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Thrombophilia in hepatocellular carcinoma

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Abstract

Background: Chronic liver disease and hepatocellular carcinoma (HCC) can cause a disturbance in the coagulation system. In this study, we aimed to assess the risk factors for venous thromboembolism either acquired or hereditary in patients with HCC.

Results: Serum levels of proteins C and S, AT activity, and lipoprotein (a) were significantly lower in both HCC and cirrhotic patients while homocysteine levels were significantly higher in HCC patients. The prevalence of activated protein C resistance (APCR) and factor V Leiden (FVL) mutation was higher in HCC patients but with no significant differences between the studied groups. With multivariate analysis, prothrombin time, Fbg, protein C and S deficiency, increased lipoprotein (a), hyperhomocysteinemia, APCR, and FVL mutation were independent risk factors for thromboembolic complications in HCC patients.

Conclusions: Thrombophilic abnormalities are prevalent in HCC patients, and they have a substantial increased risk of venous thromboembolism.

Keywords: Hepatocellular carcinoma, Liver cirrhosis, Venous thromboembolism, Thrombophilia

Background

Hepatocellular carcinoma (HCC) is the most prevalent type of primary malignancy of the liver [1] and usually develops in patients with cirrhosis [2].

Since the liver has an important role in the synthesis and metabolism of coagulation factors, it regulates the blood clotting and anticoagulant system. Liver disease, such as liver cirrhosis, hepatitis, and HCC, can impair the liver's ability to produce clotting factors and anticoagulant proteins [3].

In addition, patients with advanced HCC have abnormal coagulation and fibrinolysis, which is related to tumor progression [4].

Chronic liver disease and HCC patients have a substantially increased risk of venous thromboembolism (VTE) as deep venous thrombosis (DVT) or pulmonary embolism (PE) [5].

In addition, portal vein thrombosis (PVT) is a common complication of HCC and non-malignant chronic liver disease. It shows worse liver functions, less tolerance to treatment, and worse prognosis [6].

Routine laboratory coagulation tests such as thrombin time (TT), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (Fbg), and D-dimer are commonly used to detect coagulation disorders [7].

Furthermore, hyperhomocysteinemia [8] and activated protein C resistance (APCR) have an association with venous thromboses in patients with cancer [9].

In addition, genetic defects as protein C, protein S, antithrombin (AT) deficiencies [10], and factor V Leiden (FVL) mutation [11], also, acquired coagulation disorders as increased levels of antiphospholipid antibodies have been discovered in patients with PVT [12].

We aimed to evaluate the presence of different coagulation defects either hereditary or acquired in cirrhotic patients and HCC and show their relationship with different thrombotic complications.

Patients and methods

Data were collected from cirrhotic patients with and without HCC, who were admitted to the Hepato-Gastroenterology Unit of Internal Medicine and Tropical Departments, Faculty of Medicine, Zagazig University, between March 2016 and April 2017.

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Selection of cases

In this cross-sectional study, a total number of 140 patients with liver cirrhosis and HCC and 45 healthy volunteers were included. The sample size is calculated by using Epi-Info version 7. The study samples were systematically and randomly selected. The studied groups were matched for age and sex.

Our cases were divided into three groups as follows:

Control group: It included 45 apparently healthy volunteers, 23 males and 22 females, matched for age and gender.

Cirrhotic group: It included 70 cirrhotic patients without HCC, 40 males and 30 females. Liver cirrhosis was confirmed by biochemical and imaging findings. In addition, cirrhotic patients were classified according to Child-Pugh's score.

HCC group: It included 70 cirrhotic patients with HCC, 42 males and 28 females. HCC diagnosis was confirmed by serum AFP level ≥ 400 ng/ml with a hepatic space-occupying lesion, which is diagnosed by triphasic CT or MRI.

Exclusion criteria

We excluded the following:

1. Patients on procoagulant or anticoagulant therapy or have blood transfusions within 1 month of starting the study
2. Patients treated with anti-tumor treatment drugs or surgery
3. Patients with venous thromboembolism, pulmonary embolism, or disseminated intravascular coagulation, which can influence plasma coagulation levels within 1 month of study
4. Patients suffering from hematological malignancies, cancer, chronic inflammatory diseases, and apparent portal vein invasion by the tumor
5. Smokers and alcoholics

Ethics approval and consent to participate

Approvals for performing the study were obtained from Internal Medicine, Tropical Medicine, and Clinical Pathology Departments, Zagazig University Hospitals, after taking Institutional Review Board (IRB) approval. Written informed consent was taken from the patients or their relatives if patients were severely ill to participate in this study.

Methods

All participants subjected to a detailed history taking and clinical examination, and routine laboratory tests such as complete blood count, liver and kidney function tests, PT, PC, INR, APTT, TT, Fbg, blood sugar, and viral markers.

The following are the specific laboratory tests:

- The serum α-fetoprotein levels were measured by Cobas electrochemiluminescence.
- Proteins C and S, antithrombin (AT) activity, and lipoprotein (a) were determined by ELISA.
- Activated protein C resistance (APCR) was measured by recording the activated partial thromboplastin time (APTT) in the absence and presence of APC.
- Plasma total homocysteine was measured by the IMX homocysteine assay.
- Molecular analysis of FVL mutation, using factor V gene mutation assay by genomic DNA isolation from EDTA blood and polymerase chain reaction.

The following are the investigations of thromboembolic complications:

- DVT was diagnosed by Doppler ultrasound [13].
- PE was confirmed by either computerized tomography (CT) of the chest or ventilation-perfusion scan [13].
- PVT was diagnosed by either Doppler ultrasound, CT, or MRI [14].

Statistical analysis

Variables were computerized and analyzed using SPSS version 19 (IBM Corporation, USA). Continuous variables were expressed as the mean ± standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for non-normally distributed data. Mann-Whitney U test was used for non-parametric distribution. For comparisons of quantitative variables among the three groups, one-way ANOVA was used if the data was parametric, while the Kruskal-Wallis H (KW) test was used if the data was non-parametric. Post-hoc Fisher's least significant difference (LSD) tests were used if significant differences were found between the three groups. Chi-square test (χ^2) was used for comparison between qualitative variables in different groups. P value > 0.05 indicates non-significant results. P value < 0.05 indicated significant results. Linear regression analysis served to assess the impact of thrombophilic parameters as predictors of thrombotic complications by both univariate and multivariate models.

Results

With regard to the etiologies of chronic liver disease or Child-Pugh's scores, there was no difference between HCC and cirrhotic patients. The mean values of MELD scores were significantly higher in HCC patients compared to cirrhotic patients. Serum AFP levels were statistically significantly increased in patients with HCC compared to

other groups. The majority of cirrhotic and HCC patients were child C but without significant difference Table 1.

Prothrombin time was significantly higher, while prothrombin concentration was significantly lower in HCC and cirrhotic patients compared to the control group.

TT, APTT and Fbg levels were significantly higher in HCC patients when compared with the control and cirrhotic groups. The serum levels of proteins C and S, antithrombin, and lipoprotein (a) were significantly lower in both HCC and cirrhotic patients in comparison with controls. While in patients with HCC, serum homocysteine levels were significantly higher when compared to cirrhotic patients and controls Table 2.

The prevalence of APCR and FVL mutation was higher in HCC patients, but without significant differences between the groups.

Univariate analysis of various thrombophilic parameters in HCC showed that prothrombin time, Fbg, protein C and S deficiency, antithrombin deficiency, increased lipoprotein (a), hyperhomocysteinemia, APCR, and FVL mutation were significantly associated with the development of thrombotic complications in HCC patients. With further multivariate analysis, prothrombin time, Fbg, protein C and S deficiency, increased lipoprotein (a), hyperhomocysteinemia, APCR, and FVL mutation were independent risk factors for thromboembolic complications in HCC patients Table 3.

In-between 14 cases with thromboembolic complications in HCC, 8 of them (57.1%) had at least 1 thrombophilic parameter. Seven out of 8 cases with thromboembolic complications had more than 1 risk factor of thrombosis. We had 8 cases with PVT (57.1%), 4 cases with PE (28.5%), and 2 cases with DVT (14.3%) Table 4.

Discussion

VTE is a common complication in patients with malignant disease and can be the earliest signs of an underlying malignancy [15].

Hypercoagulable state occurs in the malignancy due to the ability of tumor cells to activate the coagulation system [16].

Within the liver, hepatocytes are involved in the synthesis of many coagulation factors that can be significantly decreased in patients with liver disease as HCC [17].

In addition, tumor cells produce several procoagulant factors and proinflammatory cytokines such as tissue factor (TF), tumor necrosis factor (TNF-α), cancer procoagulant (CP), vascular endothelial growth factor (VEGF), and interleukin-1β (IL-1β) which support tumor metastasis and invasion [18].

TNF-α, IL-1β, and VEGF reduce activation of the protein C system which is one of the endogenous anticoagulant systems [19].

Table 1 Demographic data and parameters of the studied groups

Variables	Control group	Cirrhotic patients	HCC patients	*P* value	Post hoc analysis
Number	45	70	70		
Age	54.8 ± 7.19	55 ± 6.43	56.87 ± 6.26	0.148*	
Sex (male/female)	23/22	40/30	42/28	χ^2 0.6413	
Etiology					
Chronic hepatitis C	–	45	48	χ^2 0.8369	
Chronic hepatitis B	–	9	10		
Non-alcoholic steatohepatitis	–	8	5		
Autoimmune hepatitis	–	6	4		
Cryptogenic	–	2	3		
Child-Pugh's score					
Child A	–	3	4	χ^2 0.224	
Child B	–	20	29		
Child C	–	47	37		
MELD score	–	15 (4–25)	19 (10–40)	< 0.001**	
AFP (ng/ml)	6 (2–15)	8 (2–20)	1700 (500–3500)	0.000***	P1 = 0.97 P2 < 0.001 P3 < 0.001

Values are expressed as the mean ± standard deviation (SD) while values of MELD score and AFP are given as the median and interquartile range (IQR)
Significant difference (*P* value < 0.05)
χ^2 chi-square test, *P1* control group vs cirrhotic patients, *P2* control group vs HCC patients, *P3* cirrhotic patients vs HCC patients, *MELD* model for end-stage liver disease, *AFP* α-fetoprotein
*ANOVA test
**Mann-Whitney *U* test
***Kruskal-Wallis test

Table 2 Comparison of different thrombophilic parameters of the studied groups

Variables	Control group (*N* = 45)	Cirrhotic patients (*N* = 70)	HCC patients (*N* = 70)	*P* value	Post hoc analysis
PT (s)	12.5 ± 0.3	22.3 ± 5	20.9 ± 4.7	0.0000*	P1 < 0.001 P2 < 0.001 P3 = 0.14
Prothrombin conc.%	88.7 ± 3.7	36.6 ± 17.6	39.7 ± 15	0.0000*	P1 < 0.001 P2 < 0.001 P3 = 0.40
TT (s)	18.7 ± 1.41	19.9 ± 1.52	33.22 ± 13.62	0.0000*	P1 = 0.73 P2 < 0.001 P3 < 0.001
APTT (s)	25.20 ± 3.2	27.53 ± 4.45	43.54 ± 18.53	0.0000*	P1 = 0.55 P2 < 0.001 P3 < 0.001
Fbg (g/l)	2 (0–10)	2.5 (0–15)	10 (2–25)	0.0000***	P1 = 0.99 P2 < 0.001 P3 < 0.001
Protein C (%)	99.8 ± 26.3	49.7 ± 12.5	54.5 ± 15.3	0.0000*	P1 < 0.001 P2 < 0.001 P3 = 0.24
Protein S (%)	85.6 ± 20.4	61.8 ± 10.2	59.2 ± 18.9	0.0000*	P1 < 0.001 P2 < 0.001 P3 = 0.62
Antithrombin activity (%)	88.1 ± 10.4	49.7 ± 11.5	52.5 ± 9.7	0.0000*	P1 < 0.001 P2 < 0.001 P3 = 0.26
Lipoprotein (a) (mg/l)	20 (2–40)	7 (2–14)	11 (2–30)	0.0000***	P1 < 0.001 P2 < 0.001 P3 = 0.074
Homocysteine (μmol/l)	12 (5–18)	15 (7–29)	26 (10–45)	0.0000***	P1 = 0.13 P2 < 0.001 P3 < 0.001
APCR (*N* (%))	2 (4.4%)	6 (8.6%)	9 (12.9%)	0.3	
FVL mutation (*N* (%))	1 (2.2%)	2 (2.8%)	4 (5.7%)	0.55	

Values are expressed as the mean ± standard deviation (SD) while values of Fbg, lipoprotein (a), and homocysteine are given as the median and interquartile range (IQR)
Significant difference (*P* value < 0.05)
P1 control group vs cirrhotic patients, *P2* control group vs HCC patients, *P3* cirrhotic patients vs HCC patients, *PT* prothrombin time, *TT* thrombin time, *APTT* activated partial thromboplastin time, *Fbg* fibrinogen, *APCR* activated protein C resistance, *FVL mutation* factor V Leiden (FVL) mutation
*ANOVA test
***Kruskal-Wallis test

In this study, there were significantly decreased levels of proteins C and S, lipoprotein (a), and antithrombin in cirrhotic and HCC patients compared to controls. These results were expected because these proteins are synthesized in the liver, and their levels possibly decrease in patients with liver cirrhosis and HCC.

The liver is the main site for lipoprotein (a) synthesis and in chronic liver disease; the level of lipoprotein (a) decreased due to the decrease in its synthesis by damaged liver cells [20].

Hyperhomocysteinemia was also confirmed as a risk factor for recurrent VTE in many studies [21]. Patients with HCC had significantly higher levels of serum homocysteine compared to cirrhotic patients and controls in our study. These results were in agreement with Samonakis et al. [22].

Hyperhomocysteinemia in liver cirrhosis can be explained by impaired liver function and tissue damage that occur directly by increasing homocysteine cell leakage or indirectly by initiating cell repair [23].

Fibrinogen levels in HCC patients showed significantly higher levels than the control and cirrhotic groups. High fibrinogen levels may occur in our study due to their impaired elimination by the damaged liver cells that not only change the concentration of fibrinogen, but also make it structurally and functionally abnormal [24]. Hyperfibrinogenemia is associated with advanced HCC stage, poor prognosis and non-response to treatment [25].

Regarding genetic thrombotic risk factors, our study showed a high prevalence of APCR and FVL mutation in HCC patients but with no significant differences between

Table 3 Univariate and multivariate analysis: comparison between thrombophilic parameters in HCC patients with and without thrombotic complications

Variables	Univariate			Multivariate		
	ORs	95% CIs	*P* value	ORs	95% CIs	*P* value
PT (s)	13.12	4.64–18.12	0.00	6.78	2.65–10.89	0.00
Prothrombin conc.%	1.54	0.94–3.11	0.18	–	–	–
TT (s)	1.92	0.63–3.81	0.142	–	–	–
Fbg (g/l)	10.37	4.64–18.44	0.00	3.97	2.17–12.34	0.00
APTT (s)	2.27	0.87–3.44	0.085	2.33	0.71–7.75	0.11
Protein C deficiency (%)	11.32	3.45–18.44	0.00	4.81	3.11–10.82	0.00
Protein S deficiency (%)	10.45	4.31–16.85	0.00	4.32	2.98–11.42	0.00
Antithrombin deficiency (%)	8.98	4.21–18.32	0.00	2.71	0.64–1.74	0.068
Increased lipoprotein (a) (mg/l)	3.88	3.13–8.69	< .0001	2.784	2.23–5.36	0.01
Hyperhomocysteinemia (μmol/l)	6.24	3.41–19.24	0.000	7.06	2.15–14.6	0.000
APCR	2.11	1.03–3.07	0.03	2.53	1.12–4.71	0.04
FVL mutation	7.76	3.76–17.19	< .0001	6.12	2.25–15.41	0.0003

Significant difference (*P* value < 0.05)
ORs odds ratios, *CI* confidence interval, *PT* prothrombin time, *TT* thrombin time, *APTT* activated partial thromboplastin time, *Fbg* fibrinogen, *APCR* activated protein C resistance, *FVL mutation* factor V Leiden (FVL) mutation

the groups. This was in agreement with Samonakis et al. [22].

We found that, with univariate analysis, several factors such as prothrombin time, Fbg, protein C and S deficiency, antithrombin deficiency, increased lipoprotein (a), hyperhomocysteinemia, APCR, and FVL mutation were significantly associated with the development of thrombotic complications in HCC patients. While with further multivariate analysis of the potentially important thrombotic parameters identified in univariate analysis, prothrombin time, Fbg, protein C and S deficiency, increased lipoprotein (a), hyperhomocysteinemia, APCR, and FVL mutation showed independent significant association with thrombotic complications in HCC patient.

Table 4 Thrombophilic risk factors in HCC patients with thrombotic complications

No. of cases	Thromboembolic complications, (*N* = 14 cases)	Thrombotic risk factors
1	Portal vein thrombosis	Increased lipoprotein (a), hyperhomocysteinemia
2	Portal vein thrombosis	–
3	Portal vein thrombosis	Increased lipoprotein (a), APCR
4	Portal vein thrombosis	–
5	Portal vein thrombosis	FVL mutation
6	Portal vein thrombosis	–
7	Portal vein thrombosis	FVL mutation, APCR, hyperhomocysteinemia
8	Portal vein thrombosis	–
9	Pulmonary embolism	–
10	Pulmonary embolism	Increased lipoprotein (a), hyperhomocysteinemia
11	Pulmonary embolism	APCR, antithrombin deficiency
12	Pulmonary embolism	–
13	Deep venous thrombosis	Protein C deficiency, protein S deficiency
14	Deep venous thrombosis	Prolonged PT, low Fbg

APCR activated protein C resistance, *FVL mutation* factor V Leiden (FVL) mutation, *Fbg* fibrinogen, *PT* prothrombin time

HCC carries an exclusive situation concerning cancer-associated thrombosis [26]. We found 14 cases with thromboembolic complications, 50% of them had more than 1 risk factor of thrombosis. PVT was a frequent complication of HCC.

PVT is common in HCC and characterized by an aggressive disease progression, worse liver functions, a higher chance of complications due to portal hypertension, and in addition, poorer tolerance to treatment [27].

Since cirrhosis and liver cell failure often precede the development of HCC, the frequency of DVT and PE in patients with cirrhosis was reported to be 0.5–1.0% [28]. PE and DVT are clearly a major cause of morbidity and mortality in HCC [29].

In our study, the etiology of venous thrombosis may be single or combined deficiencies of natural anticoagulant proteins (either acquired or genetic), and the majority of deficiencies were acquired.

Similar results were obtained by Ponziani et al. [30] and DeLeve et al. [31]. They suggested that patients with PVT commonly have acquired cause of anticoagulant protein deficiencies not hereditary genetic defects.

However, a minority of PVT patients might have a hereditary anticoagulant protein deficiency [32].

The most important thrombotic risk factors in our HCC patients were hyperhomocysteinemia, increased lipoprotein (a), and APCR.

Therefore, we can suggest that thromboembolic complications in HCC are multifactorial, not only acquired but also genetic disorders.

There were some limitations to our study. First, all patients with HCC were included, irrespective of the etiology. Second, our sample size was relatively small, while larger studies were needed. Third, the rate of VTE might be underestimated if it occurs later.

The validity of our study depends on many issues. We excluded alcoholics and smokers as they are considered risk factors of VTE. In addition, cases with portal vein invasion by tumors were confirmed and excluded. We studied acquired coagulation parameters in addition to some genetic thrombotic risk factors.

Conclusion

In conclusion, thrombophilic abnormalities are prevalent in HCC patients, and they could be associated with different thromboembolic complications. The most important hypercoagulable risk factors in our HCC patients were hyperhomocysteinemia, increased lipoprotein (a), and APCR.

Abbreviations

APCR: Activated protein C resistance; APTT: Activated partial thromboplastin time; CP: Cancer procoagulant; CT: Computerized tomography; DVT: Deep venous thrombosis; Fbg: Fibrinogen; FVL: Factor V Leiden; HCC: Hepatocellular carcinoma; IL-1β: Interleukin-1β; IRB: Institutional Review Board; PE: Pulmonary embolism; PT: Prothrombin time; PVT: Portal vein thrombosis; TF: Tissue factor; TNF-α: Tumor necrosis factor-alpha; TT: Thrombin time; VEGF: Vascular endothelial growth factor; VTE: Venous thromboembolism

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Authors' contributions

FO planned the original idea of the work. TM helped in the interpretation of the results, data collection, and in the drafting of the manuscript. TA carried out the preparation and experimental work. All authors read and approved the final manuscript.

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Availability of data and materials

All data produced or analyzed during this study are included in this article.

Ethics approval and consent to participate

Approvals for performing the study were obtained from Internal Medicine, Tropical Medicine, and Clinical Pathology Departments, Zagazig University Hospitals, after taking Institutional Review Board (IRB) approval.
Written informed consent was taken from the patients or their relatives if patients were severely ill to participate in this study.

Consent for publication

Provided with the submission of the article.

Competing interests

The authors declare that they have no competing interests.

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