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PRIMER

# Primer for Value of D-dimer and protein S for diagnosis of portal vein thrombosis in patients with liver cirrhosis (Dong-Lei Zhang, Jian-Yu Hao and Ning Yang 2013)

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## Abstract

In 2013, liver cirrhosis was estimated to be responsible for over 40,000 deaths—a number that is expected to increase in coming years (Deitelzweig et al., 2013). Nearly one out of every four patients suffering from cirrhosis develops pulmonary vein thrombosis (PVT), a serious condition with the potential of leading to life-threatening complications (Zhang, Hao and Yang 2013). In their article Value of D-dimer and protein S for diagnosis of portal vein thrombosis in patients with liver cirrhosis, Dong-Lei Zhang, Jian-Yu Hao and Ning Yang look at D-dimer and Protein S (two factors playing a role in the coagulation process) as potential diagnostic factors for PVT among cirrhotic patients. This study takes a step toward establishing methods for early diagnosis and treatment of PVT in cirrhotic patients, in turn helping these patients avoid potential life-threatening complications PVT carries with it. The aim of this paper is to provide explanations of the important details in the Zhang, Hao and Yang article as well as the background information necessary to understand the article.

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**Purpose:** Provide background information necessary to understand a new study in the important field of liver disease, specifically the potentially life-threatening disease of pulmonary vein thrombosis.

**Pulmonary vein thrombosis**
A condition in which a problematic blood clot develops in the portal vein.

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## Background

In 2013, around 150,000 hospitalizations and over 40,000 deaths were estimated to be the result of cirrhosis and cirrhotic complications, and this is expected to increase in years to come (Deitelzweig et al. 2013). Within the population of patients diagnosed with cirrhosis, approximately one out of every four develop **pulmonary vein thrombosis** (PVT), a condition that can potentially lead to multiple life-threatening complications (Alkim et al. 2012; Mangia et al. 2005). One of these complications is refractory ascites: a condition in which fluid accumulates in the abdominal cavity and also causes the patient to have lower sodium excretion (Senousy and Draganov 2009). Necrosis can also occur, meaning the patient suffers the loss of metabolic functions and structural integrity of cells due to cellular damage (Rosser and Gores 1995).

In May of 2013, an article titled *Value of D-dimer and protein S for diagnosis of portal vein thrombosis in patients with liver cirrhosis* was published in the *Journal of International Medical Research* concerning PVT. The purpose of this article was to assess the value of two possible diagnostic factors (D-dimer and protein S) in the detection of PVT. This was to help work toward early diagnosis and treatment of the condition and avoid the potential

life-threatening complications the disease entails. The purpose of this present paper is to help a broader audience understand not only the rationale, methods and results of the Zhang, Hao and Yang study and also the importance of this study to the field of liver disease and medicine.

## *Pulmonary vein thrombosis and liver cirrhosis*

**Cirrhosis**
Scarring of the liver tissue.

**Cirrhosis** is a complication prevalent in advanced stages of liver disease, and consists of the presence of certain anatomical abnormalities of the liver's structure (Soharabpour, Mohamadnejad and Malekzadeh 2012). Specifically, cirrhosis means tissue in the liver being replaced by scar tissue. This can be the result of abuse to the liver or long term liver disease. When a patient suffers from cirrhosis, their liver can decrease in its ability to synthesize blood coagulation factors (Witters et al. 2008). This leads to a prolonged coagulation time or even hypocoagulation. Patients suffering from hypocagulaiton are at risk of excessive bleeding as their ability to form blood clots is impaired. However, it is also possible for the patients to suffer excessive clot formation, or hypercoagulation (Tripodi et al. 2011). This is due to the combination of increased levels in some coagulation factors and decreased levels of anticoagulant factors, such as protein C.

Portal vein thrombosis (PVT) is a condition in which a problematic blood clot forms in the portal vein—a vein responsible for 75% of the liver's blood supply (Parikh, Shah and Kapoor 2010). Again, with impaired liver function, PVT becomes a risk for patients suffering from liver cirrhosis. Along with the potential life-threatening complications of PVT previously noted, this makes the article by Zhang and colleagues important and worth understanding. Considering the risks and consequences of the condition such as refractory ascites and necrosis, studying ways to diagnose PVT early among patients with liver cirrhosis is an important step in their prevention.

Figure 1

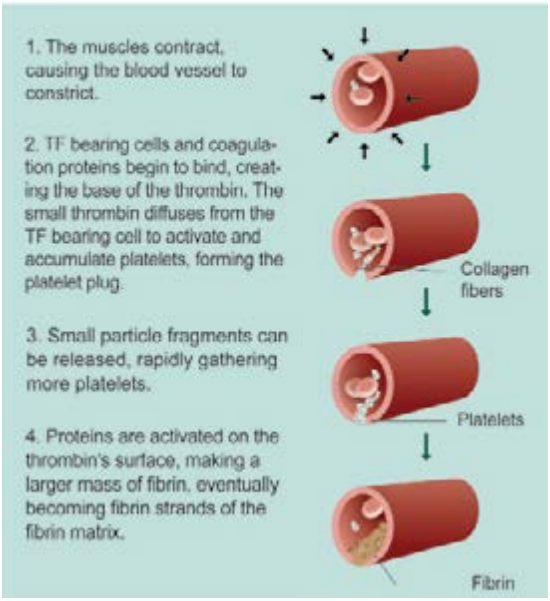


**Figure 1. The steps of blood clot formation.** The blood vessel first contracts when it is injured in order to reduce the blood flow. Cells outside the vessel are activated when they are exposed to the blood, and begin forming the base of thrombin along with other proteins. This thrombin breaks off to collect more platelets and form a platelet plug to begin clogging the wound. Proteins on the surface of this thrombin are activated to a larger mass of fibrin and eventually the fibrin matrix. Figure adapted from Pearson Education, Inc.

## *Blood coagulation: the clotting process*

PVT is fundamentally a condition of blood coagulation, or the blood clotting process. When we bleed, proteins in our blood form clots that stop the bleeding so the wounded blood vessel can heal. This coagulation process begins when tissue factor (TF) bearing cells are exposed to blood flow (Smith 2009). These TF bearing cells lie outside the vessels, so they are only exposed to blood due to an injury to that vessel. After this exposure, coagulation proteins begin binding to the TF bearing cells, creating the small base of thrombin, or a blood clot (Figure 1).

Following this initiation phase, the small thrombin will diffuse from the TF bearing cell so it can begin activating and accumulating platelets to grow in size and

strength. Soon, enough platelets will have accumulated so small particle fragments can be released to recruit more platelets at a more rapid rate. As this happens, more proteins are activated on the surface of the thrombin, leading it to become a larger mass of fibrin and eventually become fibrin strands that make up a fibrin matrix that patches up the wound. This process allows the wound to heal.

### *After healing: the fibrinolytic process*

Next, the clot must be degraded and regulated to avoid problems and restriction of the blood flow through the vessels. This process known as fibrinolysis begins as the enzyme **plasmin** breaks down fibrin and fibrinogen, and other coagulation factors (Amara et al. 2008). Before this happens, plasminogen activators, such as tissue plasminogen activator (tPA) must convert plasminogen into plasmin to begin the breakdown of the fibrin of a clot (Amara et al. 2008; Thelwell 2010).

**Plasmin**
An enzyme found in blood that is responsible for degrading different proteins in the blood.

Although tPA is produced in the endothelium of blood vessels, the plasminogen itself is synthesized in the liver (Peck-Radosavljevic 2007). Plasminogen is the precursor of plasmin, the factor responsible for breaking down the fibrin of a clot. Therefore, the liver is a vital jumping off point for fibrinolysis. As the fibrin is degraded by the plasmin, the remaining fibrin degradation products (such as D-dimer) are flowing in the blood stream to be metabolized by the liver (Anantharaju, Feller and Chedid 2002).

### *The role of the liver in the clotting and fibrinolytic processes*

The liver takes substances that are put in (or created in, as is the case of the fibrin degradation products) our body, and metabolizes them so that our body can use their components (Anantharaju, Feller and Chedid 2002). With coagulation, the liver plays a mediating role with the factors it produces. The liver makes sure that the blood clot is formed, but also ensures that the clot doesn't restrict blood flow and become troublesome (Peck-Radosavljevic 2007). Most of the procoagulation factors that work to form blood clots (such as prothrombin and Factor X, which converts prothrombin into thrombin) are synthesized in the liver; the anticoagulant factors (such as protein S and protein C, which work together to inactivate some procoagulant factors) are also synthesized in the liver (Peck-Radosavlijevic 2007). Therefore, the liver functions to not only ensure that a blood clot forms, but also that the clot is regulated so as not to restrict blood flow. When a liver is healthy, this process runs smoothly as expected. When there are complications with the liver, such as liver cirrhosis, this function is negatively affected (Jang 2009).

### *Protein S and D-dimer background: why study these factors?*

Because the liver metabolizes and produces factors involved in the coagulation process, Zhang and colleagues hypothesized that altered levels in two of these factors may indicate PVT (Zhang, Yu and Yang 2013) . During coagulation, **protein S** helps to regulate the process by working with the activated protein C to help find activated coagulation factors so they can be inactivated—this helps prevent the formation of a troublesome clot (Suleiman, Negrier and Boukerche 2013).

**Protein S**
Helps to regulate the coagulation process by working with activated protein C, helping it find activated coagulation factors so they can be inactivated so as not to form a troublesome clot.

**D-dimer** plays a role once the clot has been degraded through fibrinolysis. Once the cross-linked fibrin is degraded, D-dimer is left in the bloodstream as one of the fibrin degradation products (Haapaniemi and Tatlisumak 2009). The liver is responsible for the synthesis and metabolization of most of the factors (like D-dimer) involved in coagulation as well as fibrinolysis, and impaired liver function leads to abnormal concentrations of these factors (Zocco et al. 2009).

**D-dimer**
Fibrin fragment present in the blood after the degradation of a blood clot. Cross-linked fibrin are degraded during fibrinolysis, resulting in the formation of various fragments of fibrin, one of which is D-dimer.

As protein S is produced primarily in the liver, deteriorating liver function (i.e.

cirrhosis) has been shown to lead to decreased concentrations (Kitchens et al. 2011; Zocco et al. 2009). Protein S is responsible for metabolizing fibrin degradation products (i.e. D-dimer, for example), and it has been shown that D-dimer concentrations increase as liver function worsens (Zhang, Hao and Yang 2010). What Zhang and colleagues aim to do in the study being analyzed here is look at a potential diagnostic relationship between these two factors (D-dimer and protein S) and PVT.

## Unfolding *Value of D-dimer and protein S for diagnosis of portal vein thrombosis in patients with liver cirrhosis*

**Hepatitis**
Inflammation of the liver.

**Autoimmune Hepatitis**
Persistent inflammation of the liver with an unknown cause.

## Patients and methods

For the study, Zhang, Hao and Yang recruited 188 patients who were suffering from liver cirrhosis (46 female and 142 male); within 48 hours of being admitted, computed tomography (CT) scans were done for diagnosis of PVT (Zhang, Hao and Yang 2013). Upon analysis of the CT scans, 51 of the 188 patients were diagnosed with PVT. All 188 patients underwent the same experimental design and procedure. The data generated was analyzed together using the statistical methods described in the following sections.

### *Characteristics of the Study Population: why this group?*

The patients selected by Zhang and colleagues for the study suffered from liver cirrhosis caused by hepatitis A, hepatitis B or alcoholism. This is because these conditions are all characterized by inflammation of the liver (Atta et al. 2012; Yu et al. 2011; Pritchard and Nagy 2005).

The researchers wanted to test a possible value of D-dimer and protein S as PVT diagnostic factors among cirrhotic patients, so a uniform sample was important for making sure the results were valid. Having a uniform sample population allowed the researchers to know the different factors contributing to the diseases and symptoms being studied. Therefore they were able to have more control of the study without having the results being disturbed by some unknown source. If the sample had consisted of too much variance, the control on what factors and effects were being studied would have become significantly weakened.

### *Patient exclusion criteria: why not this group?*

Although patients suffering from cirrhosis caused by **hepatitis** B and C were included in the study done by Zhang and colleagues, those with **autoimmune hepatitis** were not. With autoimmune hepatitis, the patient has a liver that is inflamed and remains inflamed, but with an unknown cause (Czaja 1996). If the researchers did not know what was causing the liver to be inflamed, they would not have been able to actually say whether the results were actually due to D-dimer and protein S concentrations.

Patients suffering primary biliary cirrhosis (PBC) were also excluded. This condition is a variant of liver cirrhosis in which there is necrosis among the epithelial cells located in the small- and medium-sized bile ducts of the liver, and there is also portal inflammation (Silveira and Lindor 2007). Furthermore, PBC is also an autoimmune disease that eventually leads to liver failure as it destroys the bile ducts that create the bile to help our body with digestion (Siegel et al. 2008). Because of these extra factors, patients with PBC could have affected the results as the necrosis of the bile ducts and portal inflammation may play a role in PVT detection that the researcherswere not aiming to study. Therefore, they were excluded so the study and its population were more controlled.

### *Child-Pugh classification system: how to evaluate severity of cirrhosis*

Zhang and colleagues used the Child-Pugh classification system across all 188 patients

to make sub-groups based on the severity of cirrhosis. This system for determining severity of liver disease consists of looking at five variables: serum levels of bilirubin and albumin, prothrombin time, ascites and encephalopathy_(Angermayr et al. 2003). When heme is broken down, bilirubin is left as the end product (Sticova and Jirsa 2013). Bilirubin is then removed from the blood plasma once it goes through the liver, going on to be combined with certain sugars and excreted from the body through urine. Therefore, excessive amounts of bilirubin can indicate an improperly functioning liver.

**Albumin** is a protein in the plasma that plays an important role as it helps regulate fluid transport, which would include transporting bilirubin (Hulshoff et al. 2013). Furthermore, as it is synthesized in the liver, low concentrations of albumin are indicators of improper liver function (Hulshoff et al. 2013).

**Albumin**
A protein found in plasma that helps regulate fluid transport.

**Prothrombin time** is a test measuring the time it takes for the plasma portion of blood to coagulate (Tripodi et al. 2007). Since the liver plays an important role in the coagulation process, a longer coagulation time as found by this assessment can indicate improper liver function.

**Prothrombin time**
Amount of time plasma portion of blood takes to coagulate

**Ascites** pertains to the build up of fluid in the abdominal cavity, and portal hypertension is viewed as its underlying factor (Kuiper, De Man and Van Buuren 2007). With a patient diagnosed with cirrhosis, blood and plasma volumes increase so testing ascites and the tendency for portal hypertension help to evaluate the degree of liver disease.

**Ascites**
Build up of fluid in the abdominal cavity.

Lastly, **hepatic encephalopathy** is a condition in which the patients decreased liver function leads to decreased brain function, such as: lower energy level, impaired cognitive and/or motor functions, or impaired sleep-wake cycle (Schiano 2010). Assessing the severity of this condition can give further insight to the severity of the liver condition.

**Hepatic encephalopathy**
Condition in which the brain function of the patient decreases as a result of decreased liver function.

For each of the five factors, the patient receives a score of 1-3 points, with one being the least and three the most severe, adding up to an overall Child-Pugh Classification of anywhere between 5-15 (Zhang, Hao and Yang 2013). The patient is then placed into either class A (low, 5-6 points), class B (intermediate; 7-9), or class C (poor; 10-15) based on their overall score. This system is the most commonly used one due to its ease as a bedside test (Angermayr et. al. 2003).

**Specificity**
Amount of actually negative cases that lie below the given cutoff value.

**Sensitivity**
Amount of actually positive cases that lie above the given cutoff value.

## *Statistical analysis of Receiver Operating Characteristic Curve to assess value of D-dimer and protein S as potential PVT diagnostic factors: how it works*

Once Zhang and colleagues collected the concentrations of D-dimer and protein S for each of the 188 patients, they needed to assess the connection between the concentrations as diagnostic factors for PVT. Receiver Operating Characteristic (ROC) curves are used when analyzing factors for potential diagnostic capabilities (Hanley and Mcneil 1983). First, two graphs must be plotted against one another, one being patients with a disease (PVT), and the other being the patients without (no PVT) (Figure 2). The x-axis of the graph will be the factor(s) being studied for diagnosis; in this case, either D-dimer or protein S. A cutoff value must then be selected, which marks a point where anything above this value (i.e. amount of D-dimer concentration, for example) will be a positive test for PVT, and below it is negative (Park, Goo and Jo 2004). However, when it comes to clinical trials like this, the distribution between the two groups is almost never perfect and there's often overlap between the curves (Park, Goo and Jo 2004). This requires statistical analysis to be done in order to determine how related PVT diagnosis is with D-dimer and protein S concentrations.

Researchers must look at four things to evaluate the diagnostic capability of D-dimer and protein S: **specificity, sensitivity, positive predictive value (PPV)** and **negative predictive value**

Figure 2

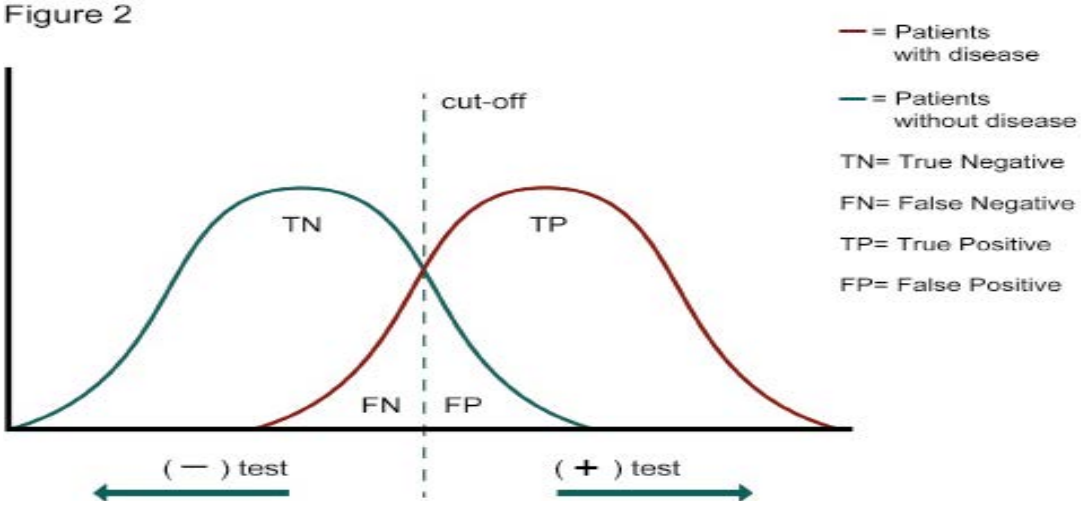


**Figure 2. Test results plotted in two curves: positive or negative.** Patients beneath the red curve have the disease, patients beneath the blue curve do not. The cut-off value is chosen to test the diagnostic capabilities of certain factors, marked here by the vertical dashed line. This states that patients with concentrations above the value have the disease, those below do not. Therefore, patients below the cut-off value that actually have the disease are false negatives. Those below the cut-off that truly don't have the disease are true negatives. Cases above the cut-off are false positives if the patient truly doesn't have the disease, but are true positives if they do. Figure adapted from Bewick, Cheek and Ball 2004 and Park, Goo and Jo, 2004.

**Positive predictive value (PPV)**
Amount of cases above the given cutoff that are actually positive.

**Negative predictive value (NPV)**
Amount of cases below the given cutoff that are actually negative.

**(NPV)**. Specificity looks at what is under the non-diseased patient curve and is the amount of truly negative cases that are below the cutoff (below cutoff value, and actually free of PVT) (Park, Goo and Jo 2004). Sensitivity looks at what is under the diseased patient curve and is the number of truly positive cases that are below the cutoff (above cutoff value, and actually diagnosed with PVT). PPV looks at patients above the cutoff value and calculates how many them are true positive cases, while NPV looks at the patients *below* the cutoff and calculates how many of them are true negatives (Bewick, Cheek and Ball 2004).

The actual ROC curve is plotted with the y-axis being sensitivity and x-axis being 1 minus specificity (see figure 3 for a diagram of an ROC curve) (Bewick, Cheek and Ball 2004). Each cutoff value is then plotted, using their sensitivity and 1-specificity at the given value, creating the curve (Park, Goo and Jo 2004). In order to see how valuable factors are in diagnosing the diseases tested, one calculates the area under the curve; an area of one would be perfection, so the closer the value is to one the better the variables are as diagnostic factors (Bewick, Cheek and Ball 2004).

## Results of *Value of D-dimer and protein S for diagnosis of portal vein thrombosis in patients with liver cirrhosis*

### *ROC curve revisited: what did the statistical analysis tell us about the diagnostic value of D-dimer and protein S?*

Using an ROC curve allows for analysis of how well certain factors are at determining a given disease. Zhang and colleagues used ROC curves to analyze the concentrations of D-dimer and protein S among their 188 patients suffering from liver cirrhosis, with 51 of them suffering from PVT. Cross-analyzing the concentrations of these two factors with patients with or without PVT allowed them to make assessments on whether they might be diagnostic factors.

When looking at class A patients (least sever liver cirrhosis), giving the ROC curve a cutoff value of >0.56mg/l of D-dimer gave a good specificity and NPV reading, meaning that many of the cases deemed PVT negative based on D-dimer concentrations truly were (Park, Goo and Jo 2004; Bewick, Cheek and Ball 2004). However, this cutoff also led to low sensitivity and PPV—not many of the cases deemed PVT positive truly were. With a cutoff of <17.39 mg/l of protein S for class A patients, there was good sensitivity and NPV, but low specificity and PPV. This means that there were few false negatives and many true negatives, but there also too many false positives and not many true positives (Bewick, Cheek and Ball 2004).

With class B patients, a >1.18 mg/l D-dimer cutoff led to good specificity and NPV—there were few false positives and many true negatives. With a <19.2 mg/l protein S cutoff, good sensitivity and NPV were reached, meaning few false negatives and many true negatives; but, there was also low specificity and PPV—too many false positives with too few true positives.

When the entire population (all 188 patients of the study) was statistically analyzed, a D-dimer cutoff of >0.92 mg/l yielded good specificity and NPV, but also low sensitivity and PPV: few false positives with a good proportion of true negatives, but too many false negatives and too few true positives. A <16.36 mg/l protein S cutoff yielded the same results.

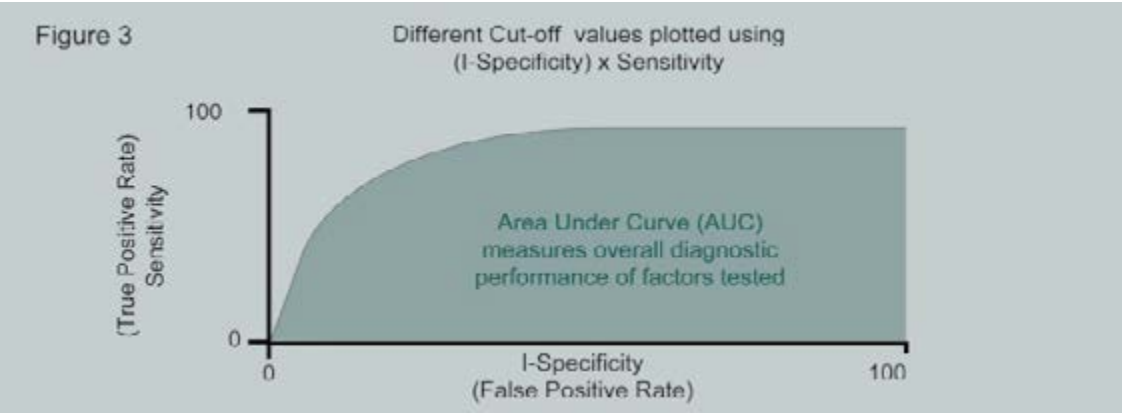


**Figure 3. ROC curve.** The Y-axis is a measurement of the true positive rate, or the sensitivity. This is the portion of the cases determined to be positive based on the concentrations of the tested diagnostic factors and the decided upon cut-off value that truly had the disease. The X-axis is the false positive rate, or the portion of cases determined to be false in the test that truly were without the disease. The area under the curve that is plotted represents the overall diagnostic performance of the factors, displaying how well they are at diagnosing the given disease. Figure adapted from Bewick, Cheek and Ball 2004 and Park, Goo and Jo, 2004.

Figure 4

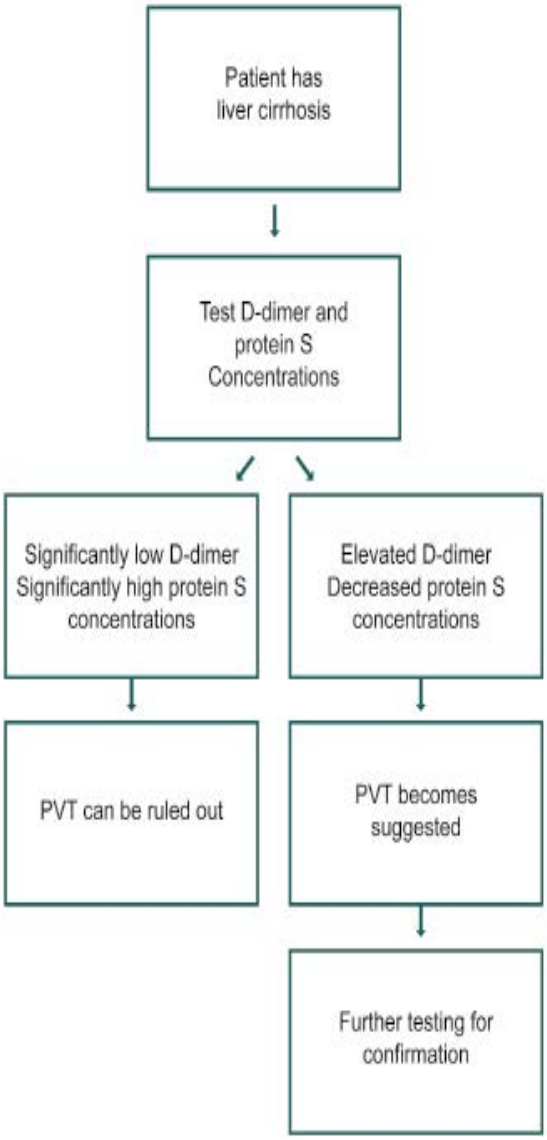


**Figure 4. This flow chart summarizes the findings of the study conducted by Zhang and colleagues.** If a patient with liver cirrhosis is suspected of having PVT, they have their D-dimer and protein S concentrations tested. If their D-dimer levels are significantly low and protein S levels significantly high, PVT can be ruled out. Elevated D-dimer levels and decreased protein S levels lead to a suspicion of PVT. Further testing is then required for confirmation.

## Discussion

Based on the results of the study, the authors determined that if a cirrhotic patient has significantly low D-dimer and significantly elevated protein S concentrations, PVT can be excluded from a potential diagnosis. However, should the patient have the combination of low protein S and high D-dimer concentrations, PVT can't be diagnosed, but it can be expected and indicate the need for further testing is indicated.

Zhang and colleagues point out that the sample population had an abnormally high rate of PVT as compared to the entire population of cirrhotic patients, but believe that this may be due to the severity of most of the cases: just over 80% were in either the B or C classification of the Child-Pugh system. The authors point out that the results and findings of this study were consistent with others previously done: deteriorating liver function is associated with increased levels of D-dimer as well as decreased levels of protein S (Zhang, Hao and Yang 2010; Zocco et al., 2009)..

### *Diagnostic value of D-dimer and protein S combined in PVT detection*

Zhang and colleagues were not able to conclude that protein S and D-dimer were conclusively diagnostic factors of PVT. However, they were able to determine that they can be used to completely rule out PVT, or to say that PVT is suspected and further testing is required (Figure 4). With Child-Pugh classes A and B (or patients low or mildly sever cases of cirrhosis), had few false negatives (high sensitivity) but too many false positives. However, though with a high amount of false positives and too few true positives, perfect sensitivity (zero false negatives) was reached with cut-off values of <0.24 mg/l of D-dimer and >25.73 mg/l protein S.

The findings in this study by Zhang and colleagues were significant enough to indicate that further testing ought to be done when D-dimer concentrations were high and protein S concentrations low. Imaging techniques such as CT scans, ultrasounds, Doppler ultrasounds, and magnetic resonance imaging (MRI) are currently used to more definitive diagnosis of PVT (Kinjo et al. 2014). The results of the study done by Zhang and colleagues showed that analyzing

D-dimer and protein S concentrations can be used to either rule out PVT or suspect presence.

Further research on this topic can be beneficial should it show that the findings by Zhang and colleagues is consistent to help avoid unnecessary testing done with imaging techniques. If looking at D-dimer and protein S can rule out PVT, then undergoing an imaging test is unnecessary. It is also helpful to know when PVT is expected based on the D-dimer and protein S concentrations. This would tell doctors that imaging techniques are required to confirm a PVT diagnosis so early treatment can begin.

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