SİROZDA SPLANKNİK ALAN TROMBOZ VE TEDAVİSİ

Dr.Birol Baysal
Memorial Ataşehir Hastanesi

3. Türkiye – Azerbaycan Ortak Hepatoloji Kursu
29-30 Eylül 2017, İstanbul

❑Tanımlama

Splanchnic Vein Thrombosis

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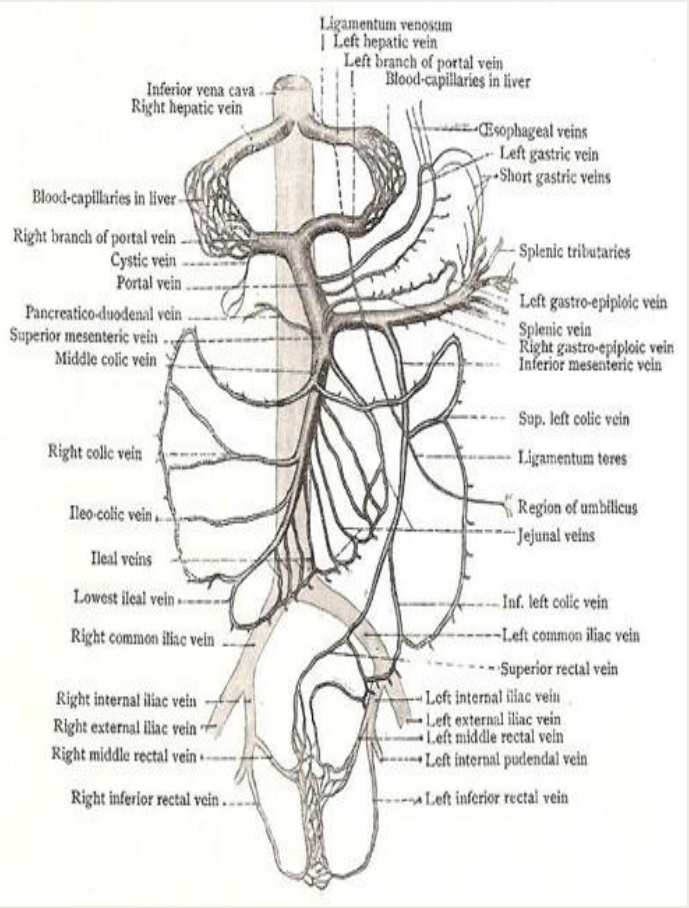
Semin Thromb Hemost 2015;41:494–502.

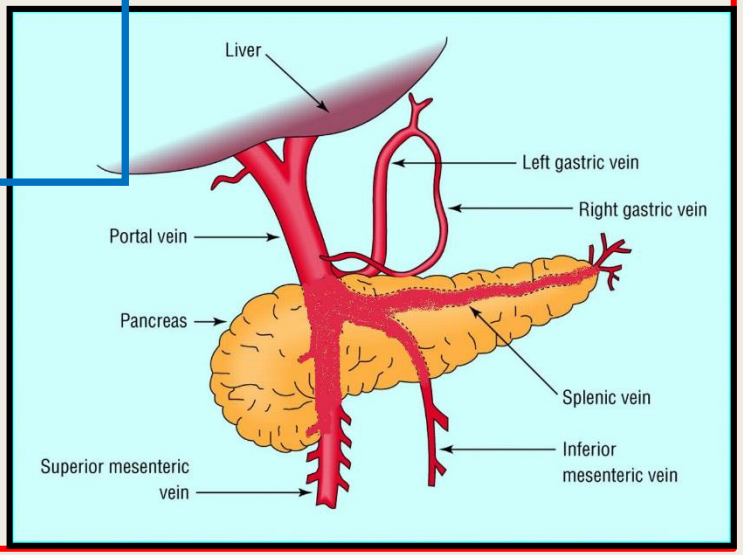
Splanchnic vein thrombosis includes thrombosis of the hepatic venous system (Budd–Chiari syndrome) and thrombosis of the portal venous system. Both conditions share uncommon prothrombotic disorders as causal factors, among which myeloproliferative neoplasms rank first. Budd–Chiari syndrome presents with acute or chronic, asymp-

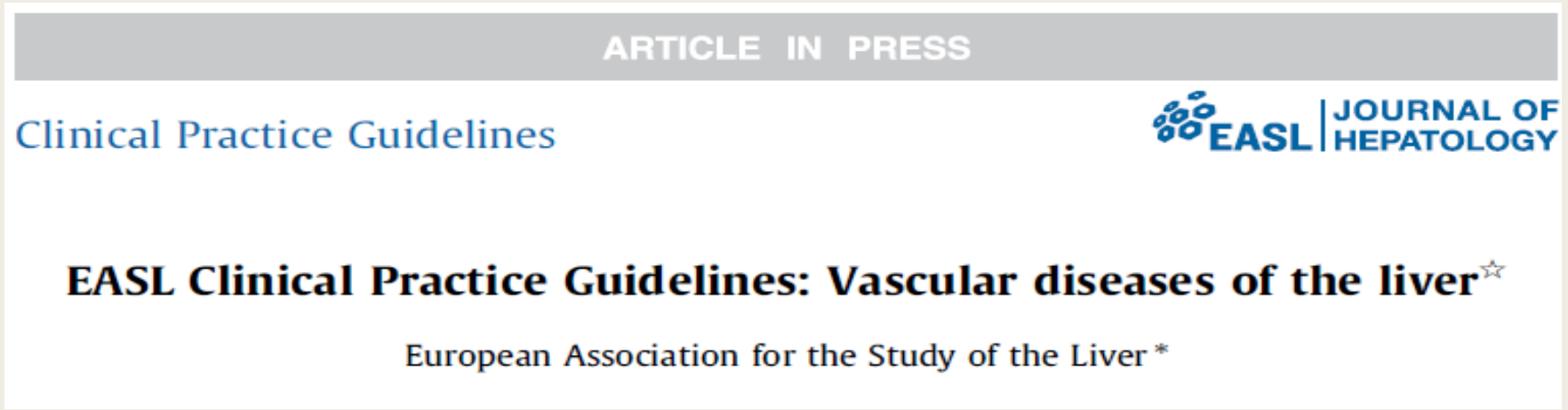
The splanchnic veins comprise the hepatic venous system (including the terminal part of inferior vena cava [IVC]) and the portal venous system (including the portal vein and its right and left branches, the mesenteric and the splenic veins). Thrombosis of the hepatic venous system is often referred to as primary Budd–Chiari syndrome (BCS). The cavernous



❑Spalanknik alan trombozu

- Hepatik venöz sistem trombozu
  - Budd-Chiari sendromu
- Portal venöz sistem
  - A. Non-sirotik portal sistem trombozu
    - a. Akut portal ven trombozu
    - b. Kronik portal ven trombozu
    - c. İzole mezenterik ven trombozu
    - d. İzole splenik ven trombozu
  - B. Sirozda portal sistem trombozu
    - a. Portal ven trombozu
    - b. PVT ± Mezenterik ven trombozu
    - c. PVT ± Splenk ven trombozu



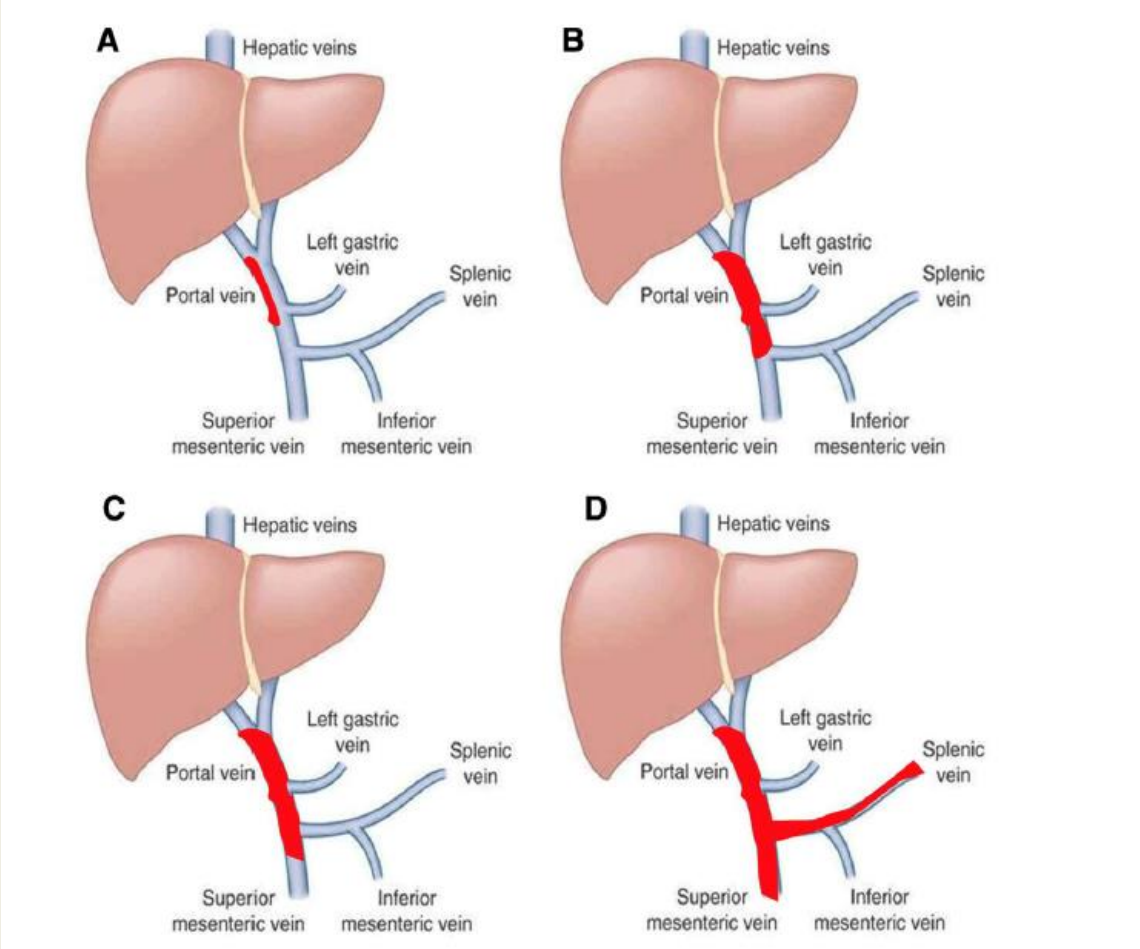


- Budd-Chiari syndrome,
- Acute portal vein thrombosis (non-cirrhotic, non-malignant)
- Extrahepatic portal vein obstruction (non-cirrhotic,non-malignant)
- Idiopathic non-cirrhotic portal hypertension
- Hepatic vascular malformations in hereditary haemorrhagic telangiectasia
- Sinusoidal obstruction syndrome – veno-occlusive disease of the liver

Journal of Hepatology 2015

- Portal vein thrombosis in cirrhosis.

❑Portal sistem trombozu



Yeni gelişen PVT

↓

Portal ven ve/veya sağ veya sol dal

↓

Porto-portal kolleteraller

↓

Portal kavernöz transformasyon

↓

Kronik PVT [2]

2-European Association for the Study of the Liver. EASL Clinical Practice Guidelines: vascular diseases of the liver. J Hepatol 2016;64:179–202.

❑PVT prevalans ve insidansı

<u>Görülme sıklığı</u>[(1)]:

- BCS
  - 1 000 000 : 1.4
- PVT
  - 100 000 : 2.5

Sirozlu hastada PVT [(2)]

— Kompanse KCS:	% 1
— Dekompanse KCS:	% 8-25

Sirozlu hastada PVT [(2)]

—US	% 5-24
—Otoposi	% 6-64
Non HCC KC TX adayı[(3)]	% 25
KCS + HCC	%35

1-Valla D. Splanchnic Vein Thrombosis. Semin Thromb Hemost. 2015 ;41:494-502.
2-Fimognari FL et al.. Portal vein thrombosis in liver cirrhosis. Intern Emerg Med. 2008 ;3:213-8
3-Chawla YK et al. Portal vein thrombosis. J Clin Exp Hepatol 2015;5:22–40.

❑PVT Risk faktörleri

- **Ana risk fakörleri-Virchow’s triad**

1. Hiperkoagülopati
2. Azalmış portal kan akım hızı
3. Vasküler endotelial lezyonlar,

❑ PVT Risk faktörleri-Hiperkoagülapati

Siroz

- ❖ **Portal sistem trombozu**
- ❖ Alt ekstremite trombozu
- ❖ Pulmoner ven trombozu

Prokoagülan faktör= Faktör V

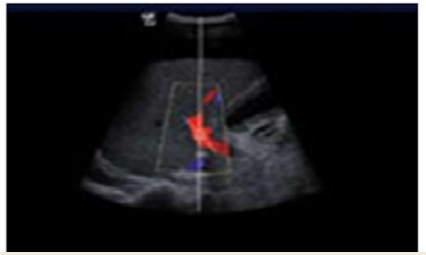
Protein C activity;
- Protein S activity;
- Antithrombin activity;
- Factor-V-Leiden gene (G1691A) mutation, APC ratio;
- Prothrombin gene (G20210A) mutation;
- Methylentetra-hydrofolate reductase C677T mutation;
- Paroxysmal nocturnal hemoglobinuria;
- Transglutaminase antibodies;
- Behcets disease clinical investigation;
- Myeloproliferative disorders:
  - JAK2 V617F mutation;
  - Calreticulin exon 9 mutation;
  - Bone marrow biopsy;
- Antiphospholipid syndrome:
  Anticardiolipin antibodies;
- Anti-beta 2GP1;
- Lupus anticoagulant.

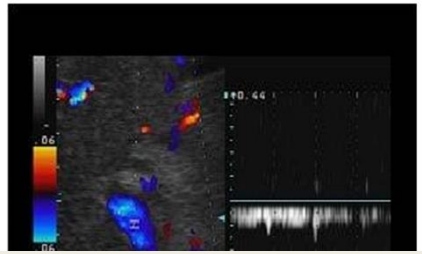
❑Risk faktörleri

- **Ana risk fakörleri-Virchow's triad**

1. Hiperkoagülopati
2. **Azalmış portal kan akım hızı**
3. Vasküler endotelial lezyonlar,
   - ❖ Von Willebrand faktör

Portal vein flow velocity	<15 cm/sec	>15 cm /sec	OR (95%CI)
PVT Incidence	47.8%	2%	44.9 (5.3 - 382.7)





M.A. Zocco et al. / Journal of Hepatology 51 (2009) 682–689

❑Risk faktörleri

4-İleri evre karaciğer hastalığı- Child B and C stage,

5-Portosistemik kolleteraller (PTH komplikasyonları)

6-HCC ve malinite, portal ven invazyonu

7-Batın içi inflamatuar olaylar (SBP, pankreatit, kolesistit apandisit, divertikülit vb

8-Endoskopik, cerrahi ve invaziv girişimler

9-Pulmoner emboli, DVT veya PVT öz geçmişi

von Köckritz L, et al.Portal vein thrombosis in patients with cirrhosis. Gastroenterol Rep (Oxf). 2017 May;5:148-156

Management of Nonneoplastic Portal Vein Thrombosis in the Setting of Liver Transplantation: A Systematic Review

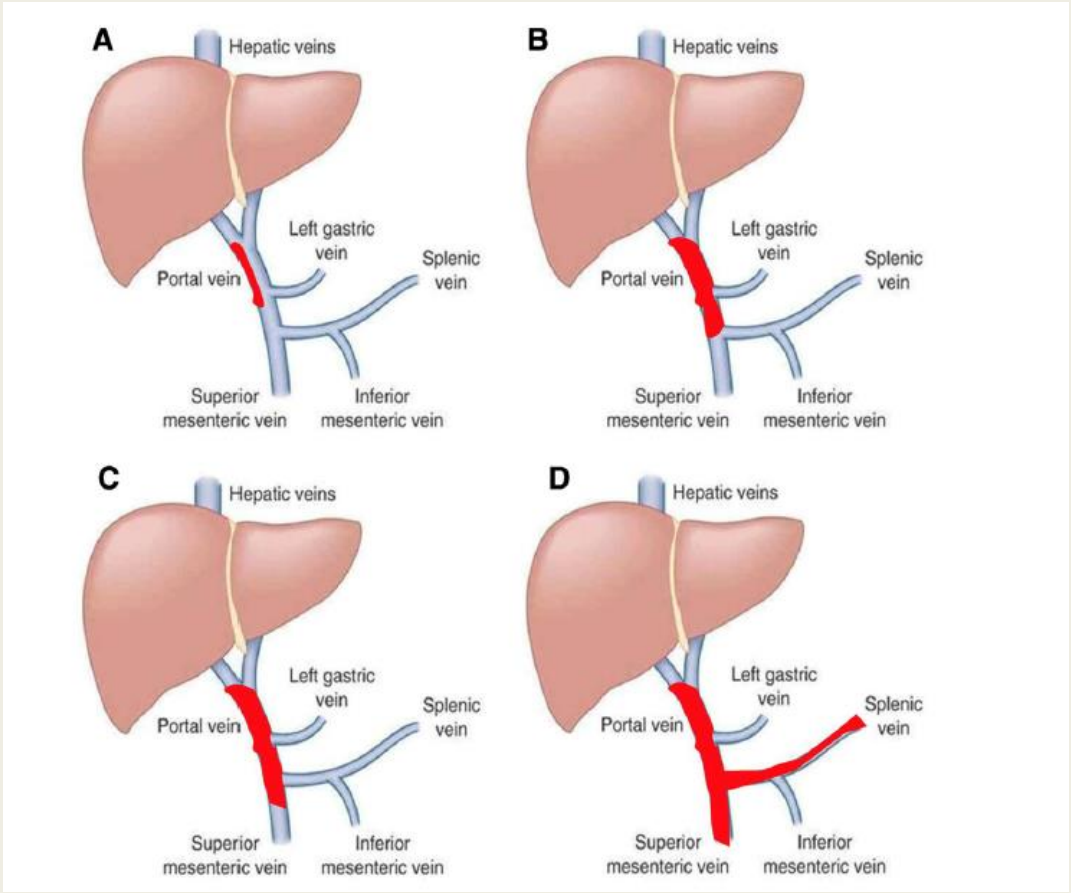
Transplantation • Volume 94, Number 11, December 15, 2012

Kryssia I. Rodríguez-Castro,[1] Robert J. Porte,[2] Elena Nadal,[3] Giacomo Germani,[2,3] Patrizia Burra,[3] and Marco Senzolo[1,4]

TABLE 1. Classifications of nonneoplastic portal vein thrombosis in patients with cirrhosis

Publication	Grade I	Grade II	Grade III	Grade IV
Stieber (*8*)	(Segmental) thrombosis of the PV trunk (partial or complete)	Thrombosis extension to SMV; patent SV (partial or complete)	Thrombosis extension to SV (partial or complete)	Diffuse, with involvement of SMV and SV, including the confluence (complete)
Nonami (*1*)	Thrombosis of intrahepatic PV branches	Thrombosis of the right or left portal branch of the PV or at the bifurcation	Partial obstruction of the portal vein trunk	Complete obstruction of the portal vein trunk
Gayowski (*9*)	Partial (mural) thrombosis of the main portal trunk extending to or below the confluence with residual flow	Complete thrombosis of the main portal trunk not extending to the confluence of the SMV and SV	Complete thrombosis of the main portal trunk extending to the level of the confluence	Complete thrombosis of the main portal trunk with extension below the confluence
Yerdel (*10*)	Minimally or partially thrombosed PV (thrombosis <50% of the vessel lumen) with or without minimal extension into the SMV	>50% occlusion of the PV, including complete thrombosis, with or without minimal extension into the SMV	Complete thrombosis of both PVT and proximal SMV; patent distal SMV	Complete thrombosis of the PV and proximal and distal SMV
Jamieson (*11*)	Thrombosis confined to the PV beyond the splenomesenteric confluence (partial or complete)	Thrombosis extending into the proximal SMV but with a patent vessel in the mesentery	Diffuse thrombosis of the splanchnic venous system but with large accessible collaterals	Extensive thrombosis of the splanchnic venous system but with only fine collaterals
Charco (*12*)	Thrombosis confined to the PV (partial or complete)	Thrombosis that extends all the way to the proximal portion of the SMV with permeability of the mesenteric confluence	Diffuse thrombosis of the splanchnic system with presence of dilated collateral veins	Diffuse thrombosis with presence of fine collateral veins
*Bauer (*13*)	Occlusion <25% (PVT, SV, or SMV)	Occlusion 26%–50% (PVT, SV, or SMV)	Occlusion 51%–75% (PVT, SV, or SMV)	Occlusion >76% (PVT, SV, or SMV)

*Refers to percentage of occlusion of the vessel (a grade is assigned to each vessel, according to the degree of occlusion).
PV, portal vein; PVT, portal vein thrombosis; SMV, superior mesenteric vein; SV, splenic vein.



Liver transplantation 22:352–365, 2016

Table 1. New classification of portal vein thrombosis

Site of portal vein thrombosis
Type 1: Trunk only
Type 2: Branch only; 2a, one branch; 2b, both branches
Type 3: Trunk and branches
Degree of portal venous system occlusion
O: Occlusive: no flow visible in portal vein lumen on imaging/ Doppler study
NO: Non-occlusive: flow visible in portal vein lumen through imaging/Doppler study
Duration and presentation
R: Recent (first time detected in previously patent portal vein, presence of hyperdense thrombus on imaging, absent or limited collateral circulation, dilated portal vein at the site of occlusion)
Ch: Chronic (no hyperdense thrombus; previously diagnosed PVT on follow-up, portal cavernoma and clinical features of portal hypertension)
As: Asymptomatic
S: Symptomatic: features of acute PVT (with or without acute bowel ischemia) or features of portal hypertension
Extent of portal vein system occlusion
S: Splenic vein
M: Mesenteric vein
SM: Both
Type and presence of underlying liver disease
Cirrhotic, non-cirrhotic liver disease, post-liver transplant, hepatocellular carcinoma, local malignancies and associated conditions

Sarin SK et al.Toward a comprehensive new classification of portal vein thrombosis in patients with cirrhosis. Gastroenterology 2016;151:574–7

❑Klinik

- ❑ Asemptomatik: Takip USG da tespit edilen
- ❑ Dekompansasyon bulgularının gelişmesi nedeni ile yapılan değerlendirmelerde

  Özofagus varis kanaması.: Tekrarlayan ve endoskopik olarak kontrolde güçlük

  Yeni asit gelişimi vb
- ❑ PVT un süperior mezenterik vene ilerlemesi.(1)

  Mezenter iskemi bulgusu – karın ağrısı
- ❑ Post TX klinik durumunda kötüleşme(2)

Amitrano L, et al. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. J Hepatol. 2004 May;40(5):736-41. PubMed PMID: 15094219.

Rodriguez-Castro KI, et al.Management of nonneoplastic portal vein thrombosis in the setting of liver transplantation: a systematic review. Transplantation 2012;94: 1145–1153.

❑SMV tutulumu/iskemi

- Akut PVT yayılımı
- Mortalite %60,

- Hızlı/doğru tanı ve yeterli tedavi
- Karın ağrısı-nonspesifik
- Devamlılık gösteren karın ağrısı
- İleus
- Rektal kanama
- Asit
- Organ yetersizliği

Laktik asidoz
CRP
Lökositoz

Akut batın tablosu

Cerrahi, barsak rezeksiyonu

European Association for the Study of the Liver. EASL Clinical Practice Guidelines: vascular diseases of the liver. J Hepatol 2016;64:179–202.

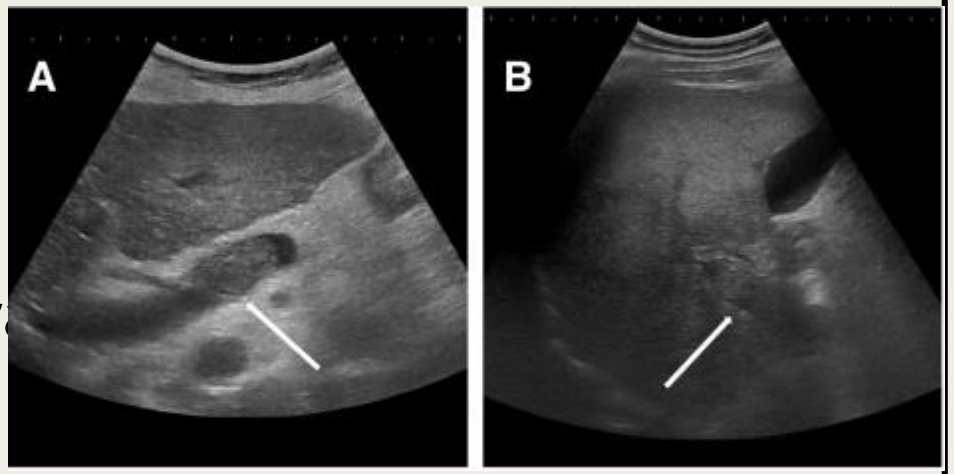
❑Portal ven trombozunda tanı

- **USG** *Asmptomatik hastalarda rutin takip USG*

  Dekompansasyon bulgusu olan hastalarda değerlendirme USG

- **Doppler USG:** Komplet PVT sensitivite %90

  Parsiyel PVT sensitivite %50[1]



  - ❖ Solid izoekoik veya hiperekoik matery
  - ❖ Portal kan akımının azalması/yokluğu
  - ❖ Parsiyel ve total tıkanıklık
  - ❖ Portal kavernom
  - ❖ CEUS[2]

1-Rodriguez-Castro KI, et al. Management of nonneoplastic portal vein thrombosis in the setting of liver transplantation: a systematic review. Transplantation 2012;94:1145–1153.

2-Rossi S et al. Contrast-enhanced versus conventional and color Doppler sonography for the detection of thrombosis of the portal and hepatic venous systems. AJRAm J Roentgenol 2006;186:763-73.

❑Portal ven trombozunda tanı

Kontrastlı CT veya MRI-Portal venöz faz

- ❑ **Tanı**
- ❑ **Trombozun portal sistem yayılımı(1)**
  - Mezenterik ve splenik vene
  - İntrahepatik portal ven dallarına

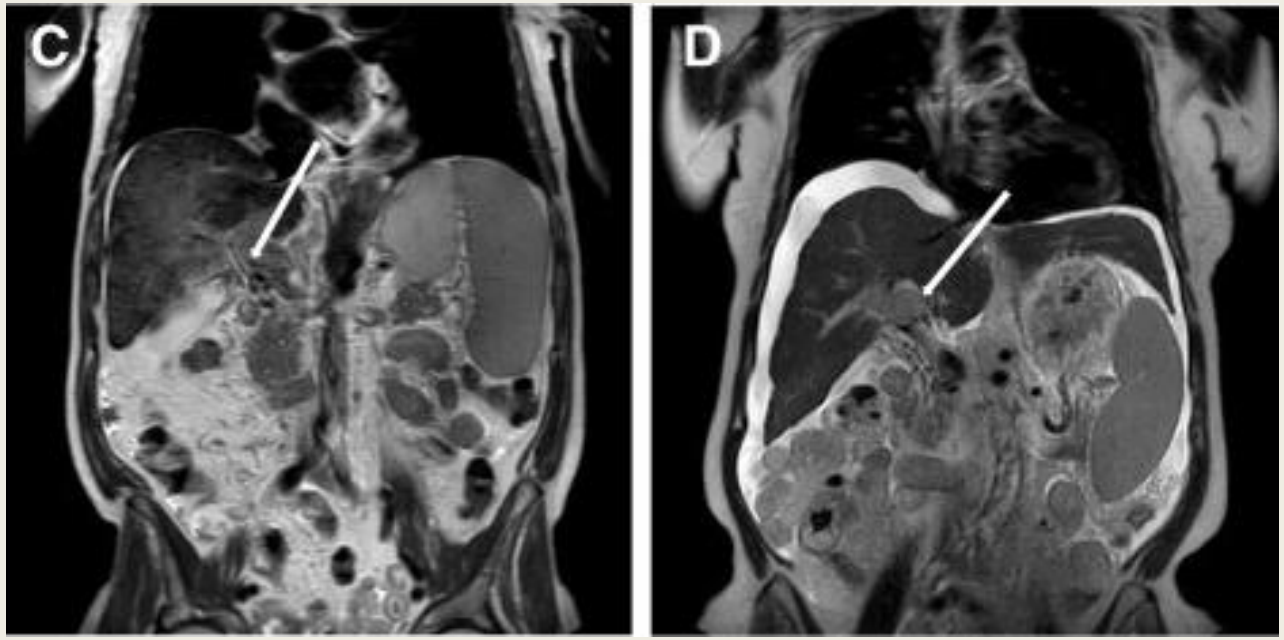
  Mezenter infark ve iskemi
- ❑ **HCC ve malinite tanısı**
- ❑ **Malign tromboz tanıs(2)**

  Portal ven invazyonu

  Portal ven çap artışı>23 mm

  İntratrombotik arteriyal neovaskülarizasyon

  Arteryal fazda trombozun kontrast tutması



1-DeLeve LD ET AL; American Association for the Study Liver Diseases. Vascular disorders of the liver. Hepatol Baltim Md 2009;49:1729–64.-

2-Tublin ME, et al. Benign and malignant portal vein thrombosis: differentiation by CT characteristics. AJR Am J Roentgenol 1997;168:719–723

❑PVT Tedavi

- ❑ *Lokalizasyonu*
- ❑ *Yaygınlık derecesi*
- ❑ *Gelişme hızı (Akut/Kronik)*
- ❑ *Risk faktörler*
- ❑ *KC hastalığın evresi*

Tedavi planı oluşturulmalıdır

❑Portal ven trombozunda tedavi

- **Antikoagülan tedavi**
  - *1-Heparin (UFH)*
  - *2-LMWH [Enoksaparin (®Clexane), Nadroparin (®Fraxiparin) vb]*
  - *3-Fondaparinux*
  - *4-VKA,coumadine*
  - *5-Direct oral antikcoagulants (DOAC)*
- **Girişimsel teknikler**
  - *TIPS*
  - *Trombolitik tedavi*
- **Cerrahi**

❑Heparin ve heparin türevleri

- **Heparin**

Antitrombin III tarafından faktör II a, IXa, Xa Xıa , XIIa, XIIIa inhibe edilmesini potansiyalize eder.

- **LMWH [Enoksaparin** (®Clexane), N**adroparin** (®Fraxiparin) vb]

Antitombin III tarafından faktör XIIa, Xa ve kallikrein'in inhibe edilmesini potansiyalize eder. Fakat IXa ve XIa nın inhibe edilmesini değiştirmez.

- **Fondaparinux**
- **Antitrombin III tarafından faktör Xa inhibe edilmesini** potansiyalize eder.

❑ Karaciğer hastalarında heparin kullanımı/güvenirliği

❑ Sirozda, ileri karaciğer hastalıklarında antitrombin sentezi azalır. Etkilimi ?

Sirozlu hastalarda antitrombin düşük olmasına karşın LMWH antikoagülasyon etkinliği daha duyarlıdır

Senzolo M et al Increased anticoagulant response to low-molecular-weight heparin in plasma from patients with advanced cirrhosis. J Thromb Haemost 2012:1823–1829.

❑ Sirotik hastalarda LMWH güvenli mi ?

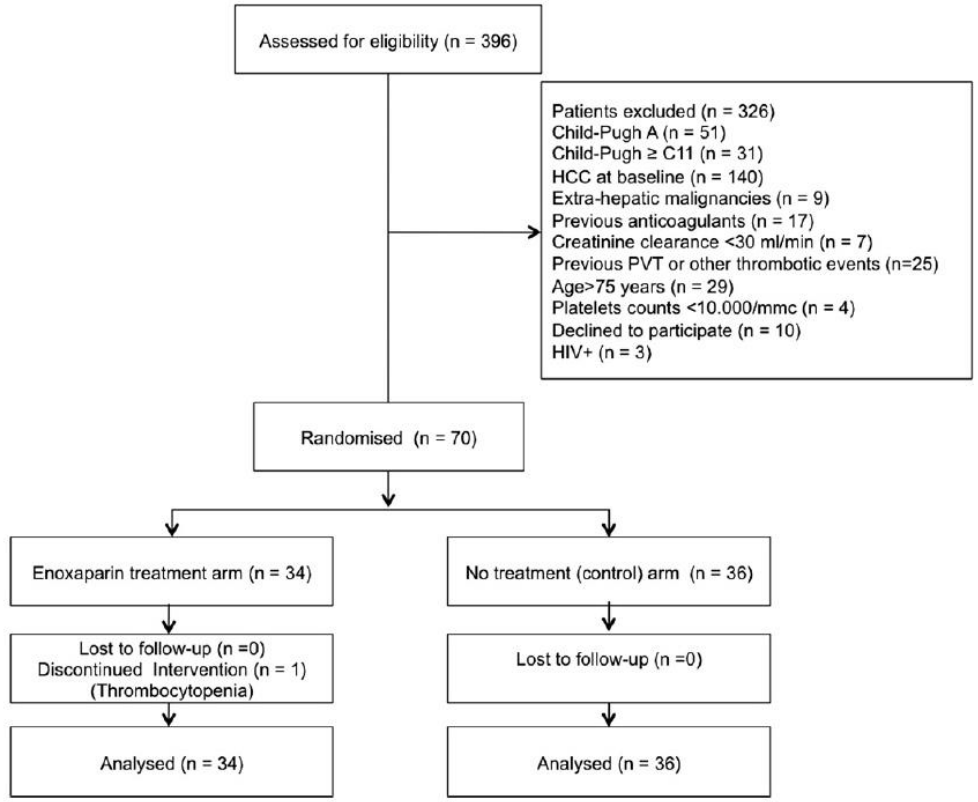
Sabit profilaktik dozda (4000 IU / gün SC) kullanıldığında ve laboratuvar gözlemi olmaksızın LMWH'nin PVT'li hastalarda etkili ve güvenilir olduğunu göstermiştir

Villa E et al.Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology 2012;143:1253–1260.

❑Karaciğer hastalarında heparin kullınımı/güvenirliği

Enoxaparin Prevents Portal Vein Thrombosis and Liver Decompensation in Patients With Advanced Cirrhosis

ERICA VILLA,* CALOGERO CAMMÀ,‡ MARCO MARIETTA,§ MONICA LUONGO,* ROSINA CRITELLI,* STEFANO COLOPI,‖ CRISTINA TATA,‖ RAMONA ZECCHINI,* STEFANO GITTO,* SALVATORE PETTA,‡ BARBARA LEI,* VERONICA BERNABUCCI,* RANKA VUKOTIC,* NICOLA DE MARIA,* FILIPPO SCHEPIS,* AIMILIA KARAMPATOU,* CRISTIAN CAPORALI,‖ LUISA SIMONI,¶ MARIAGRAZIA DEL BUONO,* BEATRICE ZAMBOTTO,* ELENA TUROLA,* GIOVANNI FORNACIARI,# SUSANNA SCHIANCHI,# ANNA FERRARI,* and DOMINIQUE VALLA**,‡‡,§§



RCT

4000 IU/ gün Enoxaprin, 48 hafta

Child Pugh B siroz + Non HCC

PVT oluşumu engellemiş, 0 vs 6

Dekompansasyon gelişme oranı azalmış, %11,7 vs %59,4

Mortalite %20 azalmış 8 vs 13

Kanama komplikasyonunda artış olmamış

❑ Karaciğer hastalarında heparin kullınımı/güvenirliği

Eur J Gastroenterol Hepatol. 2015 Aug;27(8):914-9. doi: 10.1097/MEG.0000000000000351.

Efficacy and safety of anticoagulation therapy with different doses of enoxaparin for portal vein thrombosis in cirrhotic patients with hepatitis B.

Cui SB[1], Shu RH, Yan SP, Wu H, Chen Y, Wang L, Zhu Q.

RESULTS: Of the 65 patients, 51 patients (78.5%) achieved complete/partial recanalization of PVT after 6 months of anticoagulation therapy. Child-Pugh scores were lower in the 51 patients who achieved complete/partial recanalization than those of the 14 nonresponders (P<0.01). No patients showed variceal bleeding during anticoagulation therapy in the two groups. The rates of nonvariceal bleeding with the use of 1.5 mg/kg every 24 h (23.5%) were higher than those with the use of 1 mg/kg every 12 h (6.4%).

CONCLUSION: Anticoagulation therapy with different doses of enoxaparin for PVT in hepatitis B patients with cirrhosis is efficient and safe, and 1 mg/kg enoxaparin subcutaneously every 12 h is a better anticoagulation regimen in the treatment of PVT in cirrhotic patients.

1 mg (0.01 ml) enoksaparin sodyum=100 anti-Xa IU.

Clexane 4000 anti-Xa IU= 40 mg enoksaparin sodyum
Clexane 6000 anti-Xa IU= 60 mg enoksaparin sodyum
Clexane 8000 anti-Xa IU= 80 mg enoksaparin sodyum

❑ Vitamin K antigonistleri[Warfarin (Coumadine)]

- **VKA**

K vitamini bağımlı koagülasyon faktörlerinin (II a, VIIa, Xıa, Xa) karboksilasyonuna inhbe ederek etki gösterir

- Sirozda protrombin zamanı sıklıkla uzamıştır.
- Sirozda terapötik aralığa ulaşılmak için daha küçük VKA dozları gerekir
- Siroz hastaların da INR 2-3 aralığına ulaşması için gerekli dozu tanımlayan çalışma yoktur
- Sirozda INR kullanımı tartışmalıdır
- Modifiye edilmiş INR (INR-Liver) ???

Tripodi A et al. The international normalized ratio to prioritize patients for liver transplantation: problems and possible solutions. J Thromb Haemost 2008;6:243–248.

❑Direct oral anticoagulants (DOAC)

- ❑ **Dabigatran** ⟹ Trombin inhibe eder
- ❑ **Rivaroksaban** ⟹ Faktör Xa
- ❑ **Apixaban** ⟹ Faktör Xa

❖ Sirozlu hastalar kasıtlı olarak faz III çalışmalarından çıkarılmıştır

❖ Rivaroksaban tedavisinin şiddetli semptomatik karaciğer hasarı ile ilişkili olabile

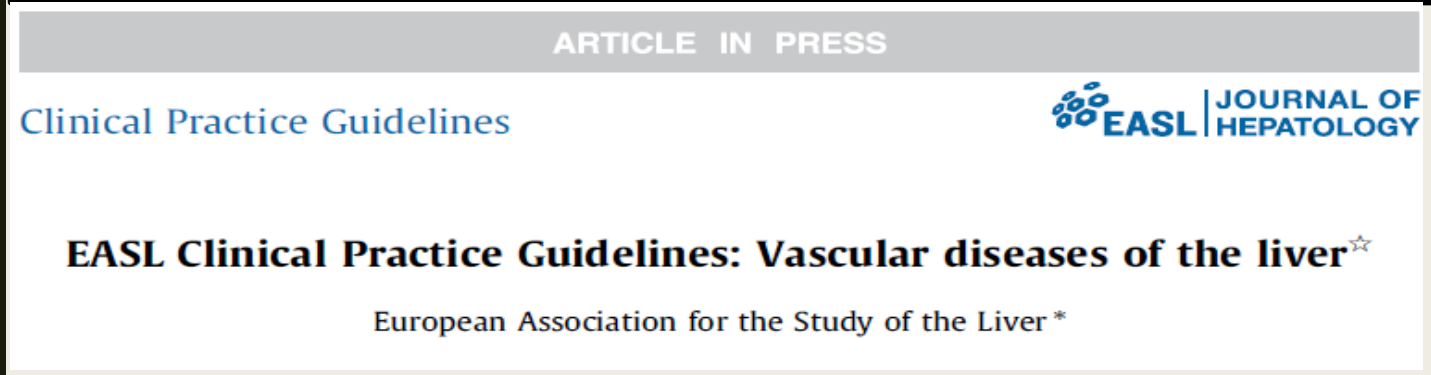
Liakoni E et al.Symptomatic hepatocellular liver injury with hyperbilirubinemia in two patients treated with rivaroxaban. JAMA Intern Med 2014;174:1683–1686.

❖ 2016 da gelen ilk yayınlar sirotik hastalarda güvenli

De Gottardi A et al. Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis. Liver Int 2016; 25

Intagliata NM ert al. Direct oral anticoagulants in cirrhosis patients pose similar risks of bleeding when compared to traditional anticoagulation. Dig Dis Sci 2016;61:1721–7.

❑Sirozda PVT tedavisinde antikoagülan etkinliğini değerlendirme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Clinical Practice Guidelines

EASL | JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Vascular diseases of the liver☆

European Association for the Study of the Liver*

5 cohort

163 hasta

çoğu parsiyel PVT

Antikoagülan (LMWH veya VKA)

- ❑ 6 ay tedavi → Tromboz kaybolması % 55-75
- ❑ Tedaviye başlama süresi 6 aydan kısa
- ❑ Retromboz olasılığı %38
- ❑ Total kanama komplikasyonu 9/163 (5%)
  - ➢ Hastaların 3 de PTH ile korole
- ❑ Trombosit sayısı 50.000 ↓ olması kanama risk faktörü

Journal of Hepatology 2015

❑Portal ven trombozunda tedavi

TIPS

- Portal basıncı ⇓ Portal kan akımı ⇑
- Başarılı TIPS uygulmasında rekanalizasyon %80
- Portal kavernom varlığında başarı düşüktür.
- Başarı oranı antikoagülan tedaviye eşittir
- Antikoagülan tedaviye kontraendikasyon varlığında
- Antikoagülan tedavi ile yeterli yanıt alınamayan, progresyon ve yayılma gösteren tromboz varlığında

Luca A et al. Short- and long-term effects of the transjugular intrahepatic portosystemic shunt on portal vein thrombosis in patients with cirrhosis. Gut 2011;60:846–52.

❑Portal ven trombozunda tedavi

- Cerrahi-Portal-caval şant

- TIPS ile kontrol altına alınamayan
  - *Mesenter iskemi*
  - *Refrakter varis kanaması*

- KC fonksiyonları korumuş hastalarda
  - *Child-Pugh A*
  - *Kompanse Child-Pugh B*

❑Sonuç

- Karaciğer sirozunda PVT tedavi konusu önemini korumaya devam ediyor
- Konun netleşmesi için randomize kontrollü çalışmalara ihtiyaç vardır. Bu sonuçlar ulaşana kadar her ünite kendi tedavi algoritmasının oluşturması daha doğru olacaktır