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***Retrospective Study***

**PAI-1 4G-4G and MTHFR 677TT in non-hepatitis C virus /** **hepatitis B virus related liver cirrhosis**

Pasta L *et al*. Genetic thrombophilia for anti-fibrosis liver therapy

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**Abstract**

**AIM:** To evaluate the different role of thrombophilia, in patients with and without viral etiology, the thrombophilic genetic factors (THRGFs), PAI-1 4G-4G, MTHFR677TT, V Leiden 506Q and Prothrombin 20210A, have been studied as risk factors in 1089 patients with liver cirrhosis (LC), enrolled from January 2000 to January 2014.

**METHODS:** All Caucasian LC patients, consecutively observed in a seven-year period, were included; the presence of portal vein thrombosis (PVT) and Budd Chiari Syndrome (BCS) was registered. The differences between the proportions of each THRGF, in relation to presence or absence of viral etiology, and the frequencies of the THRGF genotypes with those predicted in a population by Hardy-Weinberg equilibrium, were registered.

**RESULTS:** 417/1079 patients (38.6%) showed thrombophilia: 217 PAI-1 4G-4G, 176 MTHFR C677TT, 71 V Leiden Factor, 41 Prothrombin G20210 A, 84 more than 1 THRGF; 350 presented no viral liver cirrhosis (NVLC), and 739 did, called viral liver cirrhosis (VLC), of whom 56 patients HCV+ HBV. PAI-1 4G-4G, MTHFRC677TT, presence of at least one TRHGF and presence of > 1 THRGF, were statistically more frequent in patients with NVLC *vs* patients with VLC: all *χ*2 > 3.85 and *P* < 0.05. Patients with PVT and/or BCS with at least one TRHGF were 189/352 (53.7%). Hardy-Weinberg of PAI-1 and MTHFR 677 genotypes deviated from that expected from a population in equilibrium, in patients with NVLC (respectively *χ*2 = 39.3; *P* < 0.000 and *χ*2 = 27.94; *P* < 0.05), whereas the equilibrium was respected in VLC.

**CONCLUSION:** MTHFR 677TT is near twofold and PAI-1 4G-4G more than threefold more frequent in NVLC *vs* patients with VLC; Hardy-Weinberg equilibrium of these two polymorphisms, confirms this data in NVLC. We suppose that PAI-1 4G-4G and MTHFR 677TT could be considered as factors of fibrosis and thrombosis mechanisms, and increasing the inflammation response, cause the hepatic fibrosis and augmented intrahepatic vascular resistance typical of LC. PAI-1 4G-4G and MTHFR 677TT screening of LC patients could be useful, mainly in those with NVLC, to identify patients in which new drug therapies, based on the attenuation of the HSC activation, or other mechanisms, could be easier evaluated.

**Key words:** PAI-1 4G-4G; MTHFR677TT; V Leiden 506Q; Prothrombin 20210A; Liver cirrhosis; Portal vein thrombosis; Budd chiari syndrome; Fibrogenesis

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**Core tip:** This study on thrombophilia in 1079 patients with liver cirrhosis, showed that PAI-1 4G-4G and MTHFR C677TT, are statistically more frequent in 359 patients with no viral liver cirrhosis *vs* 739 patients with viral liver cirrhosis. In the same patients, PAI-1 and MTHFR 677 genotypes deviated from that expected from a population in Hardy-Weinberg equilibrium. PAI-1 4G-4G and MTHFR 677TT could be considered as factors increasing the response inflammation mechanisms, causing fibrogenesis and augmented intrahepatic vascular resistance, typical of liver cirrhosis. New drug therapies, based on the attenuation of these mechanisms, could be very easily evaluated in these patients.

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**INTRODUCTION**

We studied the thrombophilic genetic factors (THRGFs), PAI-1 4G-4G, MTHFR677TT, V Leiden 506Q and Prothrombin 20210A, as risk factors in patients with liver cirrhosis (LC). We have published two studies on the prevalence of these THRGFs in LC. The first study included 214 patients with LC, enrolled from January 2000 to December 2007[1]. In this study we demonstrated the significant role of PAI-1 4G-4G, MTHFR C677TT and Prothrombin G20210A in patients with hepatocellular carcinoma (HCC) *vs* healthy controls, but we did not analyze the role of THRGF in patients with LC. The second study included 865 patients from June 2008 to January 2014[2]. In this we demonstrated the pivotal role of PAI-1 4G-4G and MTHFR 677TT in patients with alcohol and cryptogenic LC, and provided the hypothesis that thrombo-fibrogenetic mechanisms of PAI-1 4G-4G and MTHFR 677TT could have a role in the development of LC, mainly in patients without HCV and HBV etiology.

To evaluate the different role of thrombophilia, in patients with and without viral etiology, we analyzed the total number of patients with LC recruited by our group, by asking the question if these THRGFs could be potential markers of liver fibrogenesis, mainly in patients without virus etiology.

We built a file with data of the individual patients with LC, resulting from the two studies above described from 2000 to 2014[1,2]**,** and we compared the results of the analysis, with those from the literature, that can support the hypothesis of a pathogenetic role of thrombophilia in liver fibrogenesis.

**MATERIAL AND METHODS**

***Patients***

The first study included 214 patients with LC, enrolled from January 2000 to December 2007[1], and the second, 865 patients from June 2008 to January 2014[2].

**Inclusion criteria:** all Caucasian patients with diagnosis of LC, consecutively observed in the Medicine and Liver Department of an Emergency Hospital of Palermo, were included. Exclusion criteria: Non-Caucasian patients, or with biliary cirrhosis, autoimmune cirrhosis, celiac disease, HCC, and other neoplasm were excluded. The presence of PVT and the extension of the thrombosis to mesenteric or splenic vein was registered, and accepted when unambiguous diagnostic evidence was detected by proper imaging techniques. All patients underwent endoscopy and the size of esophageal varices was recorded as large–medium/small-absent. All patients were asked if they had had episodes of gastrointestinal bleeding in their history. The local human research committee has approved this study protocol.

We analyzed data of patients in relation to the various etiology; the patients were also analyzed separately in two subgroups: the first with virus C, and or B, and the second one with alcohol and cryptogenic cirrhosis, as our second study showed that only these last patients showed significant frequency of THRGFs.

***Thrombophilic genetic factors and definition of thrombophilia***

To evaluate the role of PAI-1, MTHFR677, V Leiden 506Q and Prothrombin 20210A mutations, genotyping of these polymorphisms was performed by PCR-RFLP according with Patnaik *et al*[3], in heterozygous and homozygous status. We have defined genetic thrombophilia the presence of at least one of the following THRGFs: PAI-1 4G-4G, MTHFR677TT, V Leiden Q506, Prothrombin 20210A, as in our previous studies[1,2]. All patients signed an informed consent and the study was conform to the ethical guidelines of the 1975 Helsinki Declaration

***Statistical analysis***

We looked at the differences between the proportions of each THRGF, in relation to presence or absence of viral etiology, using the contingency tables[4]. We considered only statistically significant differences, if the *χ*2 > 3.84 and *P* value < 0.05.

Moreover, we compared the observed frequencies of the THRGF genotypes, with those predicted in a population by Hardy-Weinberg equilibrium, using a web interactive calculator[5].

**RESULTS**

The whole group consisted of 1079 patients: 336 patients showed PVT and 16 Budd Chiari syndrome; 53 patients showed mesenteric and or splenic vein thrombosis associated with PVT; large-medium esophageal varices were present in 445 patients, and 360 patients had had at least one gastrointestinal bleeding episode.

The main demographic and clinical characteristics of patients, declared in the previous original studies[1,2], are synthesized in Table 1. The patients were separated in two subgroups: The first with alcohol and cryptogenic cirrhosis, i.e. without viral etiology, (350 patients), called no viral cirrhosis (NVLC), and the second with virus B and or C (739 of whom 56 patients HCV+ HBV), called viral liver cirrhosis (VLC). **No statistical differences were found between NVLC** *vs* **VLC demographic and clinical characteristics:** all *χ*2 > 3.85 and *P* < 0.05.

A total of 189/352 patients with PVT and or BCS showed at least one TRHGF; in 177 PAI-1 4G-4G and or MTHFR 677TT were present.

Table 2 shows the frequencies of the studied THRGFs in the 1079 patients with cirrhosis of various etiology, and in relation to the presence of virus. A total of 417/1079 patients (38.6%) showed thrombophilia: 217 PAI-1 4G-4G, 176 MTHFR C677TT, 71 V Leiden Factor, 41 Prothrombin G20210 A, 84 with more than 1 THRGF: (82 patients with 2 THRGFs; 2 patients, 3).

No one V with Leiden 506Q or Prothrombin 20210A homozygous was present. The proportion of PAI-1 polymorphisms 4G-5G and 5G-5G was respectively 123 and 121 in NVLC, and 354 and 280 in VLC; the proportion of MTHFR polymorphisms C677T and CC677 was, respectively, 161 and 112 in NVLC, and 364 and 266 in VLC.

NVLC and VLC showed at least one THRGF in 198/350 and 199/729 patients respectively.

We tested statistical differences of the single THRGF between patients with NVLC and VLC, with 2-way contingency table analysis. Table 2 shows the corresponding *χ*2 , P values and odd ratios with 95% with confidence intervals (OR, with 95% CI). V Leiden Factor and Prothrombin G20210 did not show statistical differences. PAI-1 4G-4G, MTHFRC677TT, presence of thrombophilia and presence of > 1 THRGF were statistically more frequent in patients with NVLC *vs* patients with VLC: all *χ*2 > 3.85 and P< 0.05. A total of 178/350, (50.8%) NVLC *vs* 179/729 (24.5%) VLC showed a significant proportion of PAI-1 4G-4G and or MTHFRC677TT: *χ*2 = 73.8, *P* value < 0.000, 95%CI: 3.2 (2.4 - 4.2).

Hardy-Weinberg of PAI-1 and MTHFR 677 genotypes deviated from that expected from a population in equilibrium, in patients with NVLC (respectively *χ*2 = 39.3; *P* < 0.000 and *χ*2 = 27.94; *P* < 0.05 respectively), whereas the equilibrium was respected in VLC. Leiden Q506 and Prothrombin 20210A Hardy-Weinberg equilibrium was respected in the two groups of patients.

**DISCUSSION**

This study was planned to evaluate the proportions of THRGFs, PAI-1 4G-4G, MTHFR677TT, V Leiden 506Q and Prothrombin 20210A, in a very numerous sample of patients with LC, recruited in two prospective studies[1,2]. In the second of these studies, we found that thrombo- and fibrogenetic mechanisms of PAI-1 4G-4G and MTHFR 677TT, could have a role in the development of LC, mainly in patients without HCV and HBV.

Many authors are studying for many years the intrinsic mechanisms of fibrogenesis in liver diseases with and without virus associated. In our study 417/1079, (38.6%) patients with LC showed thrombophilia. We did not found any correlation with Factor V Leiden and Prothrombin 20210A, even if many authors found them correlated to hepatic fibrogenesis[6,7]. We mainly focused our attention on the role of PAI-1 4G-4G and MTHFR677TT. The prevalence of PAI-1 4G-4G in patients with LC is more frequent than that of MTHFR 677TT in our study: 217 and 176. A total of 357/1079 (33.1%) showed the presence of PAI-1 4G-4G and or MTHFR677TT, with a significant difference between patients with NVLC *vs* VLC: 178/350 (50.8%) and 179/729 (24.5%).

MTHFR 677TT is near twofold and PAI-1 4G-4G more than threefold more frequent in NVLC *vs* patients with VLC, as shown in table 2. Moreover, Hardy-Weinberg equilibrium of these two polymorphisms, confirms these data in NVLC.

A limitation of this study is the inability to compare our data, since there are no comparable data published, mainly for PAI-1 4G-4G. The study was a single centre one, and the patients belong exclusively to the single Caucasian Race, coming almost exclusively from Sicily; this could lead to a high genetic frequency of these two genes, on the base of the geographical belonging, typical of populations of the islands, as in the case of Wilson's disease in Sardinia[8].

We did not estimate the correlation between the degree of liver fibrosis and presence of thrombophilia markers; this correlation must be evaluated in the future studies, including other factors as deficiency of protein C, S, antithrombin III, increased serum level of factor VIII, resistance to thrombomodulin action, etc. In these future studies, suitable systems to measure the speed of the portal flow, another risk factor for thrombosis development, should also be developed. Finally, the relationship between the flow velocity and the presence of thrombophilia should be studied.

In relation to PAI-1 4G-4G, there are many studies demonstrating the role of this THRGF, associated with the highest serum PAI-1 activity[9], in liver fibrosis process. PAI-1 has an active role in liver fibrosis in rats[10], through a pathogenic mechanism leading to the hepatic stellate cell (HSC) activation[11]. The relation between ethanol, liver and PAI 1 in alcoholic liver diseases was very recently reviewed by Liu[12]; alcohol up-regulates PAI-1 and its level can be used as an index for the severity of the disease. Patients with nonalcoholic steato-hepatitis showed significantly higher PAI-1 values than those with normal liver as found by Verrijken *et al*[13]. These observations seem sufficient to explain why patients with PAI-1 4G-4G have an increased risk of fibrosis progression until to LC development, in patients without HCV or HBV.

There are many drugs active on fibrolysis, with the goal of lowering the PAI-1 synthesis. Some models of the action of these drugs on PAI 1 activity are below reported; the final objective of these drugs is the reduction of the activation of HSC caused by PAI 1. Sauchinone blocks the TGF-β1-induced phosphorylation of Smad 2/3, the transcript levels of plasminogen activator inhibitor-1, and matrix metalloproteinase-2 as well as autophagy in HSC[14].

Spironolactone partially reverses the effects of aldosterone that promotes HSC activation and the expression of TGF-β1, PAI-1, and collagen in hepatic fibrosis progression partially mediated by TGF-β1, as studied by Shenglan *et al*[15].

Statins lead to a profound amelioration in HSC phenotype activated by the oxidant and inflammatory pathways, and counteract the stimulatory effect of TNF-α on secretion and expression PAI-1. Other treatments are under evaluation for the treatment of liver fibrosis as reported by Gracia-Sancho *et al*[16]; the last futuristic treatment is the use of nanoparticles to transport and deliver nitric oxide (NO) into the HSC[17].

In relation to MTHFR 677TT and fibrogenesis, there are many evidences that MTHFR 677TT has a role on the progression of liver diseases. Patients with MTHFR 677TT have higher serum total homocysteine as reported by Devlin *et al*[18]. MTHFR 677TT polymorphism promotes liver fibrosis progression in patients with recurrent hepatitis C[19], and steatosis and fibrosis in patients with chronic hepatitis C[20].

Hyperhomocysteinemia determines a damage on endothelial cells, reduces the flexibility of vessels, and adversely affects the process of hemostasis. In addition, hyperhomocysteinemia enhances the adverse effects of risk factors such as hypertension, smoking, and impaired glucose, lipid and lipoprotein metabolism, as well as promoting the development of inflammation as found by Baszczuk *et al*[21]. Hyperhomocysteinaemia is highly prevalent in LC, but not in other chronic liver diseases, mainly in patients with MTHFR 677TT; it may contribute to fibrogenesis and vascular complication of LC as reported by Ventura *et al*[22]. The hyperhomocysteinemia causes endothelial dysfunction as studied by Cheng *et al*[23]. According with this last study, hyperhomocysteinemia causing oxidative stress, determines loss of the normal phenotype of liver sinusoidal endothelial cells (LSEC); the consequent cross-talk between LSEC and HSC induces activation of the latter ones, which in turn proliferate, migrate and increase collagen deposition around the sinusoids, contributing to fibrogenesis, architectural disruption and angiogenesis, as reported by Gracia-Sancho *et al*[16].

In relation to the therapy of MTHFR 677TT polymorphism and the consequent increase of serum homocysteine, there are not drugs tested for patients with this polymorphism, but the folic acid therapy. The therapy for obtain a decrease in the concentration of homocysteine in serum is the administration of folic acid in a dose of 15 mg/d, asrecently demonstrated in patients with primary arterial hypertension by Baszczuk *et al*[24].

At the end of the game, in conclusion both PAI-1 4G-4G and MTHFR 677TT cause HSC activation, now recognized as the origin of liver fibrogenesis. This imbalance of the PAI-1 4G-4G and MTHFR 677TT allele frequency, is a possible evidence of the role of these two polymorphisms in pathogenesis of LC, through SHC activation, today considered the key of the liver fibrogenesis.

As reported very recently, by Trautwein *et al*[25], there is necessity for accelerating progress in understanding mechanisms of hepatic fibrosis and defining therapeutic targets, to establish clinical trial designs that can accurately assess efficacy of antifibrotic drugs.

For these reasons, we think important to find patients at the greatest risk for disease progression, also to ensure that these risk factors can be balanced between placebo and control groups, in randomized controlled trials. In our study, PAI-1 4G-4G and MTHFR 677TT were present up to 50% of the patients with NVLC; we think that these genetic factors could be reliably used to stratify risk in clinical trials on new drugs, aimed at obtaining reduction of fibrosis or increase of fibrolysis, to be evaluated also in patients with HBV and or HCV infection.

We think that the drugs causing the lowering of HSC activation, could be better tested in patients with genetic markers asPAI-1 4G-4G e MTHFR 677TT. These patients could be representative of the tip of the iceberg of a population that produces fibrosis in the liver but also in other organs (heart, lung, kidney, and skin), as reported by Ghosh *et al*[26], in relation to PAI-1 and by Reilly *et al*[27] in relation to MTHFR 677TT.

We suppose that PAI-1 4G-4G and MTHFR 677TT may increase the inflammation response, participating to the activation of HSC, causing hepatic fibrosis and augmented intrahepatic vascular resistance in cirrhosis, as suggested by Fernandez[28]. These two genetic markers share the ultimate goal of increase the activation of HSC, directly or by the action of LSEC on HSC.

We hope that all the studies on this argument can suggest new perspectives for developing strategies more effective in lowering fibrosis progression. The common project could be the attenuation of the HSC activation and consequently of liver fibrosis.

In conclusion PAI-1 4G-4G and MTHFR 677TT could be considered as factors of thrombosis and fibrosis mechanisms, that lead to the development of the cirrhosis and augmented intrahepatic vascular resistance.

PAI-1 4G-4G and MTHFR 677TT screening of patients could be useful, mainly in those with alcoholic or cryptogenic cirrhosis, to identify patients in which new drug therapies, based on the attenuation of the HSC activation, or other mechanisms could be more easily evaluated.

The recent articles of Lee *et al*[29] and Gracia-Sancho *et al*[16] deal with the new drugs, in the attempt to develop new strategies of combined therapies directed towards multi-target different pathophysiological mechanisms (i.e. microvascular dysfunction ? angiogenesis, or fibrosis ? microvascular dysfunction); the goal of new therapies includes efforts to inhibit fibrogenesis and promote resolution of fibrosis. The evaluation of genetic profile of thrombophilia (obviously as complete as possible), of patients with chronic liver diseases, could be considered a noninvasive method to assess the dynamics of fibrogenesis and fibrolysis on genetic base.

As an immediate clinical application of the results of our study, according to the principles of the translational medicine[29], we think advisable to screen patients with chronic liver disease for genetic predisposition to liver fibrogenesis, also in patients with hepatic virus diseases, where these genetic markers can lead to a lower response to the antiviral drugs.

In conclusion, it could be recommended that a complete analysis of the risk of progression of liver fibrosis should include all thrombophilia factors.

In patients with MTHFR 677TT, folic acid supplementation should be prescribed. Patients with PAI-1 4G-4G and perhaps MTHFR 677TT, represent a subset of patients in which trials on statins, anti aldosteron, antioxidants and other drugs should be tested to obtain more rapid results, although none of these drugs are approved yet. The combination therapies should include their association with antiviral treatment and non-selective beta-blockers. In patients with portal vein thrombosis or severe portal hypertension or deep vein thrombosis, thrombo-prophylaxis with low molecular weight heparins should be recommended, according to Rodriguez-Castro *et al*[30].

**COMMENTS**

***Background***

In the authors’ study 417/1079, (38.6%) patients with liver cirrhosis showed thrombophilia and PAI-1 4G-4G and MTHFR C677TT are statistically more frequent in 359 patients with no viral liver cirrhosis, *vs* 739 patients with viral liver cirrhosis. In the same patients, PAI-1 and MTHFR 677 genotypes deviated from that expected from a population in Hardy-Weinberg equilibrium.

***Research frontiers***

Many authors are studying for many years the intrinsic mechanisms of fibrogenesis in liver diseases with and without virus associated. We suppose that PAI-1 4G-4G and MTHFR 677TT could be considered as factors of fibrosis and thrombosis mechanisms, and increasing the inflammation response, cause the hepatic fibrosis and augmented intrahepatic vascular resistance typical of LC.

To introduce briefly the current hotspots or important areas in the research field as related to your study.

***Innovations and breakthroughs***

PAI-1 4G-4G and MTHFR 677TT could be considered as factors increasing the response inflammation mechanisms, causing fibrogenesis and augmented intrahepatic vascular resistance, typical of liver cirrhosis.

***Applications***

PAI-1 4G-4G and MTHFR 677TT screening of hepatic chronic liver diseases patients could be useful, mainly in those with no virus related diseases , to identify patients in which new drug therapies, based on the attenuation of the HSC activation, or other mechanisms, could be easier evaluated.

***Terminology***

Genetic thrombophilia is involved in fibrosis and thrombosis mechanisms and, increasing the inflammation response, cause the hepatic fibrosis and augmented intrahepatic vascular resistance typical of chronic liver diseases. In this study, we have defined genetic thrombophilia the presence of at least one of the following THRGFs: PAI-1 4G-4G, MTHFR677TT, V Leiden Q506, Prothrombin 20210A.

***Peer-review***

In relation to PAI-1 4G-4G, there are many studies demonstrating the role of this THRGF, associated with the highest serum PAI-1 activity, in liver fibrosis process. In relation to MTHFR 677TT and fibrogenesis, patients with MTHFR 677TT had higher serum total homocysteine, and there are many evidences that MTHFR 677TT has a role on the progression of fibrosis in liver diseases.

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**Table 1 Main demographic and clinical characteristics of patients with hepatitis C virus/hepatitis B virus liver cirrhosis, defined virus liver cirrhosis and alcohol and cryptogenic, aggregated as non-virus cirrhosis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Total (%) | VLC (%) | Alcohol (%) | Crypto (%) | NVLC (%) |
| Patients | 1079 (100) | 729 (100) | 102 (100) | 248 (100) | 350 (100) |
| Age (range) | 57 (19-83) | 60 (24-83) | 55 (19-80) | 49 (19-83) | 51 (19-83) |
| Male sex | 620 (57.5) | 384 (52.7) | 81 (79.4) | 155 (62.5) | 236 (67.4) |
| PVT/BCS | 352 (32.6) | 230 (31.5) | 45 (44.1) | 77 (31.0) | 122 (34.8) |
| MVT/ SVT | 53 (4.9) | 33 (4.5) | 6 (5.8) | 14 (5.6) | 20 (5.7) |
| L-M varices | 445 (41.2) | 574 (78.7) | 48 (47.0) | 150 (60.4) | 245 (70.0) |
| N° Bleeding  | 360 (33.3) | 265 (36.3) | 41 (40.1) | 54 (21.7) | 95 (27.1) |
| Child A/B/C  | 416/242/430(38.5/22.4/39.8) | 241/194/294 (33.0/26.6/40.3) | 31/53/17 (30.3/51.9/16.6) | 129/31/83(52.0/12.5/33.4) | 165/48/17 (47.1/13.7/39.1) |

**No statistical differences between VLC** *vs* **NVLC group:** All *χ*2 > 3.85 and *P* < 0.05. VLC: Virus liver cirrhosis; NVLC: Non-virus cirrhosis; PVT: Portal vein thrombosis; BCS: Budd chiari syndrome.

**Table 2 Frequencies of thrombophilic genetic factors, PAI-1 4G-4G, MTHFR 677TT V, Leiden 506Q and Prothrombin 20210A in patients with hepatitis C virus/hepatitis B virus liver cirrhosis, alcohol and cryptogenic, aggregated as non-virus cirrhosis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|    | A)VLC(%) | Alcohol (%) | Crypto(%) | B) NVLC(%) | A) *vs* B)*χ*2: *P* value; OR (95%CI) |
|  |  |  |  |  |  |
| Patients | 729 (100) | 102 (100) | 248 (100) | 350 (100) | - |
| PAI-1 4G-4G | 95 (13.0) | 33 (32.3) | 89 (35.8) | 122 (34.8) | 68.2: 0.000; 3.6 (2.6 - 4.9) |
| MTHFR 677TT  | 99 (13.5) | 14 (13.7) | 63 (25.4) | 77 (22.0) | 11.7: 0.001; 1.8 (1.3 - 2.5) |
| V Leiden 506Q | 41 (5.6) | 9 (8.8) | 22 (8.8) | 30 (8.6) | 3.3: 0.09; 1.5 (0.9 - 2.6) |
| Prothr.20210A  | 25 (3.4) | 3 (2.9) | 13 (5.2) | 16 (4.5) | 0.8: 0.39; 1.4 (0.7 2.7) |
| At least 1 THRGF | 218 (29.9) | 43 (42.1) | 156 (62.9) | 199 (56.9) | 72.5: 0.000; 3.1 (2.4 - 4.1) |
| > 1 THRGF | 40 (5.4) | 14 (13.7) | 30 (12.0) | 44 (12.5) | 16.5: 0.000; 2.5 (1.6 - 4.0) |

VLC: Virus liver cirrhosis; NVLC: Non-virus cirrhosis; PVT: Portal vein thrombosis; BCS: Budd chiari syndrome; THRGF: Thrombophilic genetic factors.