16 Gennaio 2015
2\textsuperscript{nd} Workshop
\textbf{TIPS:}
\textit{Esperienze a Confronto}

\textbf{Caso clinico interattivo}
\textbf{Trombosi portale}
\textit{Maria Grazia Lucà}
Gastroenterologia ed Epatologia dei Trapianti HPGXXIII
PVT (Portal Vein Thrombosis)
EHPV (ExtraHepatic Portal Vein Obstruction)

RACCOMANDAZIONI LINEE GUIDA AASLD 2009

RACCOMANDAZIONI AISF 2010

Revisione letteratura 2011-2014
PVT (Portal Vein Thrombosis)  
EHPV (ExtraHepatic Portal Vein Obstruction)  

- ostruzione del tronco portale principale +/- rami portali intraepatici principali e segmentali +/- 
  vene splenica e/o mesenterica superiore e inferiore  
- trombosi acuta e trombosi cronica  
- **Cavernoma portale**: rete di collaterali porto-portali a flusso epatopeto, conseguenti 
  all’ostruzione del tronco portale.  

E’ condizionata da:  

**Patologia di base**: presenza/assenza di cirrosi /neoplasia  
**Acuzie**:  
  - **trombosi acuta** → ischemia  
  - **trombosi cronica** → cavernoma → ipertensione portale 
    e biliopatia portale  
**Estensione** → arcate venose mesenteriche → infarto intestinale → mortalità 20-50%  
**Meccanismi compensatori** → varici esofagee
Clinical presentation

- **Recent** EHPVO: can be assumed when patients present with symptoms such as abdominal pain, ascites, or fever in the absence of portal cavernoma and porto-systemic collaterals. Patients also can be asymptomatic (5;D).

**PVT in cirrhosis** further increase in portal hypertension, with increased risk of complications, decreased liver perfusion, and worsening of liver function

- **Chronic** EHPVO: is associated with portal cavernoma.
**Thrombosis and hemorrhage in the critically ill cirrhotic patients: five years retrospective prevalence study**

*Mucino-Bermejo J et al*  
*Ann Hepatol - 2015*

A five years retrospective study including every cirrhotic patient admitted to ICU between January 2007 and December 2012. ... The incidence of hemorrhage was 48.5%, the overall incidence of thrombotic complications was 13.66%. Variceal bleeding was the most prevalent hemorrhagic event and portal vein thrombosis the most common thrombotic event.

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**Vascular disorders of the liver: Recommendations from the Italian Association for the Study of the Liver (AISF) ad hoc committee**

*Marco Senzolo, Oliviero Riggio, Massimo Primignani*  
*Digestive and Liver Disease - 2010*

EHPVO is an important complication of liver cirrhosis. Its reported incidence in compensated disease is between 0.6% and 5%, but becomes much higher (up to 25%) in advanced disease.
1. Consider a diagnosis of acute PVT in any patient with abdominal pain of more than 24 hours duration, whether or not there is also fever or ileus.

2. If acute PVT is suspected, CT scan, before and after injection of vascular contrast agent, should be obtained for early confirmation of diagnosis. If CT scan is not rapidly available, obtain Doppler-sonography.

3. In patients with acute PVT and high fever and chills, septic pylephlebitis should be considered, whether or not an abdominal source of infection has been identified, and blood cultures should be routinely obtained (Bacteroides).

4. In acute PVT, the possibility of intestinal infarction should be considered from presentation until resolution of pain. The presence of ascites, thinning of the intestinal wall, lack of mucosal enhancement of the thickened intestinal wall, or the development of multiorgan failure indicate that intestinal infarction is likely and surgical exploration should be considered.
Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: Results of a longitudinal study
Nery F et Al

Hepatology - 2014

1,243 adults with cirrhosis without PVT
Progression of liver disease defined by the development of: ascites, hepatic encephalopathy, variceal bleeding, prothrombin <45%, serum bilirubin >45 µmol/L, albumin <28 g/L, and/or creatinine >115 µmol/L.

5-year cumulative incidence of PVT 10.7%. PVT was mostly partial and varied over time. The development of PVT **independently associated** with baseline esophageal varices (P?=?0.01) and prothrombin time (P?=?0.002), but not with disease progression before PVT, or prothrombotic mutations.

Disease progression **independently associated** with baseline age (hazard ratio 1.55; 95% confidence interval 1.11-2.17), body mass index (HR 1.40; 95% CI: 1.01-1.95), prothrombin time (HR 0.79; 95% CI: 0.70-0.90), serum albumin (HR 0.97; 95% CI: 0.94-0.99), and esophageal varices (HR 1.70; 95% CI: 1.21-2.38) but not with the prior development of PVT (HR 1.32; 95% CI: 0.68-2.65).

<table>
<thead>
<tr>
<th>Models</th>
<th>Univariate Models</th>
<th>Multivariate Models Adjusted for the Baseline Prognostic Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver disease progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Partial PVT</td>
<td>1.58</td>
<td>1.51</td>
</tr>
<tr>
<td>- Partial or Complete PVT</td>
<td>1.48</td>
<td>1.32</td>
</tr>
<tr>
<td>Decompensation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Partial PVT</td>
<td>1.77</td>
<td>1.60</td>
</tr>
<tr>
<td>- Partial or Complete PVT</td>
<td>1.61</td>
<td>1.37</td>
</tr>
</tbody>
</table>

In patients with cirrhosis, the development of PVT is associated with the severity of liver disease at baseline, but does not follow a recent progression of liver disease. There is no evidence that the development of PVT is responsible for further progression of liver disease.
OBIETTIVI DELLA TERAPIA

- Prevenire estensione del trombo e consentire ricanalizzazione (parziale fino a 90% dei casi e totale fino al 40%) per prevenire infarto intestinale ed ipertensione portale
- Beneficio documentato anche nei cirrotici, almeno in Classe A e B di Child (ricanalizzazione parziale fino al 30% e completa 20% - sanguinamento 9%), a differenza delle PVT cronica

_Plessier, Hepatology 2010_
_Delgado, Clin Gastroenterol Hepatol 2012_

RACCOMANDAZIONI AASLD PER LA TERAPIA

Eparina a basso peso molecolare fino a
- Stabilizzazione clinica
- Necessità di procedure invasive

TAO previa EGDS e profilassi del sanguinamento g-i

Fattori di rischio trombotico reversibili?

SI
- TAO per almeno 3 (6) mesi

NO
- TAO a vita

Considera TAO long-term nei pazienti con estensione della trombosi alla vena mesenterica
Se evidenza di infezione inizia la terapia antibiotica
FATTORI DI RISCHIO SISTEMICI PER TVP
PERCENTUALI MEDIE RIPORTATE IN LETTERATURA DAL 1997 AL 2006 – AASLD 2009

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>PVT Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloproliferative disorders</td>
<td>30%-40%</td>
</tr>
<tr>
<td>Atypical</td>
<td>14%</td>
</tr>
<tr>
<td>Classical</td>
<td>17%</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>6%-19%</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>0%-2%</td>
</tr>
<tr>
<td>Behçet's disease</td>
<td>0%-31%</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td>6%-32%</td>
</tr>
<tr>
<td>Factor II mutation</td>
<td>14%-40%</td>
</tr>
<tr>
<td>Protein C deficiency*</td>
<td>0%-26%</td>
</tr>
<tr>
<td>Protein S deficiency*</td>
<td>2%-30%</td>
</tr>
<tr>
<td>Antithrombin deficiency*</td>
<td>0%-26%</td>
</tr>
<tr>
<td>Plasminogen deficiency*</td>
<td>0%-6%</td>
</tr>
<tr>
<td>Recent pregnancy</td>
<td>6%-40%</td>
</tr>
<tr>
<td>Recent oral contraceptive use</td>
<td>12%</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>12%-22%</td>
</tr>
<tr>
<td>TT877 MTHFR genotype</td>
<td>11%-50%</td>
</tr>
</tbody>
</table>

Un genotipo trombofilico (soprattutto POLIMORFISMO – mutaz 20210 - DEL GENE PER LA PROTROMBINA) è stato riportato in quasi il 70% dei cirrotici con PVT

Amitrano I, Hepatology 2010

Myeloproliferative neoplasms (MPNs) are the most common cause of nonmalignant, noncirrhotic portal vein thrombosis. Mean prevalence of MPNs 31.5% and JAK2V617F 27.7%

JAK2V617F screening in splanchnic vein thrombosis (SVT) patients without typical hematologic MPN features identified MPN in 15.4% of screened PVT patients. Results validate routine inclusion of JAK2V617F in the diagnostic workup of SVT patients.

Smalberg JH, Blood 2012

Thrombophilic factor analysis ... case-control study, investigated the frequency of Janus kinase 2 (JAK2) (JAK2 V617F), Factor V Leiden (FVL G1691A), and Prothrombin (G20210A) mutations in cirrhotic patients with PVT ...

... evidence that a relevant proportion of cirrhotic patients with PVT harbours a JAK2 V617F mutation.

Saugel B, J thromb thrombolysis 2014

antithrombin, protein C and protein S concentrations not associated with the pathogenesis of PVT in liver cirrhosis

Anticoagulation
The aim of anticoagulant treatment is to promote portal vein repermeation and prevent extension of thrombosis to the SMV to avoid intestinal infarction.

In acute EHPVO the early use of anticoagulation leads to repermeation and prevents the development of portal hypertension in more than 40% of cases should be considered also in extensive thrombosis if recent (<6 months), since at least partial portal vein repermeation might be achieved and further progression avoided.

In acute forms should be performed with heparin, followed by warfarin when invasive procedures are no longer needed, targeting the INR at a 2–3 range. Low molecular weight heparins (LMWH) are currently preferred ... Anti-Xa levels should be monitored in severely obese or pregnant patients and in presence of renal insufficiency.

Follow-up of patients can be performed with doppler ultrasound at 1, 3 and every 6 months.
Anticoagulation

Repermeation of the portal vein has never been shown to occur after the first 6 month of treatment.

Anticoagulation should be carried out for at least 6 months. However, long term anticoagulation is currently recommended, irrespectively of the achievement of portal vein repermeation, in the presence of thrombophilia, or a personal or familial history of thrombosis or in the case of intestinal ischemia to prevent the risk of further progression.

Negative predictive factors for repermeation are a long time elapsed between EHPVO onset and the start of anticoagulation treatment, ascites at baseline, whether clinically detectable or at imaging, and co-existence of splenic vein thrombosis.

In chronic EHPVO, the use of anticoagulation is controversial, given the risk of portal hypertension-related bleeding. However, provided that prophylactic measures to prevent bleeding are adopted (i.e. beta-blockers and/or banding ligation) and effective, these patients may be treated with anticoagulants, particularly in the case of a persistent prothrombotic condition carrying the risk of thrombosis recurrence or progression.
Cirrhosis = general prothrombotic condition
• TAO can prevent PVT and decompensation of cirrhosis
• In non-cirrhotic hepatic vein or portal vein thrombosis the benefit-to-risk ratio of TAO favorable
• TAO for PVT in cirrhosis ➔ recanalization achieved in 40% while bleeding in less than 10%, exceptionally fatal. Partial thrombosis and prolonged TAO predicts for recanalization
• Monitoring TAO in cirrhosis is a challenge

AASLD guidelines neither recommend nor negate TAO for PVT in cirrhosis
• No RCT
• Natural history of asymptomatic PVT in cirrhosis not well defined
• Monitoring TAO difficult in cirrhosis
• Risk of bleeding from varices requires preventative therapy
• Age of the thrombus difficult to gauge and TAO may not result in repermeation
• The risk of not using TAO in PVT in cirrhosis needs to be better defined to recommend routine anticoagulation
• Evidenza epidemiologica di aumentato rischio di trombosi venose profonde non splancniche nei cirrotici

• La cirrosi è il maggior fattore di rischio di PVT e questo rischio correla con la severità delle cirrosi

• La riduzione del flusso portale probabilmente gioca un ruolo indipendente

• Potrebbero essere coinvolte mutazioni (Fatt di Leiden, JAK2, ...) protrombotiche

• L’ipertensione portale è il fattore che correla con l’aumentato rischio di sanguinamento nel cirrotico

• [...] I PAZIENTE CIRROTICI CON ALTERAZIONE DI INR E PLT NON SONO DA CONSIDERARE ‘SPONTANEAMENTE ANTICOAGULATI’, MA PIUTTOSTO ‘IN STATO PRETROMBOTICO’ (‘rebalanced’ hemostatic system)

• Non ancora stabilito se la PVT ha un ruolo causale nella progressione della cirrosi o è un mero indicatore di una malattia avanzata
Un trial randomizzato controllato (Villa E et Al, Gastroenterology 2012) ha dimostrato che nei pazienti con cirrosi in classe funzionale B7-C10 di Child-Pugh la somministrazione di Enoxaparina 4000 U/die per 48 sett previene lo sviluppo di PVT e lo scompenso della cirrosi e riduce la mortalità.

La anticoagulazione con LMWH e/o VKA è stata associata con ricanalizzazione in circa il 50% dei casi.

Non è ancora noto l'impatto di tale ricanalizzazione sulla cirrosi.

NON E’ ANCORA DEFINITA LA MIGLIOR TERAPIA ANTICOAGULANTE E IL MIGLIOR MODO DI MONITORARLA.
nella cirrosi vi è un equilibrio poco stabile tra fattori pro-emostatici ed anti-emostatici (‘rebalanced’ hemostatic system)

- la tromboprofilassi deve essere fatta; non sono protetti da trombosi arteriose (soprattutto in NAFLD)

- la terapia anticoagulante per la TVP è efficace e, probabilmente, lo è la profilassi

- la scelta ottimale di farmaci e dosaggi non è ancora definita

**PVT:**

- **prevenzione: dati insufficienti per raccomandarla**

- trattamento di scelta con LMWH (con dosi ridotte in pz con cirrosi end-stage e aumentati fattori di rischio per emorragia come insufficienza renale e trombocitopenia severa).

- La TAO con antagonisti della Vit K non può essere incoraggiata non solo per elevato rischio di sanguinamento, ma anche per la mancanza di un target definito di INR

*Lisman T, J Hepatology 2013*
Antithrombotic drugs that are registered for clinical use and recommended for prevention or treatment of venous or arterial events in the most current guidelines.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>(Potential) indications</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Cyclooxygenase inhibitor</td>
<td>Treatment/prevention arterial thrombosis</td>
<td>Cost, experience and proven efficacy in general population, limited data suggests safety in cirrhosis</td>
<td>Aspirin resistance difficult to detect, GI bleeding risk</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Reversible P2Y12 inhibitor</td>
<td>Secondary prevention arterial thrombosis</td>
<td>No change in pharmacokinetics in Child-Pugh A and B cirrhosis</td>
<td>Variable response to treatment due to genetics and drug-interaction, bleeding risk</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Reversible P2Y12 inhibitor</td>
<td>Secondary prevention arterial thrombosis</td>
<td>More consistent inhibition of platelet function compared to clopidogrel</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Irreversible P2Y12 inhibitor</td>
<td>Secondary prevention arterial thrombosis</td>
<td>Does not require metabolic activation by the liver</td>
<td>Bleeding risk</td>
</tr>
<tr>
<td>Extended release-dipyridamole</td>
<td>Adenosine uptake inhibitor and phosphodiesterase inhibitor</td>
<td>Treatment/prevention ischemic stroke</td>
<td>Beneficial effects on portal circulation</td>
<td>Affects renal function in patients with ascites</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>Antithrombin-dependent inhibition of FXa and thrombin</td>
<td>Prevention DVT, prevention/treatment of coronary syndromes, cardiac surgery</td>
<td>Cost, fully reversible with protamine</td>
<td>Risk of HIT, dependent on antithrombin monitoring, aPTT difficult, not ideal for long-term treatment, mode of administration (i.e.)</td>
</tr>
<tr>
<td>Low molecular weight heparin</td>
<td>Antithrombin-dependent inhibition of FXa and (to a lesser extent) thrombin</td>
<td>Prevention/treatment DVT and PVT</td>
<td>Reduced risk for HIT, route of administration (i.e. s.c. vs. i.v. for UFH)</td>
<td>Antithrombin dependence, issues with anti Xa monitoring, only partial reversal by protamine, not ideal for long-term treatment, accumulation in renal failure</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Antithrombin-dependent inhibition of FXa</td>
<td>Prevention/treatment DVT and PVT</td>
<td>Further reduction in risk of HIT compared to other heparins, synthetic drug</td>
<td>Antithrombin dependence, issues with anti Xa monitoring, no established reversal agent, not ideal for long-term treatment, accumulation in renal failure</td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
<td>Reduce functional levels of vitamin K-dependent proteins</td>
<td>Prevention/treatment DVT and PVT</td>
<td>Cost, experience and proven efficacy in general population, mode of administration</td>
<td>Issues with monitoring in patients with already elevated INR, bleeding</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Direct factor Xa inhibitor</td>
<td>Prevention/treatment DVT and PVT</td>
<td>Lack of antithrombin dependence, mode of administration, wider therapeutic window than VKAs</td>
<td>Lack of experience, no established antidote, GI bleeding risk, accumulation in renal and liver disease</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Direct thrombin inhibitor</td>
<td>Prevention/treatment DVT and PVT</td>
<td>Lack of antithrombin dependence, mode of administration, wider therapeutic window than vitamin K antagonists</td>
<td>Lack of experience, no established antidote, GI bleeding risk, accumulation in renal and liver disease</td>
</tr>
</tbody>
</table>

Lisman T, J Hepatology 2013
Antithrombotic treatment of splanchnic vein thrombosis (SVT) is a clinical challenge. Depending on the site of thrombosis, patients are at risk of developing liver insufficiency, portal hypertension, or bowel infarction and may experience recurrence in both the splanchnic veins and other vein segments. To prevent recurrence, anticoagulant therapy should be started as soon as possible after diagnosis and is often continued for an indefinite period of time. However, active bleeding is not infrequent at the time of SVT diagnosis, and major risk factors for bleeding, such as esophageal varices or a low platelet count, are frequently present in these patients.

In real-world clinical practice, a proportion of SVT patients are left untreated because the risks associated with anticoagulant therapy are felt to exceed its benefits. However, the majority of patients receive anticoagulant drugs, with heterogeneous timing of initiation, drug choice, and dosages. Evidence to drive treatment decisions is limited because no randomized controlled trials have been carried out in these patients. This review provides practical guidance for the use of anticoagulant drugs in patients presenting with SVT, including symptomatic as well as incidentally detected events.

**Cirrhotic, symptomatic PVT patient:** consider full therapeutic dose LMWH (1 mg/kg twice daily) after careful assessment and treatment if necessary of esophageal varices. Empiric dose reduction (50% of therapeutic dose or more, based on individual risk assessment) if additional risk factors for bleeding are identified. Delay starting of LMWH if major risk factors for bleeding coexist, until successfully managed. Delay VKA initiation and start only when the patient is stable and no additional major bleeding risk factors are identified, also according to patient preference.
TIPSS PER LA TERAPIA DELLA PVT

**QUANDO**
acuta e cronica / cirrosi sì e no

**CON QUALE OBIETTIVO**
disostrofizzazione e trattamento della IP

**CON QUALI RISULTATI**
????

- Non c'è nulla di definito nelle linee guida
- In passato 'controindicazione relativa'
- Interesse in aumento e ruolo in evoluzione
Portal vein obstruction

Hepatic and portal vein thrombosis were considered by the AASLD Practice Guidelines as relative contraindications to TIPS because of the technical difficulties in constructing the shunt in the absence of a normal anatomy of the portal and the hepatic vein systems.

Dati recenti suggeriscono che la TIPS non è controindicata e gioca un ruolo importante nel management della PVT

Mancano RCTs, ma numerosi Studi caso-controllo e osservazionali hanno ormai ben documentato i buoni risultati

La TIPS è fattibile quando i rami portalì intraepatici sono pervi e visibili; i trombi portalì possono essere ‘clirati’ dopo la TIPS anche in assenza di tp anticoagulante e senza significativo embolismo polmonare
Short- and long-term effects of the transjugular intrahepatic portosystemic shunt on portal vein thrombosis in patients with cirrhosis.

A. Luca et al

Gut 2011

- 57% the portal venous system was completely recanalised
- 30% marked decrease in thrombosis
- 13% no improvement
- 95% of patients with complete recanalisation after TIPS maintained a patent portal vein.

Predictors of complete recanalisation were a less severe and extensive PVT, de novo diagnosis of PVT, and absence of gastrooesophageal varices.

- Patients treated with transjugular intrahepatic portosystemic shunt (TIPS) between January 2003 and February 2010 in a tertiary-care centre.

How might it impact on clinical practice in the foreseeable future?

- TIPS is a rational option in the management of patients with cirrhosis complicated by non-tumoural and non-cavernous PVT. This may be especially valuable, particularly in patients eligible for liver transplantation in whom extension of the thrombosis may increase the risks associated with surgery.
- Prospective randomised studies should investigate whether TIPS is a better option than anticoagulation, or whether it should be reserved for anticoagulation failures/contraindications.
A retrospective chart review was conducted of patients with liver cirrhosis awaiting liver transplant who were diagnosed with PVT between January 2005 and November 2011.

PVT is frequently seen in patients with end stage liver disease with prevalence of 13%. Hypercoagulable disorder was detected in 5% of the patients screened. Careful use of anticoagulation is safe and effective in patients with PVT.

Wemer KT, Dig Dis Sci 2013

- fino al 25% dei cirrotici senza HCC e 33% di quelli con HCC
- 56% parziale e 44% completa; più comune in Autoimmuni, ma anche criptogenetiche, alcoliche, pazienti maschi e con pregresso trattamento di varici
- incidenza aumenta col peggioramento della funzione epatica e con la presenza di HCC (anche in assenza di trombo neoplastico), ma il MELD non correla con aumento di rischio di PVT
- combinazione di MELD > 25 e PVT controindicazione a LDLT per mortalità fino a 75%
- in pz con pregressa PVT e senza profilassi post-LTx: retrombosi 6-10%
- sopravvivenza a 1 mese e a 1 anno compromessa in presenza di PVT
- raccomandato iniziare un trattamento alla diagnosi prima del Tx e prima possibile dopo il Tx

Rodriguez-Castro KI, Transplantation 2013
Portal Vein Thrombosis Is Not Associated With Increased Mortality Among Patients With Cirrhosis
Berry K et Al
Clin Gastroenterol Hepatol - 2014

Among patients with cirrhosis on liver transplant waiting lists, patients with PVT have lower mortality than patients without PVT

66,506 transplant-naive adults with cirrhosis without hepatocellular carcinoma from 2002 through 2013 from the time of transplant listing until the time of liver transplantation or death before transplantation.

mean follow-up period of 1.78 years
17,757 (27%) patients died before liver transplantation
29,179 (44%) patients underwent transplantation,
19,570 (29%) patients were still alive without having undergone transplantation.

Compared with patients who did not have PVT, patients with PVT had lower mortality (adjusted hazard ratio 0.88; 95% confidence interval 0.81-0.96), a similar risk of transplantation (0.95; 95% , 0.89-1.02), and a lower risk of the combined outcome of death or transplantation (0.92; 95%, 0.88-0.97).

Independent predictors of mortality included age, model for end-stage liver disease score, serum albumin level, ascites, encephalopathy, diabetes, hepatitis C virus infection, and low body mass index (<24.4 kg/m²).