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NOVI ASPEKTI PRIMENE ANTIKOAGULANTNE TERAPIJE KOD COVID-19 PACIJENATA – OD PROFILAKSE DO TERAPIJE KOMPLIKACIJA

Sažetak: Pacijenti sa COVID-19 oboljenjem imaju povećan rizik za trombozu i arterijskog i venskog sistema zbog ekstenzivne sistemske inflamacije, aktivacije trombocita, endotelne disfunkcije i staze. D-dimer je važan prognostički marker mortaliteta kod COVID-19 pacijenata i njegove povećane vrednosti ukazuju na oštećenje tkiva i inflamaciju. Incidenca venskog tromboembolizma (VTE) je između 16 i 49% kao komplikacija težih oblika COVID-19 infekcije kod pacijenata smeštenih u jedinice intenzivne nege. Profilaktičke doze niskomolekularnog heparina (LMWH) treba da primaju svi hospitalizovani pacijenti sa COVID-19 infekcijom u odsustvu aktivnog krvarenja. Najsigurnije je prilagođavanje doze niskomolekularnog heparina (LMWH) prema telesnoj težini, posebno kod gojaznih pacijenata. Nefrakcionisani heparin (UFH) se primenjuje kod pacijenata sa klirensom kreatinina manjim od 30 ml/min. Terapijsku dozu antikoagulacije treba obustaviti ako je broj trombocita $<50 \times 10^9$/L ili fibrinogena <1.0 g/L. Klinički značajni neželjeni događaji krvarenja su veći kod onih koji su primali terapijske doze u odnosu na one sa standardnim tromboprofilaktičkim dozama. Trombolitička terapija se preporučuje kod pacijenata sa dokazanom plućnom embolijom (PE) i hemodinamskom nestabilnošću ili znacima kardiogenog šoka, a koji nisu u visokom riziku od krvarenja. Kod hospitalizovanih COVID-19 pacijenata sa visokim kliničkim rizikom za razvoj venskog tromboembolizma (VTE) i vrednostima D-dimera većim od 2600 ng/ml može se razmotriti primena terapijskih doza LMWH u dozama koje su prilagođene prema telesnoj težini pacijenta, a u odsustvu većeg rizika od krvarenja.

Ključne reči: COVID-19, D-dimer, venski tromboembolizam, plućna embolija, niskomolekularni heparin, antikoagulantna terapija

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Komplikacije SARS-COV2 infekcije i mehanizmi tromboze

SARS-CoV-2 virus uzrokuje kliničke simptome različite težine i zahvata više organskih sistema. Posebno je teža klinička slika kod starijih pacijenata i kod pacijenata sa komorbiditetima. Jedna od komplikacija COVID-19 infekcije je koagulopatija koja dovodi do tromboze i može da dovede do multiorganskog oštećenja i smrti (1). COVID-19 koagulopatiju karakteriše i mikrovaskularna tromboza. Stanje koagulopatije uključuje povećan D-dimer i fibrinogen, povećan broj trombocita, prolongirano protrombinsko vreme (PT), što dovodi do produženog protrombotičnog stanja koje favorizuje venski tromboembolizam, posebno kod težih formi COVID-19 infekcije, nezavisno od primenjene tromboprofilakse (2).

Pacijenti sa COVID-19 oboljenjem imaju povećan rizik za trombozu i arterijskog i venskog sistema zbog ekstenzivne sistemske inflamacije, aktivacije trombocita, endotelne disfunkcije i staze. Sa sadašnjeg aspekta, smatra se da je endotelna disfunkcija jedan od najznačajnijih mehanizama koji dovodi do koagulopatije kod COVID-19 oboljenja (3). SARS-CoV-2 infekcija dovodi do proinflamatornog stanja sa aktivacijom niza proinflamatornih citokina: IL-6, IL-1b, IL-2, IL-4, TNF-alfa, IFN-gama, C-reaktivnog proteina (CRP) i D-dimera. Proinflamatorni citokini dovode do aktivacije i replikacije proinflamatornih ćelija u cirkulaciji, koje dovode do endotelnog oštećenja, aktivacije trombocita i patološke aktivacije koagulacije (4). SARS-CoV-2 može dovesti do COVID-19 udruženog hiperviskoznog stanja i hiperproteinemije, koja predstavlja važnu vezu između inflamacije i koagulopatije. Direktni citotoksični efekti SARS-CoV-2 virusa na endotelne ćelije su još jedan od mehanizama koji dovodi do endotelopatije i koagulopatije putem vezivanja "spike" proteina SARS-CoV-2 virusa za ACE2 receptore na površini endotelnih ćelija i dovodi do njihovog oštećenja, čime se aktivira koagulaciona kaskada i dalja produkcija proinflamatornih citokina (IL-6 i TNF-alfa). IL-6 je ključni faktor aktivacije transkripcije fibrinogena. Kod pacijenata sa težim formama COVID-19 oboljenja, smeštenim u jedinicama intenzivne nege, dokazani su i visoki nivoi von Willebrand factor (VWF) antigena, povećana aktivnost faktora VIII (FVIIIa), solubilnog P-selektina, što dalje potvrđuje endotelnu disfunkciju tokom infekcije. U studiji Tang i sar., koji su analizirali 183 COVID-19 pacijenta u jedinici intenzivne nege, pokazalo se da su pacijenti koji su umrli od posledica infekcije imali signifikantno više nivoe D-dimera i fibrin degradacionih produkata (FDP), produženo protrombinsko vreme (PT) i aktivirano parcijalno tromboplastinsko vreme (aPTT) u odnosu na pacijente koji su preživeli infekciju (5). COVID-19 koagulopatija kod blažih i srednje teških oblika infekcije se karakteriše povišenim fibrinogenom, D-dimerom i CRP-om, a minimalno prolongiranim aPTT i PT, kao i blažom formom trombocitopenije (75–100x10^9/L). Kod težih oblika COVID-19 infekcije, koagulopatija se karakteriše težim oblikom trombocitopenije (manje od 50x10^9/L), smanjenim nivoom fibrinogena (manje od 1.0 g/L) , što upućuje na diseminovanu intravaskularnu

koagulaciju (DIC). U jednoj studiji sa 35 pacijenata koji su imali prolongirano aPTT više od 90% pacijenata je imalo lupus antikoagulans (LA), čije prisustvo ukazuje na udruženu tendenciju ka trombozi i razvoj sekundarnog antifosfolipidnog sindroma (6).

Tokom COVID-19 infekcije u poremećaje koagulacije uključena je i aktivacija komplementa: C3a i membranski aktivni kompleks (C5b-9) učestvuju u aktivaciji trombocita, porasta C5a u plazmi i celularne ekspresije tkivnog faktora (TF). Uzajamno dejstvo između inflamacije, aktivacije komplementa i koagulacione kaskade su ključni u razumevanju patofiziologije COVID-19 oboljenja i odgovorni su za započinjanje diseminovane intravaskularne koagulacije (7).

Smatra se da kod COVID-19 infekcije pulmonalna intravaskularna mikrotromboza, kao posledica oštećenja endotela alveola, vezivanjem SARS-CoV-2 virusa za ACE2 receptore alveolarnog epitela, dovodi do razvoja hipoksemije u ranim stadijumima akutnog respiratornog distres sindroma (ARDS), citokinske oluje i hiperkoagulabilnog stanja (8). Pulmonalna tromboza (PT) se češće kod SARS-CoV-2 infekcije javlja primarno u plućima nego kao posledica embolizacije iz tromboziranih dubokih vena (DVT) (9).

Direktno virusno miokardno i mikrovaskularno oštećenje uzrokuje izloženost subendotelijuma i kolagena, što dovodi do aktivacije trombocita, a endotelna trauma dovodi do aktivacije puteva tkivnog faktora (TF), preko aktivacije FVIIa i disregulacije kalikrein/kinin sistema, koji doprinosi daljoj aktivaciji koagulacije. SARS-CoV-2 i trombocitna interakcija dovodi do aktivacije i degranulacije trombocita, koje dalje potencira protrombotično vaskularno stanje (10).

D-dimer ima visoku negativnu prediktivnu vrednost za plućni tromboembolizam (PE). Kod pacijenta bez razvoja VTE očekuju se normalne vrednosti D dimera – manje od 0.5 μg/mL. D-dimer je važan prognostički marker mortaliteta kod COVID-19 pacijenta i njegove povećane vrednosti ukazuju na oštećenje tkiva i inflamaciju (11). Vrednosti D-dimera >2 μg/mL (što je četvorostruko veća vrednost od gornje granice referentnih vrednosti) pokazale su se kao značajan prediktor povećanog intrahospitalnog mortaliteta u jednoj studiji koja je obuhvatila 343 hospitalizovana pacijenta sa COVID-19 oboljenjem (senzitivnost 92,3%, specifičnost 83,3%) (5).

Pored trombotičnih komplikacija kod COVID-19 oboljenja postoji i povećan rizik za krvarenja i pojačana fibrinolitička aktivnost, što se manifestuje signifikantnim porastom D-dimera. Proinflamatorni citokini aktivirajući endotelne ćelije dovode do oslobađanja plazminogen aktivator inhibitora-1 (PAI-1) i tPA, što može dovesti do značajnije aktivnosti PAI-1 i redukcije trombolize (12).

Diseminovana intravaskularna koagulacija (DIC) je potencijalni letalni mehanizam kod COVID-19 oboljenja koji dovodi do poremećaja fibrinolize i multiorganske disfunkcije. Klinički znaci koji uključuju manifestni DIC uključuju krvarenje, trombocitopeniju, prolongiran PT, prolongirano aPTTT, povišen D-dimer i fibrin degradirajuće produkte (FDP) i periferne mikroangipatske promene (13). Sepsom

indukovana koagulopatija (SIC) je termin koji definiše rani DIC, gde su broj trombocita i protrombinsko vreme signifikantno poremećeni kod pacijenata kod kojih je potvrđena sepsa. Incidenca DIC-a kod hospitalizovanih COVID-19 pacijenata je 2,2%, a u patomehanizam je uključena sepsa u kombinaciji sa endotelnom aktivacijom, aktivacijom leukocita, taloženjem fibrina, što dovodi do difuzne inflamacije i koagulopatije (14).

Trombocitopenija se često javlja kod virusnih infekcija i SARS-CoV-2 ometa hematopoezu u koštanoj srži. Tokom formiranja mikrotromba u pulmonalnoj cirkulaciji, endotelnom oštećenju, kao i hiperreaktivnosti trombocita dolazi do njihove potrošnje i razgradnje, što dovodi do trombocitopenije. Trombocitopenija $<50 \times 10^9$/L se retko viđa kod COVID-19 oboljenja i najčešće niže vrednosti ukazuju na razvoj DIC-a i može služiti kao prognostički marker težine infekcije i povećanog mortaliteta (15). Kardijalno specifični troponini: Troponin T (cTnT) i Troponin I (cTnI) su visokosenzitivni markeri miokardnog oštećenja i povišeni su kod miokardnog infarkta, miokarditisa i akutne plućne embolije (PE). Povišena vrednosti troponina kod COVID-19 pacijenata se mogu smatrati markerom loše prognoze i povećanog mortaliteta (16).

Hospitalizovani COVID-19 pacijenti imaju povećan rizik za razvoj venskog tromboembolizma (VTE). Incidenca venskog tromboembolizma (VTE) je između 16 i 49% kao komplikacija težih oblika COVID-19 infekcije kod pacijenata smeštenih u jedinice intenzivne nege (17). Dutch studija je posmatrala incidencu i ukupni rizik od VTE i arterijskih trombotičnih komplikacija kod 184 COVID-19 pacijenta, gde je utvrđena incidenca od 31% trombotičnih događaja, od kojih je plućni embolizam (PE) bio najučestalija trombotična komplikacija (81% svih trombotičnih događaja). Kao značajni faktori rizika, pored sistemske inflamacije i endotelne disfunkcije, uključeni su i dehidracija, gastrointestinalne komplikacije, imobilizacija, gojaznost i drugi pridruženi komorbiditeti (dijabetes, hipertenzija, srčana insuficijencija) (18).

Farmakološka tromboprofilaksa i terapija venskog tromboembolizma kod pacijenata sa COVID-19 infekcijom

Sadašnje preporuke su da profilaktičke doze niskomolekularnog heparina (LMWH) treba da primaju svi hospitalizovani pacijenti sa COVID-19 infekcijom u odsustvu aktivnog krvarenja ili ako imaju trombocitopeniju (broj trombocita manji od $25x10^9$) ili nivoe fibrinogena manje od 0.5 g/L. Po sadašnjim vodičima abnormalne vrednosti PT i aPTT nisu kontraindikacija za primenu farmakološke tromboprofilakse, u odsustvu aktivnog krvarenja. Ako je farmakološka profilaksa kontraindikovana trebalo bi koristiti mehaničku tromboprofilaksu (19).

Kao prva linija terapije preporučuje se niskomolekularni heparin (LMWH), a nefrakcionisani heparin (UFH) kod pacijenata sa klirensom kreatinina manjim od 30 ml/min. I niskomolekularni i nefrakcionisani heparin imaju sekundarni benefit

kod COVID-19 pacijenata zahvaljujući sekundarnim antiinflamatornim efektima i antivirusnim efektima. Mišljenja su da heparini vezuju "spike" protein SARS-CoV-2 virusa i smanjuju nivoe IL-6 u cirkulaciji (20).

Preporučuje se merenje nivoa anti-Xa za monitoring nefrakcionisanog heparina (UFH) i praćenje njegovog terapijskog učinka, s obzirom na moguće artefaktne abnormalnosti PTT i aPTT tokom COVID-19 infekcije i moguće rezistencije na heparin. Nijedan vodič ne preporučuje doziranje LMWH u odnosu na nivoe anti-Xa. Najsigurnije je prilagođavanje doze niskomolekularnog heparina (LMWH) prema telesnoj težini, posebno kod gojaznih pacijenata. Terapijsku dozu antikoagulacije treba obustaviti ako je broj trombocita $< 50 \times 10^9$/L ili fibrinogena < 1.0 g/L (19).

Klinička korist od „pojačane" ili „visokodozne" tromboprofilakse koristeći visoke doze (često i dva puta veće od standardnih profilaktičkih doza), iako manje od terapijskih doza, ostaje kontroverzna. Nekoliko opservacionih studija iz SAD, Holandije, Francuske i Kine sugerišu da rutinske profilaktičke doze antikoagulanasa mogu biti nedovoljne da spreče pojavu VTE kod visoko-rizičnih COVID-19 pacijenata, pogotovo kod onih koji imaju povišene koagulacione parametre: D-dimer, PT, aPTT. Ovo se može posebno odnositi na pacijente primljene u jedinice intenzivne nege, gde se incidenca primarno venskih trombotičkih komplikacija kreće od 31% do 69% kod COVID-19 pacijenata. I dalje ostaje nejasno da li tretman terapijskim dozama antikoagulantne terapije poboljšava ishod, bez povećanog rizika od krvarenja kod pacijenata koji su klinički suspektni za VTE (21).

Velika retrospektivna kohortna studija od 2.773 hospitalizovana COVID-19 pacijenta nije pokazala razliku u intrahospitalnom mortalitetu kod onih koji su primali profilaktičke u odnosu na one koji su primali terapijske doze antikoagulantne terapije (22,5% prema 22,8%). Druge dve slične retrospektivne studije nisu pokazale razlike u preživljavanju kod pacijenata na terapijskim u odnosu na one sa profilaktičkim dozama antikoagulanasa. Druga retrospektivna multicentrična kohortna studija iz SAD, koja je uključila 3.480 pacijenata sa COVID-19 oboljenjem, pokazala je redukciju mortaliteta i kod terapijskih i kod profilaktičnih doza u odnosu na one pacijente koji nisu primali tromboprofilaksu (22).

Klinički značajni neželjeni događaji krvarenja su veći kod onih koji su primali terapijske doze u odnosu na one sa standardnim tromboprofilaktičkim dozama. Jedna studija iz SAD je pokazala da se kod 19 pacijenata iz studije (0,5%) razvio hemoragijski insult kod onih koji su primali terapijsku dozu antikoagulansa (89,5% pacijenata uključenih u studiju). Na osnovu dostupnih dokaza ne preporučuje se rutinska primena terapijskih doza antikoagulantne terapije. Benefit od terapijskih doza antikoagulantne terapije je za sada kontroverzan i potrebna je dalja potvrda na osnovu retrospektivnih studija (23).

Prednosti direktnih oralnih antikoagulanasa (DOAC) uključuju lakše planiranje otpusta i praćenje pacijenata, s obzirom na to da nije potreban laboratorijski monito-

ring. DOAC imaju duže vreme poluživota od UFH i LMWH, što može komplikovati urgentne invazivne procedure i razvoj bubrežnog oštećenja. Potreban je oprez kod njihove primene kod pacijenata sa već oštećenom bubrežnom funkcijom, a drugi rizik može uključivati potencijalni efekat vezan za bioraspoloživost i kliničku efikasnost zbog interakcije sa drugim lekovima, poput deksametazona koji može smanjiti nivoe DOAC-a preko indukcije P-gp i CYP3A4 indukcije enzima u jetri (24).

U jednoj prospektivnoj studiji, koja je sprovedena u Italiji, obuhvaćeno je 844 COVID-19 pacijenta koji su uzimali DOAC pre hospitalizacije. Pacijenti sa DOAC su razvili akutnu hipoksemičnu respiratornu insuficijenciju mnogo češće u odnosu na pacijente koji nisu uzimali DOAC i imali su veću stopu smrtnosti (44,6% prema 19,8%, $P < 0,001$) (25).

Retrospektivna studija, koja je sprovedena u SAD, analizirala je 3.625 pacijenata sa srednje teškom i teškom kliničkom slikom COVID-19 infekcije, pokazala je da terapijska antikoagulacija koja uključuje apixaban ima sličnu efikasnost kao i enoxaparin u smanjenju mortaliteta kod hospitalizovanih COVID-19 pacijenata (26).

Nakon kliničkog poboljšanja i kada se planira otpust pacijenta, klinički stabilni pacijenti sa VTE mogu se prevesti sa niskomolekularnog heparina (LMWH) na DOAC ili vitamin K antagoniste sa planom lečenja najmanje 3 meseca u odsustvu dodatnih faktora rizika za trombozu (24).

Ticagrelor, inhibitor trombocitnog receptora P2Y12, blokira trombocitnu aktivaciju i agregaciju, može se razmatrati kao alternativa tromboprofilaksi. Ticagrelor može redukovati oštećenje pluća tokom razvoja pneumonije, redukujući nivoe proinflamatornih citokina (IL-6, TNF-α, IL-8). Ticagrelor je dostupan jedino kao oralni terapijski agens i limitirana je njegova primena kod pacijenata na mehaničkoj ventilaciji, gde se može razmatrati primena Cangrelora, sličnog P2Y12 inhibitora za intravensku primenu. Još nema dokumentovanih kliničkih studija u njihovoj efikasnosti i primeni kod COVID-19 oboljenja (22).

Sigurnost i efikasnost aspirina za profilaksu VTE i dalje je nepoznata. Kod onih sa kardiovaskularnim oboljenjem, jedna kohortna studija od 412 COVID-19 pacijenta koji su uzimali aspirin tokom 24h od prijema u bolnicu ili 7 dana pre prijema u bolnicu utvrdila je da je njegova upotreba nezavisno povezana sa manjim rizikom od mehaničke ventilacije, prijema u jedinice intenzivne nege i intrahospitalnog mortaliteta. Iako bi smanjenje stope mikrotromboze bio pretpostavljeni mehanizam dejstva, ostaje da se vidi korist aspirina kod COVID-19 pacijenata bez kardiovaskularnog oboljenja (27).

Trombolitička terapija se preporučuje kod pacijenata sa dokazanom plućnom embolijom (PE) i hemodinamskom nestabilnošću ili znacima kardiogenog šoka, a koji nisu u visokom riziku od krvarenja. Periferna tromboliza se preporučuje u odnosu na kateter-vođenu trombolizu kod COVID-19 pacijenata (28).

Nekoliko studija je identifikovalo laboratorijske modele stratifikacije na osnovu pragova nivoa D-dimera kako bi se identifikovali pacijenti koji bi trebalo da primaju

profilaktičku ili terapijsku dozu antikoagulansa, čak i sa niskom kliničkom sumnjom na VTE. Oni sa nivoom D-dimera koji je stalno < 1,000 μg/L trebalo bi da primaju standardne profilaktičke doze, a kod onih sa inicijalnim nivoom < 1,000 μg/L pri prijemu, ali sa signifikantnim porastom tokom hospitalizacije na 2000–4000 μg/L, može se razmatrati dijagnostika pacijenta za DVT ili PE, posebno za pacijente sa klinički ispoljenim simptomima. Kada dijagnostičke procedure nisu izvodljive, a klinička sumnja za VTE je visoka, preporučuju se terapijske doze niskomolekularnog heparina (LMWH), a pod uslovom da je mali rizik od krvarenja (29).

U jednoj velikoj multicentričnoj studiji sprovedenoj u SAD pokazano je da serumski nivoi D-dimera veći od 2600ng/mL (referentne vrednosti 0–292 ng/mL) predstavljaju diskriminatorni faktor za pojavu VTE. Jedna studija sprovedena u Francuskoj pokazala je prediktivnu vrednost za razvoj PE sa "cutoff" vrednostima D-dimera većim od 2.590 ng/ml i vrednosti D-dimera veće od 2.590 ng/ml udružene su sa 17 puta većim rizikom za pojavu PE. Ovo podržava široku upotrebu merenja D-dimera kao skrininga za PE kod hospitalizovanih COVID-19 pacijenata (30).

Zaključci

Kod svih hospitalizovanih pacijenata sa COVID-19 infekcijom preporučuju se profilaktičke doze niskomolekularnog (LMWH) ili nefrakcionisanog (UFH) heparina. Kod hospitalizovanih COVID-19 pacijenata sa visokim kliničkim rizikom za razvoj venskog tromboembolizma (VTE) i vrednostima D-dimera većim od 2.600 ng/ml može se razmotriti primena terapijskih doza LMWH u dozama koje su prilagođene prema telesnoj težini pacijenta, a u odsustvu većeg rizika od krvarenja.

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NEW ANTICOAGULANT THERAPY ASPECTS TO THE COVID-19 PATIENTS – FROM PROPHYLAXIS TO COMPLICATIONS TREATMENT THERAPY

Summary: COVID-19 patients have a high risk of thrombosis of the arterial and venous systems due to extensive systemic inflammation, platelet activation, endothelial dysfunction, and stasis. D-dimer is an important prognostic marker of mortality caused by COVID-19 patients and its increased values indicate tissue damage and inflammation. The incidence of venous thromboembolism (VTE) is between 16 and 49% as a complication of more severe forms of COVID-19 infection in patients hospitalized in intensive care units. Prophylactic doses of low molecular weight heparin (LMWH) should be given to all hospitalized patients with COVID-19 infection in the absence of active bleeding. The safest way is to adjust the low molecular weight heparin (LMWH) dose according to body weight, especially in obese patients. Unfractionated heparin (UFH) is used in patients with a creatinine clearance of less than 30 ml/min. The therapeutic dose of anticoagulation should be discontinued if the platelet count is $<50 \times 10^9$/L or fibrinogen <1.0 g/L. Clinically significant bleeding events are higher in those who received therapeutic doses compared to those with standard thromboprophylaxis doses. Thrombolytic therapy is recommended in patients with proven pulmonary embolism (PE) and hemodynamic instability or signs of cardiogenic shock, who are not at high risk of bleeding. In hospitalized COVID-19 patients with a high clinical risk of developing venous thromboembolism (VTE) and D-dimer values greater than 2600 ng/ml, the use of therapeutic doses of LMWH in doses adjusted to the patient's body weight should be considered, in the absence of a higher risk of bleeding.

Keywords: COVID-19, D-dimer, venous thromboembolism, pulmonary embolism, low molecular weight heparin, anticoagulant therapy.

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SARS-COV2 infection complications and thrombosis mechanisms

The SARS-CoV-2 virus causes clinical symptoms of varying severity and affects multiple organs. The clinical picture is especially difficult in elderly patients and patients with comorbidities. Significant complications of COVID-19 infection is coagulopathy, lead to thrombosis and can cause multiorgan damage and lethal outcome (1). COVID-19 coagulopathy is also characterized by microvascular thrombosis. The coagulopathy condition includes increased D-dimer and fibrinogen, increased platelet count, prolonged prothrombin time (PT), leading to a prolonged prothrombotic state that favours venous thromboembolism, especially in severe forms of COVID-19 infection, independent of thromboprophylaxis (2).

Patients with COVID-19 disease have an increased risk of thrombosis of arterial and venous systems due to extensive systemic inflammation, platelet activation, endothelial dysfunction, and stasis. From the present aspect, endothelial dysfunction is considered to be one of the most important mechanisms leading to coagulopathy in COVID-19 disease (3). The SARS-CoV-2 infection leads to a pro-inflammatory state with the activation of several pro-inflammatory cytokines: IL-6, IL-1b, IL-2, IL-4, TNF-alpha, IFN-gamma, C-reactive protein (CRP) and D- dimers. Pro-inflammatory cytokines lead to the activation and replication of pro-inflammatory cells in the circulation leading to endothelial injury, platelet activation and pathological activation of coagulation (4). The SARS-CoV-2 can lead to COVID-19 associated hyper-viscosity and hyperproteinemia, which is an important link between inflammation and coagulopathy. The direct cytotoxic effects of the SARS-CoV-2 virus on endothelial cells are another mechanism that leads to endothelial injury and coagulopathy by binding the "spike" protein of the SARS-CoV-2 virus to ACE2 receptors on the surface of endothelial cells and leading to their damage, activates the coagulation cascade and further production of proinflammatory cytokines (IL-6 and TNF-alpha). IL-6 is a key factor in activating fibrinogen transcription. In patients with more severe forms of COVID-19 disease, hospitalized in intensive care units, high levels of von Willebrand factor (VWF) antigen, increased activity of factor VIII (FVIIIa), soluble P-selectin, have been demonstrated, further confirming endothelial injury during infection. Tang et al., study has been analyzed 183 COVID-19 patients in the intensive care unit. Patients who died from infection were shown to have significantly higher levels of D-dimer and fibrin degradation products (FDP), prolonged prothrombin time (PT), and activated partial thromboplastin time (aPTT) to patients who survived the infection (5). COVID-19 coagulopathy in mild and moderate forms of infection is characterized by elevated fibrinogen, D-dimer and CRP, and minimally prolonged aPTT and PT, as well as a milder form of thrombocytopenia (75–100x10^9/L). In severe forms of COVID-19 infection, coagulopathy is characterized by severe thrombocytopenia (less than 50x10^9/L), decreased fibrinogen levels (less than 1.0 g/L), suggesting

disseminated intravascular coagulation (DIC). In one study of 35 patients who had prolonged aPTT, more than 90% of patients had lupus anticoagulant (LA), the presence of which indicates an associated tendency toward thrombosis and the development of the secondary antiphospholipid syndrome (6).

During COVID-19 infection, complement activation is also involved in coagulation disorders: C3a and membrane-active complex (C5b-9) participate in platelet activation, plasma C5a increase and cellular expression of tissue factor (TF). The interaction between inflammation, complement activation, and the coagulation cascade is crucial in understanding the pathophysiology of COVID-19 disease and is responsible for initiating disseminated intravascular coagulation (7).

In COVID-19 infection, pulmonary intravascular micro thrombosis, as a consequence of alveolar endothelial damage by binding of the SARS-CoV-2 virus to ACE2 receptors of the alveolar epithelium, is thought to lead to the development of hypoxemia in the early stages of acute respiratory distress syndrome (ARDS), cytokine "storm" and hypercoagulability (8). Pulmonary thrombosis (PT) is more common in SARS-CoV-2 infection primarily in the lungs than as a consequence of embolization from deep veins thrombosis (DVT) (9).

Direct viral myocardial and microvascular damage causes subendothelial and collagen exposure, leading to platelet activation, and endothelial trauma leads to tissue factor (TF) pathway activation through FVIIa activation and dysregulation of the kallikrein-kinin system, which contributes to the further coagulation. SARS-CoV-2 and platelet interaction lead to platelet activation and degranulation, which further promotes the prothrombotic vascular condition (10).

D-dimer has a high negative predictive value for pulmonary thromboembolism (PE). In the patient without developing normal D- dimer values are expected to be less than 0.5 μg/mL. D-dimer is an important prognostic marker of mortality in COVID-19 patients and its increased values indicate tissue damage and inflammation (11). D-dimer values > 2 μg/mL (four times higher then upper limit of the reference values) were shown to be a significant predictor of increased in-hospital mortality in one study involving 343 hospitalized patients with COVID-19 disease (sensitivity 92.3%, specificity 83.3 %) (5).

In addition to thrombotic complications in COVID-19 disease, there is an increased risk of bleeding and increased fibrinolytic activity, which is manifested by a significant increase in D-dimer. Proinflammatory cytokines activating endothelial cells lead to the release of plasminogen activator inhibitors-1 (PAI-1) and tPA, which can lead to more significant PAI-1 activity and reduction of thrombolysis (12).

Disseminated intravascular coagulation (DIC) is a potentially lethal mechanism in COVID-19 disease that leads to fibrinolysis disorders and multiorgan dysfunction. Clinical signs of overt DIC include bleeding, thrombocytopenia, prolonged PT, prolonged aPTTT, elevated D dimer, and fibrin degradation products (FDP), and peripheral

micro-angiopathic changes (13). Sepsis-induced coagulopathy (SIC) is a term that defines early DIC, where platelet count and prothrombin time are significantly disrupted in patients with confirmed sepsis. The incidence of DIC in hospitalized COVID-19 patients is 2.2%, and sepsis is included in the pathomechanism in combination with endothelial activation, leukocyte activation, fibrin deposition, which leads to diffuse inflammation and coagulopathy (14).

Thrombocytopenia often occurs in viral infections and SARS-CoV-2 interferes with hematopoiesis in the bone marrow. During micro thrombus formation in the pulmonary circulation, endothelial damage, as well as the hyper-reactivity of platelets, their consumption and decomposition occur, which leads to thrombocytopenia. Thrombocytopenia $<50 \times 10^9$/ L is rarely seen in COVID-19 disease and usually lower values indicate the development of DIC and may use as a prognostic marker of infection severity and increased mortality (15).

Cardiac-specific troponins: Troponinin T (cTnT) and Troponin I (cTnI) are highly sensitive markers of myocardial damage and are elevated in myocardial infarction, myocarditis, and acute pulmonary embolism (PE). Elevated troponin levels in COVID-19 patients can be considered as a marker of poor prognosis and increased mortality (16).

Hospitalized COVID-19 patients have an increased risk of developing venous thromboembolism (VTE). The incidence of venous thromboembolism (VTE) is between 16 and 49% as a complication of more severe forms of COVID-19 infection in patients hospitalized in intensive care units (17). The Dutch study observed the incidence and overall risk of VTE and arterial thrombotic complications in 184 COVID-19 patients, where an incidence of 31% of thrombotic events was found, of which pulmonary embolism (PE) was the most common thrombotic complication (81% of all thrombotic events). In addition to systemic inflammation and endothelial dysfunction, significant risk factors include dehydration, gastrointestinal complications, immobilization, obesity, and other associated comorbidities (diabetes, hypertension, heart failure) (18).

Pharmacological thromboprophylaxis and venous thromboembolism therapy in COVID-19 patients

Current recommendations are that prophylactic doses of low molecular weight heparin (LMWH) should be given to all hospitalized patients with COVID-19 infection in the absence of active bleeding or if they have thrombocytopenia (platelet count less than $25x10^9$) or fibrinogen levels less than 0.5 g / L. According to current guidelines, abnormal PT and aPTT values are not a contraindication for the use of pharmacological thromboprophylaxis, in the absence of active bleeding. If pharmacological prophylaxis is contraindicated, mechanical thromboprophylaxis should be used (19).

Low-molecular-weight heparin (LMWH) is recommended as first-line therapy, and unfractionated heparin (UFH) in patients with creatinine clearance less than 30 ml/min. Both, low molecular weight and unfractionated heparin, have a secondary benefit in COVID-19 patients due to secondary anti-inflammatory and antiviral effects. Heparins bind spike proteins of the SARS-CoV-2 virus and reduce circulating IL-6 levels (20).

It is recommended to measure anti-Xa levels to monitor unfractionated heparin (UFH) and monitor its therapeutic effect, given possible artefact abnormalities of PTT and aPTT during COVID-19 infection and possible heparin resistance. There are no instructions that recommend dosing LMWH relative to anti-Xa levels. The safest way is to adjust the dose of low molecular weight heparin (LMWH) according to body weight, especially in obese patients. The therapeutic dose of anticoagulation should be discontinued if platelet count $<50 \times 10^9$ / L or fibrinogen <1.0 g/L (19).

The clinical benefit of "enhanced" or "high-dose" thromboprophylaxis using high doses (often twice the standard prophylactic dose), although less than therapeutic doses, remains controversial. Several observational studies from the USA, the Netherlands, France and China suggest that routine prophylactic doses of anticoagulants may be insufficient to prevent VTE in high-risk COVID-19 patients, especially in those with elevated coagulation parameters: D dimer, PT, aPTT. This applies to the patients admitted to intensive care units, where the incidence of primarily venous thrombotic complications ranges from 31% to 69% in COVID-19 patients. It remains unclear whether treatment with therapeutic doses of anticoagulant therapy improves outcome, without an increased risk of bleeding in patients who are clinically suspected of having VTE (21).

A large retrospective cohort study of 2773 hospitalized COVID-19 patients showed no difference in intrahospital mortality in those who receive prophylactic versus those receiving therapeutic doses of anticoagulant therapy (22.5% vs. 22.8%). The other two similar retrospective studies showed no differences in survival in patients on therapeutic versus those with prophylactic doses of anticoagulants. Another retrospective multicenter cohort study from the USA that included 3480 patients with COVID-19 disease showed a reduction in mortality at both therapeutic and prophylactic doses compared to those patients who did not receive thromboprophylaxis (22).

Clinically significant bleeding events are higher in those who received therapeutic doses compared to those with standard thromboprophylaxis doses. One US study found that 19 patients (0.5%) developed hemorrhagic stroke in those receiving a therapeutic dose of anticoagulant (89.5% of patients included in the study). Based on the available evidence, routine administration of therapeutic doses of anticoagulant therapy is not recommended. The benefit of therapeutic doses of anticoagulant therapy is currently controversial and further confirmation is needed based on retrospective studies (23).

The advantages of direct oral anticoagulants (DOAC) include facilitation of discharge planning and outpatient follow-up, as no laboratory monitoring is required.

DOACs have a longer half-life than UFH and LMWH, which can complicate urgent invasive procedures and the development of renal impairment. Caution should be exercised when using them in patients with impaired renal function, and other risks may include a potential effect on bioavailability and clinical efficacy due to interactions with other drugs, such as dexamethasone, which may reduce DOAC levels through P-gp induction and CYP3A4 induction enzymes in the liver (24).

One prospective study conducted in Italy included 844 COVID-19 patients taking DOAC before hospitalization. Patients with DOAC developed acute hypoxemic respiratory failure more frequently compared to patients who did not take DOAC and had a higher mortality rate (44.6% vs. 19.8%, P <0.001) (25).

A retrospective study conducted in the United States, analyzing 3625 patients with moderate or severe clinical condition of COVID-19 infection, showed that therapeutic anticoagulation involving apixaban had similar efficacy as enoxaparin in reducing mortality in hospitalized COVID-19 patients (26).

Following clinical improvement and when patient discharge is planned, clinically stable patients with VTE may be switched from low molecular weight heparin (LMWH) to DOAC or vitamin K antagonists with a treatment plan for at least 3 months in the absence of additional risk factors for thrombosis (24).

Ticagrelor, an inhibitor of the platelet receptor P2Y12, blocks platelet activation and aggregation, can be considered as an alternative to platelet prophylaxis. Ticagrelor can reduce lung damage during the development of pneumonia, reducing the levels of proinflammatory cytokines (IL-6, TNF-α, IL-8). Ticagrelor is only available as an oral therapeutic agent and its use is limited in patients on mechanical ventilation, where the use of Cangrelor, a similar P2Y12 inhibitor for intravenous administration, may be considered. There are no documented clinical studies in their efficacy and application in COVID-19 disease (22).

The safety and efficacy of aspirin for VTE prophylaxis remain unknown. In those with cardiovascular disease, a cohort study of 412 COVID-19 patients taking aspirin within 24 hours of hospital admission or 7 days before hospital admission found that its use was independently associated with a lower risk of mechanical ventilation, admission to units' intensive care and in-hospital mortality. Although a reduction in the rate of micro thrombosis would be the assumed mechanism of action, the benefit of aspirin remains to be seen in COVID-19 patients without cardiovascular disease (27).

Thrombolytic therapy is recommended in patients with proven pulmonary embolism (PE) and hemodynamic instability or signs of cardiogenic shock, who are not at high risk of bleeding. Peripheral thrombolysis is recommended prefer than catheter-guided thrombolysis in COVID-19 patients (28).

Several studies have identified laboratory models of stratification based on D-dimer thresholds to identify patients who should receive a prophylactic or therapeutic dose of anticoagulant, even with low clinical suspicion of VTE. Those with a D-di-

mer level consistently <1,000 μg / L should receive standard prophylactic doses, and those with an initial level <1,000 μg/L on admission, but with a significant increase during hospitalization to 2000-4000 μg / L, patient diagnosis for DVT or PE may be considered, especially for patients with clinically evident symptoms. When diagnostic procedures are not feasible and clinical suspicion of VTE is high, therapeutic doses of low molecular weight heparin (LMWH) are recommended, provided there is low risk of bleeding (29).

A large multicenter study conducted in the United States showed that serum D-dimer levels greater than 2600 ng/mL (reference values 0–292 ng/mL) represent a discriminant factor for the occurrence of VTE. One study conducted in France showed a predictive value for the development of PE with "cutoff" values of D-dimer greater than 2590 ng/ml and values of D dimer greater than 2590 ng/ml were associated with a 17-fold higher risk of PE occurrence. This supports the widespread use of D-dimer measurements as PE screening in hospitalized COVID-19 patients (30).

Conclusions

Prophylactic doses of low-molecular-weight (LMWH) or unfractionated (UFH) heparin are recommended to all hospitalized patients with COVID-19 infection. In hospitalized COVID-19 patients with a high clinical risk of developing venous thromboembolism (VTE) and D-dimer values greater than 2600 ng/ml, the use of therapeutic doses of LMWH in doses adjusted to the patient's body weight should be considered, in the absence of a higher risk of bleeding.

There is no conflict of interest.

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