

## Risk Factors Stratifications for Portal Venous Thrombosis (PVT)

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### Abstract

There is an ongoing increment in the incidence of Portal venous thrombosis. Many factors play a role in the pathogenesis of the PVT. In this study, commorbidities including cirrhosis, chronic viral hepatitis B and C, alcoholic-induced cirrhosis, acquired immune deficiency syndrome (AIDs), hypertension (HTN), chronic lung diseases, diabetes mellitus (DM) and obesity were examined to see their predictability of developing PVT.

Portal venous thrombosis (PVT) is a complete or partial occlusion of the portal vein. The most common etiology behind the development of PVT includes but limited to inherited hyper-coagulopathy disorders, cirrhosis, hepatocellular carcinoma, abdominal infection or inflammation. In this study, comorbidities including liver cirrhosis in general, Hepatitis B, C and alcoholic cirrhosis, AIDs, HTN, DM, obesity were examined to see their predictability of developing PVT. Approximately 4408 patients with portal venous thrombosis and randomly selected 4231 without portal venous thrombosis were identified for the study. After controlling for age, sex and race, People with liver cirrhosis are about 8 times more likely to have portal venous thrombosis than non liver cirrhosis group. We conclude that among cancers, Hepatocellular carcinoma patients have the highest chance of developing PVT while people with lung cancer and prostate have almost the same risk of non cancer patient for developing PVT.

**Keywords:** Portal venous thrombosis; Cancer; Cirrosis; Hepatocellular carcinoma

### Introduction

Portal venous thrombosis (PVT) is a complete or partial occlusion of the portal vein likely due to a reduced blood flow in the portal vein causing clot formation in the spleno-porto-mesenteric venous system in conjunction with the hypercoagulability, which occurs in advanced liver disease. The most common etiologies behind the development of PVT are inherited hyper-coagulopathy disorders, cirrhosis, malignancy especially the hepatocellular carcinoma, abdominal infection or inflammation, and up to 25% from idiopathic etiologies [1].

The pathogenesis process behind the development of PVT is developing a thrombus inside the portal vein or embolization from distant source in patients with high prothrombotic disorders. In Malignancy, PVT formed from either a micro-invasion of the portal vein, an external compressing lesion/mass or hyper-coaguable state. In cirrhosis, the decrease in blood flow in the portal system, bacterial translocation, and thrombophilic state all represents a major factor in developing PVT. While the inflammatory reactions whether its cute or chronic such as pancreatitis or inflammatory bowel disease, these inflammatory processes can predispose to the developing PVT [2-4].

The largest published data on PVT is reported from Sweden which, based on autopsy reports, demonstrated that cirrhosis and malignancies are the most common predisposing factors for developing PVT. The study identified 254 patients representing 1% from 23797 autopsies with a PVT diagnosis, 28% had cirrhosis, 23%

primary and 44% secondary hepatobiliary malignancy, 10% major abdominal infectious or inflammatory disease and 3% had a myeloproliferative disorder. Although the prevalence of PVT is estimated to be low in the general population but in cirrhosis, the prevalence is estimated between 4-20% as its increases with age and the severity of liver disease as it's the highest among liver transplant candidates [5-9].

Hepatocellular carcinoma (HCC), especially in people with cirrhosis, is among the malignancies with the highest correlation of PVT formation. As many as 40% of the patients with HCC have PVT at the time of diagnosis carrying a poor prognostic indicator as metastatic lesions are frequently coexist. [10,11] 44% of non-HCC neoplastic PVT thrombosis occurs from direct invasion, both local compression and hypercoaguable states comprise a large percentage as well. The majority of PVT of non-HCC malignancies is associated with malignancies from gastrointestinal tract source (pancreas, stomach, and colon) followed by lung cancer and very rarely from breast cancers [9,12].

Naomi et al. in her study found that in the cirrhosis population without underlying malignancy, the most common causes associated with PVT were chronic viral hepatitis and alcohol-related cirrhosis with percentages of 31% and 18 respectively [13]. In decompensated cirrhosis patients who are candidates for liver transplantation, the incidence of PVT increased to approximately 25% and, again, is considered a poor prognostic factor. Subsequently, the survival rate is lower than survival from the group without PVT and has been shown to have inferior post-transplant outcome [14-16].

In this study, comorbidities including liver cirrhosis in general, Hepatitis B, C and alcoholic cirrhosis, AIDs, Hypertnesion, Diabetes, obesity were all examined to see their predictability of developing PVT in hopes to broaden the breadth of medical knowledge of PVT and allow better risk stratification.

## Methods

We preformed a retrospective analysis using the National Inpatient Sample (NIS) database for 2010. The NIS is a database and software tool developed for the Healthcare Cost and Utilization Project (HCUP). The NIS is the largest publicly available inpatient health care database in the United States. It contains data from more than 7 million hospital stays each year. Weighted, it estimates more than 35 million hospitalizations nationally. Admissions for the 2010 NIS totaled over 7 million. The variables included in this study were identified using ICD9 codes for 2010. This ICD9 codes were used to identify the case group. Control group was identified randomly from the 7 million patients who don't have a diagnosis of cirrhosis. The procedure used in SPSS for selecting control group is called arbitrary random equivalent number. Case-Control (Portal venous thrombosis-Non portal venous thrombosis) design is used. All genders and race were with an age of 18-year-old and above were included. The coexisting comorbidities including Hepatitis C, B, AIDs, cirrhosis, chronic lung disease, inflammatory bowel disease and others were identified in each group. A binary multivariate Logistic regression statistical test was used to examine the adjusted odd ratio of the portal venous thrombosis with each predictor. IBM SPSS Statistics for Windows, Version 19.0 was used to execute the analysis. A confidence interval (CI) of 95% and P value less than 0.05 were determined to define significance.

## Results

Approximately 4408 patients with portal venous thrombosis and randomly selected 4231 without portal venous thrombosis were identified for the study. After controlling for age, sex and race, People with liver cirrhosis are about 8 times more likely to have portal venous thrombosis than non-liver cirrhosis group. More cases with PVT found in females and Caucasians. Chronic hepatitis B viral infection related cirrhosis and Hepatitis C cirrhosis have almost equal probabilities of developing PVT (Adjusted Odd ratio is 7.9 vs. 7.2). Alcoholic liver cirrhosis adjusted odd ratio was 3.4 (Table 1).

<b>SEX</b>	Male	1779	2597	4376
		42.00%	58.90%	50.70%
	Female	2452	1811	4263
		58.00%	41.10%	49.30%
<b>Total</b>	Count	4231	4408	8639
<b>Race</b>	White	2465	2704	5169
		65.70%	67.70%	66.70%
	black	550	518	1068
		14.70%	13.00%	13.80%
	Hispanic	474	468	942
		12.60%	11.70%	12.20%

	Asian	105	162	267
		2.80%	4.10%	3.40%
	Native american	29	21	50
		0.80%	0.50%	0.60%
Others	129	120	249	
	3.40%	3.00%	3.20%	
<b>Total</b>	Count	3752	3993	7745

**Table 1:** Probabilities of developing PVT.

People with AIDs have almost 4 times more chance to have PVT than non-AIDs people (Adjusted Odd ration 3.6). People with Diabetes have about 2 times more likely to have PVT than the non-DM (Adjusted odd ration 1.89). Patients with obesity, chronic lung diseases and hypothyroidism does not have an increased risk for PVT. Patients with inflammatory bowel diseases, ulcerative colitis and Crohn's disease had an increased risk of developing PVT with an odd ratio of 2.5 and 2.4 respectively (Table 2).

Comorbidities	P Value	Adjusted odd ratio
Hepatocellular	0	124.424
CA Pancreas	0	28.194
Cholangiocarcinoma	0	77.051
CA Stomach	0.027	4.219
CA Prostate	0.003	0.322
CA Breast	0.251	1.592
CA Lung	0.394	2.287
CA Colon	0	5.18
Ulcerative Colitis	0.007	2.582
CRhons Disease	0.002	2.409
Hypothyroid	0.001	0.743
Obesity	0.106	0.863
Chronic Lung Disease	0	0.672
AIDs	0.002	3.604
Diabetes	0.003	1.89

**Table 2:** Binary multivariate logistic regression analysis.

The coexisting diagnosis of a tumor in general increases the risk for PVT by more than five times. (Odd ratio is 5.3, CI: 95%) and having a metastasis increase the risk up to 7 times. Among Cancers, hepatopancreaticobiliary cancers have the highest risk for PVT; the adjusted Odd ratio for hepatocellular carcinoma, cholangiocarcinoma and pancreatic cancers is 124, 77 and 28 respectively. Patients with colon or gastric cancer have four to five times more chance of having PVT than people without cancer (Adjusted odd ratio is 5.1 and 4.2). Breast cancer patients have about 1.5 times chance of having PVT than

non-breast cancer patients while prostate cancer has no increase in the risk for PVT (adjusted Odd ratio 0.3) (Table 2).

## Discussion

This study is unique by having the largest number of PVT patients. The large target population of the PVT (more than 4000) patients included in this study and the homogenous randomly selected control group from more than seven million gives a statistical strength to the study and makes a good representation of the general population. This study is the first one that compares many PVT predictors including malignancies, liver cirrhosis from different causes and inflammatory bowel diseases all at the same time together.

Hepatitis infection by itself was not a risk factor for PVT unless the patients have already developed cirrhosis. Odd of having PVT in Hepatitis B, C and alcoholic related cirrhosis were compared. The risk of PVT in Hepatitis B related cirrhosis and Hepatitis C cirrhosis are almost the same (Odd ratio is 7.9 vs. 7.8). Yet, after controlling for alcoholic related cirrhosis, the adjusted risk ratio of having PVT in hepatitis B related cirrhosis vs hepatitis C cirrhosis were 2.9 vs. 6 respectively. The reason behind it is unclear but it could be explained by the synergistic effect of alcohol and HCV on cirrhosis.

In this data base analysis, we found that having multiple different types of cancer had a significant increase in the development of PVT especially gastrointestinal malignancies. Hepatopancreaticobiliary cancers have the highest risk among the gastrointestinal malignancies with odd ratios mentioned above. This correlation could be explained by the fact these cancers often times have invaded the portal vein, had a compressing effect on portal vein, had high thrombotic status or combination of all of them. The Pancreatic cancer increases the risk for developing PVT fifty times and colon cancer 5 times more than people without cancer. On the other hand, people with prostate cancer have almost the same risk of non-cancer patient for developing of PVT. These findings are in consensus with previous studies showing that HCC patients have the highest risk of developing PVT followed by cholangiocarcinoma cancer and Cirrhosis [17]. In particular there is a significant conclusion to be drawn from these results, which advocates for a high suspicion of malignancy in the setting of PVT from unknown origin. Incidental PVT discovered on imaging should prompt an immediate workup for malignancy and subsequent metastasis based on the statistically significant difference among the rate of PVT found in malignancy versus any other categories included in this study.

One of the limitations of this study is that it's a retrospective one and the causation between the predictors and the outcome cannot be determined. Furthermore, the NIS database used tracks admissions, not necessarily patients. It also looks at patients that are hospitalized and therefore does not accurately reflect the healthy, generalized population. There could be also a clerical error involved as the database is taken from charts completed by humans, with human error, as well as completion of charts from many different institutions across the United States.

## Conclusion

Hepatocellular carcinoma patients have the highest chance of developing PVT follow by pancreatic cancer. People lung cancer and

prostate have almost the same risk of non-cancer patient for developing PVT. We conclude that the incidental finding of PVT on imaging should prompt the search for malignancy especially liver malignancy and pancreatic malignancy. While more research is needed to determine a specific protocol for the undertaking of this search.

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