced fibrosis and cirrhosis. An emerging risk factor for HCC, at least in the Western world, appears to be cirrhosis secondary to NASH. Additionally, there has been a higher rate of cancer in those with diabetes, and it is unclear whether this is mediated via NASH-related cirrhosis or is independent of the presence of liver disease. (**10).**

In our study we found that HCC is more prevalent in old men farmer with lower socioeconomic standards. Our study Shows statistically significant difference in serum TLR4 level between HCC group and other studied groups. This is in agreement with **Yuan X. et al**. that Shows statistically significant difference in serum TLR4 level between normal subject and HCV, HCC Patients. They stated that Persistent activation of TLR4 - induced inflammatory signaling in chronic inflammatory conditions could contribute to carcinogenesis., **(11) Mai CW, Kang YB, Pichika MR**. show statistically significant difference in serum TLR4 level between normal subject and HCC Patients. Their evidence based on elevation in TLR expression and dysfunctional immunity within the tumor microenvironment with cancer progression and reduced patient survival in a number of solid tumors. TLR activation can enhance regulatory T-cell suppressor function, favoring tumor development**.** and proliferation in hepatocellular carcinoma. **(12)**

We found also in our study that HCC group showed higher expression of LPS with range 2.5-5.76 however lower in HCV group with range 2-3.8 and least in control group with range 0.6-1.5 %. this agree with Liu X, et al.,2010 who stated that HCC group showed higher expression of LPS however lower in HCV patients provide evidence that LPS induced TLR4 signaling promotes HCC cell invasion in vitro and in vivo, and a high expression of TLR4 in HCC tissues was strongly associated with both poor cancer-free survival and overall survival in patients, which indicates that LPS is closely related to tumor invasion and metastasis, rather than only anti-tumor effects. (13)

In our study we found that the level of TLR 4 and LPS in the serum is higher in advanced stage of HCC (Group 1C) more than other stages this may be due to release of more cytokines from advanced tumor.

Ageing is associated with impaired PRR signaling, which may partly be accounted for by the reported alterations in Toll-like receptor (TLR) expression by innate immune cells from older adults, compared with those from younger individuals. Decreased surface expression of TLRs has been associated with diminished TLRs induced cytokine production in human monocytes from older individuals. Although substantial age-associated decreases in TLR gene expression have been reported in mice, the pattern is less clear in humans (Van Duin, D. et al.2017).

Sex differences in immune responses have evolved in diverse species ranging from insects to lizards, birds, and mammals; in all of these species, both innate and adaptive immune responses are typically lower in males than in females. In Drosophila melanogaster, for example, many of the genes that encode for innate signaling proteins are found on the X chromosome and show sex specific induction following fungal or bacterial infection (15).

Northoff H ET AL. stated that There were sex-specific differences in activation of inflammation-related pathways TLRs, cytosolic DNA sensing, and RIG-I like receptors, who found that men expressed higher numbers of activated genes at each time point after exercise even though luteal-phase women showed a greater extent of pathway activation than men. This difference may relate to genetic, immunological difference between our patients and their patients. (16)

According to our study there is a statistically insignificant difference of the mean value ± SD of sex as regard to serum level of LPS. also Shows a statistically insignificant difference of the mean value ± SD of sex as regard to serum level of TOL4. This may be due to small sample size.

TLR4 and LPS had highly significant correlation to both ALT and AST levels. This means that the inflammation of the liver is strongly related to TLR4 and LPS level. Our results agree with Ceccarelli et al, 2015 who reported that LPS and TLR4 levels are related to the severity of inflammation evident in liver histopathology (17).

LPS enhance the signal transduction of β2GPI in liver cancer cells leading to activation of NF-κB, which triggered downstream signal transduction and increased the expression of downstream factors. (e.g., tumor necrosis factor alpha, TNF-α; interleukin-1 beta, IL-1β and alpha-fetoprotein, AFP) This suggests that LPS enhancement of β2GPI signal transduction may play a role in promoting the development of liver cancer**. (18)**

Agents with TLR4-antagonistic activity have been shown to reduce inflammation-induced carcinogenesis by suppressing the TLR4-induced NF-κB signaling. Curcumin, the main constituent of the spice turmeric, has been found to most likely bind to MD2, thus competing with LPS, A

number of synthetic curcuminoids, such as EF24, have also been found to have anti-inflammatory activity **(19).**

While TLR4 antagonists could help reduce progression of inflammation-induced carcinogenesis or metastasis, TLR4 agonists have been shown to induce anti-tumor immunity in patients and models of established cancer **(15).**

Conclusion:

We concluded that there is strong relationship between TLR4, LPS and pathogenesis of hepatocellular carcinoma so that every cirrhotic patient with high risk of developing HCC should be close monitoring by measurement of serum TLR4 and LPS level owing to decrease incidence of developing HCC.

TLR4 and LPS measurement should be carried for all patient with HCV Who are at risk for HCC with close monitoring. Conduct a study on a Gut microbiota as therapeutic targets for HCC.

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