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EDITORIAL

Prothrombotic state and thrombotic events in COVID-19 pandemic period, including portal vein and splenic artery thromboses

Ozgur Karcioglu, Canan Akman, Göksu Afacan Ozturk

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Abstract

This editorial article is intended to perform a discussion on the manuscript entitled "Simultaneous portal vein thrombosis and splenic vein thrombosis in a COVID-19 patient: A case report and review of literature" written by Abramowitz *et al*. The article focuses on the diagnostic processes in a 77-year-old-male patient with a simultaneous portal vein and splenic artery thrombosis accompanying coronavirus disease 2019 (COVID-19). The authors postulated that splanchnic thrombosis should be on the list of differential diagnoses in a patient presenting with abdominal pain in presence of a COVID-19 infection. The tendency for venous and arterial thrombosis in COVID-19 patients is encountered, largely attributed to hypercoagulopathy. In general, venous thromboembolism mostly manifest as deep vein thrombosis (DVT), pulmonary embolism (PE) or catheter-related thromboembolic events. Acute PE, DVT, cerebrovascular events and myocardial infarction are seen as the most common thromboembolic complications in COVID-19 patients. COVID-19-associated hemostatic abnormalities include mild thrombocytopenia and increased D-dimer level. Similar to other coagulopathies, the treatment of the underlying condition is the mainstay. Addition of antiplatelet agents can be considered in critically ill patients at low bleeding risk, not on therapeutic anticoagulation, and receiving gastric acid suppression Early administration of antithrombotic drugs will have a beneficial effect in both the prevention and treatment of thrombotic events, especially in non-ambulatory patients. Low molecular weight heparin (LMWH) should be started if there is no contraindication, including in non-critical patients who are at

risk of hospitalization LMWH (enoxaparin) is preferred to standard heparin.

Key Words: Prothrombotic state; Thrombotic events; COVID-19; Pandemic; Thromboembolism

Core Tip: Venous thromboembolisms constitute a common complication of coronavirus disease 2019 (COVID-19) and mostly manifest as deep venous thromboses, pulmonary embolism, myocardial infarction or catheter-related thromboembolic events. On the other hand, portal vein and splenic artery thromboses are rarely encountered. Since the portal vein forms the confluence of the splenic and superior mesenteric veins, portal vein thrombosis may extend to the splenic or superior mesenteric veins. Prophylactic dose anticoagulation is associated with favorable efficacy and safety in those with COVID-19, including portal vein and splenic artery thromboses.

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INTRODUCTION

This editorial article is intended to perform a discussion on the manuscript entitled "Simultaneous portal vein thrombosis and splenic vein thrombosis in a COVID-19 patient: A case report and review of literature" written by Abramowitz *et al* [1]. The article focuses on the diagnostic processes in a 77-year-old-male patient with a simultaneous portal vein and splenic artery thrombosis accompanying coronavirus disease 2019 (COVID-19). The authors also pointed out that numerous disorders involving coagulation system can trigger such unusual thrombotic manifestations which are mostly attributed to hypercoagulable states. Emergent abdominal imaging has been emphasized to detect and treat thrombus and related problems expediently. They postulated that splanchnic thrombosis should be on the list of differential diagnoses in a patient presenting with abdominal pain in presence of a COVID-19 infection.

COVID-19 has caused serious illness and death all over the world. Although the illness primarily causes serious respiratory diseases, there is an increased risk of thromboembolic events. Patients with COVID-19 are increasingly being recognized as being at risk of developing prothrombotic complications such as acute mesenteric ischemia and portal vein thrombosis (PVT). Both bleeding and thrombosis can result in significant morbidity in COVID-19. The entity paves the way to arterial thromboembolic events (*i.e.*, stroke and/or extremity ischemia) as well as small vessel thrombosis, which are frequently encountered at autopsy in the pulmonary vessels.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) affected the world population *via* a global pandemic, and many people lost their lives. COVID-19 is a disease that begins with symptoms of fever, cough, and shortness of breath, and progresses to a severe infection in which systemic inflammatory response (Systemic Inflammatory Response Syndrome), acute respiratory disease syndrome, and multiple organ failure ensue with a high rate of death and disability [2].

Thrombotic events are triggered by COVID-19 infection *via* various mechanisms including platelet activation, activation of the coagulation cascade, the formation of neutrophil extracellular traps (NETs) and inflammaton pathways also known as "cytokine storm"[3]. NETs are described as a web-like material structured from DNA and various proteins resulting in a pathological process called "NETosis"[4]. These structures have pro-inflammatory properties, interfering in the pathogenesis of inflammatory processes, including atherogenesis, arterial and venous thrombosis[5]. NETs enhance the production of cytokines, as well as the pro-coagulant and pro-thrombotic status[6,7]. Cytokine storm activate the coagulation cascade, while coagulation factors can act as triggers of the cytokine storm[8-10]. The development of thrombi which plays critical role in the pathogenesis of multi-organ injury follows overproduction of inflammatory cytokines[9,10]. Figure 1 illustrates the pathological and prothrombotic mechanisms of the COVID-19 infection.

Coagulopathy and disseminated intravascular coagulation (DIC) are the most important causes of mortality in COVID-19 patients. Research showed that the risk of venous and arterial thromboembolism is associated with coagulation disorders. Patients are generally prone to excessive inflammation, embolization, hypoxia, DIC, and both venous and arterial thromboembolic events. COVID-19-associated coagulopathy affects many organs, including the lungs, brain, heart and extremities. Development of thrombi, especially in small pulmonary vessels, causes acute severe acute respiratory syndrome, resulting in death. Of note, there are studies which reported a low risk of venous and arterial thrombi in ambulatory and post-discharge COVID-19 patients, with a higher risk in post-discharge patients compared with ambulatory patients [11].

Acute pulmonary embolism (PE), deep vein thrombosis (DVT), cerebrovascular events and myocardial infarction (MI) are seen as the most common thromboembolic complications in COVID-19 patients[12,13]. Acute mesenteric ischemia is a life-threatening abdominal emergency accompanied by poor clinical outcomes[14]. Bowel wall abnormalities were detected in around one-third of abdominal computed tomography images, including pneumatosis and portal venous gas.

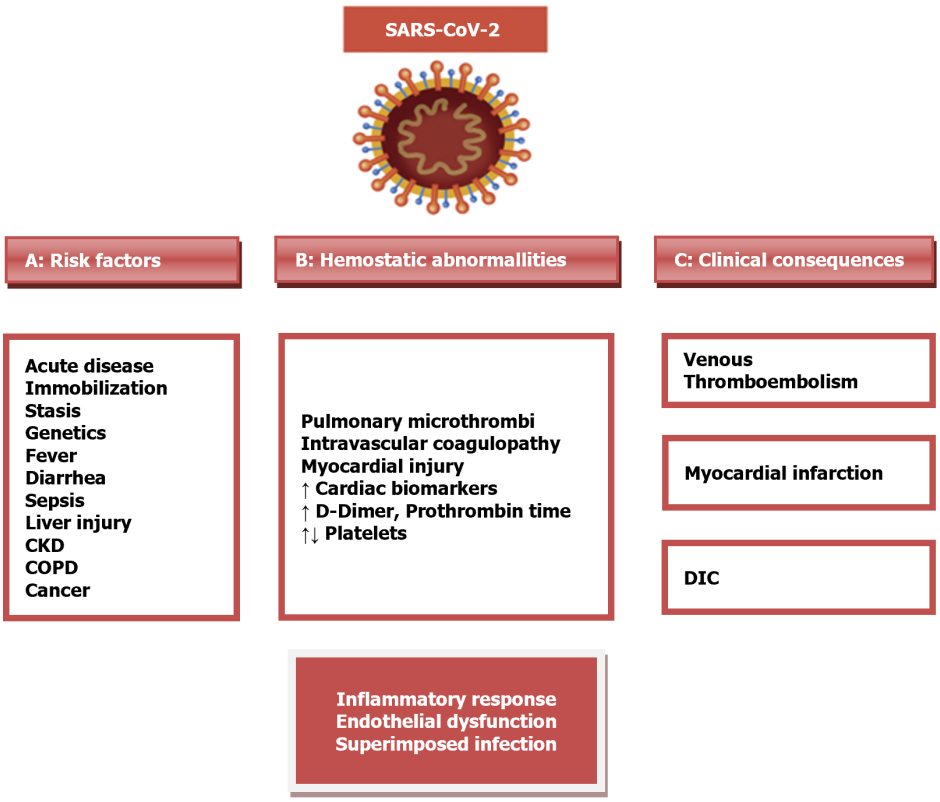

Figure 1 Schematisation of the pathological and prothrombotic mechanisms and pathways of the severe acute respiratory syndrome coronavirus 2 infection. A: Severe acute respiratory syndrome coronavirus 2 infection leads to endothelial and hemostatic activation with the release of inflammatory mediators, increase of Von Willebrand factor and tissue factor. Patients with severe infection has more remarkable inflammatory response, lymphopenia and thrombocytopenia. Liver injury, impaired coagulation and decreased antithrombin formation are observed; B: Coronavirus disease 2019 is known to trigger hemostatic irregularity and release of cardiac troponins into bloodstream; C: Disseminated intravascular coagulation is observed in cases of increased prothrombotic state, venous thromboembolism, myocardial infarction, hemostatic irregularity. CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; DIC: Disseminated intravascular coagulation; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Intestinal ischemia was diagnosed in some of these patients, which was attributed to thrombotic diseases of small vessels [15].

Cytokine storm and endothelial dysfunction ensued in the course of COVID-19 have been accused of causing significant venous thromboembolisms (VTE). Increased levels of D-dimer and fibrin degradation products are linked to high rates of adverse consequences[16]. Of note, COVID-19 patients have also increased levels of lupus anticoagulants. The macrophage activation syndrome, the complement cascade, and the renin-angiotensin system are also blamed in these pathophysiological mechanisms[17].

Pro-inflammatory cytokine release is associated with endothelial dysfunction and activation of coagulation pathways, which is reflected by elevated D-dimer levels and impaired coagulation markers. Thrombosis result in tissue ischemia combined with endothelial damage which lead to microthrombi, macrothrombi and thromboembolic events. If thrombosis develops in different organ systems as a result of excessive immune activation, multiorgan failure may ensue.

PVT is known to encompass blockade of the portal vein by a thrombus. Thrombosis can develop in the main body of the portal vein or its intrahepatic branches[18]. Since the portal vein forms the confluence of the splenic and superior mesenteric veins, PVT may extend to the splenic or superior mesenteric veins. In most cases, the entity is associated with liver failure, although it can ensue without a liver disease like malignancy, abdominal sepsis, or pancreatitis. PVT occurs in two groups of patients: Those with chronic hepatic failure and patients with prothrombotic disorders. The liver functions are mostly around expected levels in the latter group. complication of PVT include portal hypertension, ischemic bowel disease, septic PVT, and portal cholangiopathy[18,19].

In those with PVT, anticoagulation is necessary in case of impending intestinal ischemia, hepatic failure awaiting liver transplantation, and a compensated liver disease with a new diagnosis of acute PVT or PVT with asymptomatic mesenteric venous occlusion. Enoxaparin is preferable, which has not any important side effects or hemorrhagic events in cirrhotic patients.

SARS-CoV-2 is a single-stranded RNA coronavirus. It enters human cells by binding to ACE-2, which is activated mainly in lung alveoli, cardiac myocytes, vascular endothelium and other cells[2,20,21]. Depending on the type of surface, the virus can survive for up to 24-72 hours and paves the way for the transmission of infections[22]. Some mechanisms of coagulopathy that may predispose to thrombotic events are given below.

During the process of DIC, hyper-coagulopathy occurs as a result of endothelial cell dysfunction, overproduction of thrombin, and inhibition of fibrinolysis.

MARKERS OF COVID-19, HEMOSTASIS, MYOCARDIAL INJURY AND THROMBOTIC DISEASE

COVID-19-associated hemostatic abnormalities include mild thrombocytopenia and increased D-dimer level. These parameters are concurrent with the increased risk of mechanical ventilation, intensive care unit (ICU) admission, and death[23,24]. D-dimer elevation more than 2 times constitutes a risk factor for VTE. It is recommended that anticoagulant prophylaxis last more than 45 days. The severity of the disease is related to prothrombin time (PT), international normalized ratio (INR) prolongation, thrombin time prolongation, and active partial thromboplastin time test (aPTT) shortening (Figure 2)[2,25-27].

High troponin level has been associated with poor outcome in COVID-19. Nonspecific myocardial ischemia includes troponin elevation due to renal dysfunction, myocarditis, PE, and MI. It is important to consider the clinical picture in the evaluation of thrombotic events such as PE[28,29].

Ultrasonography, echocardiography (ECHO), pulmonary angiography and tomography can be used to evaluate cardiopulmonary and circulatory thrombotic events. Right ventricular dysfunction is valuable for PE. Right ventricular functions, wall motions, and clot can be examined in ECHO[30].

CLINICAL CHARACTERISTICS AND COURSE

The tendency for venous and arterial thrombosis in COVID-19 patients is encountered, largely attributed to hypercoagulopathy. In general, VTEs mostly manifest as DVTs, PE or catheter-related thromboembolic events. Thrombosis can occur in various sites, including the deep veins of the lower extremity (femoral, iliac, and popliteal veins), upper extremity, veins and more rarely, the superior vena cava, jugular vein, cerebral venous sinus, cavernous sinus, and retinal vein[17].

COVID-19 paves the way for thromboembolic complications even in the post-treatment period. It has been observed that the increased risk of VTE in patients with COVID-19 continues for a longer period of time (around two months). Pharmacological prophylaxis of VTE is recommended if the patient is elderly, has comorbid diseases (obesity, cardiovascular disease, hypertension, diabetes), has a history of VTE, and is hospitalized in the ICU, unless there are contraindications.

Due to the risk of severe thromboinflammation, and consequent DIC, anticoagulation in prophylactic dose is associated with favorable efficacy and safety in COVID-19 patients. A recent Cochrane analysis revealed that prophylactic anticoagulants may result in little or no difference in risk of VTE, hospitalisation, or adverse events when compared with antiplatelet agents (low-certainty evidence)[31]. Authors emphasized that for there were only short-term data from one study, these results should be interpreted with caution.

Low molecular weight heparins (LMWH) are preferred treatments over parenteral anticoagulation [unfractionated heparin (UFH)] due to need for frequent blood tests to monitor the achievement of therapeutic levels of aPTT. Advantages of direct oral anticoagulants (DOAC) include no need for monitoring, easy discharge planning, and outpatient management. In brief, LMWH and DOACs are the preferred agents[30]. Late cardiovascular events and all-cause mortality were high in the year following hospitalization for COVID-19. A retrospective follow-up study reported that administration of prophylactic DOAC or dipyridamole in the early post-discharge period improved long-term (393 ± 87 days) cardiovascular outcomes and all-cause mortality in patients with COVID-19[32].

Coronary artery and vascular diseases

High troponin levels and MI are observed due to the increased risk of thrombosis due to pathogenesis of COVID-19 pneumonia. The importance of risk classification (very high, high, moderate, low) in non-ST-elevation MI is given in the European Cardiology Heart Society COVID-19 guideline[33]. If the patient does not have elevated troponin levels and is clinically stable [*i.e.*, no electrocardiogram (ECG) changes, no chest discomfort], conservative treatment is recommended, whereas invasive intervention is among the recommendations in the high-risk group, should complaints continue despite medical treatment. Considering the time to obtain a COVID test and its result will take long, all patients are considered to be COVID-19 (+) in ST-elevation MI (STEMI), the diagnosis-reperfusion time should not exceed 120 minutes. Thrombolytic therapy should be considered in centers where there is no coronary catheterization laboratory[30].

There is scarce data regarding acute limb ischemia (ALI) as a complication related to thrombogenesis. A study conducted in Italy stated that ALI incidences increased during the COVID-19 pandemic period. While most of the ALI occurs in the lower extremity, it is also seen in the upper extremity. Amputation has been needed in these cases despite anticoagulant treatment[34-36].

A 6% increase in the incidence of acute ischemic stroke has been reported in those with COVID-19 infection. In addition to advanced age and comorbid diseases, the progression of acute severe respiratory failure, multiple organ failure, coagulopathy, DIC or cardiac involvement are blamed for this situation and for the increased risk of stroke. It should be noted that the SARS-CoV-2 virus is known to be an agent with neurotropic potential. Authors of multicenter studies indicated that severity of COVID-19 is associated with an increased risk of acute stroke[37]. There is a potential for both hemorrhagic and ischemic stroke due to coagulopathy.

As the clinical severity of the COVID-19 infection increases, the symptoms of the neurological condition worsen as well. In case of doubt, diffusion magnetic resonance imaging should be elicited. Recombinant tissue-type plasminogen activator should be administered intravenously if the indication for administration is verified.

COVID-19 may pave the way for the DIC, which leads to a high death toll. Supportive care, addressing the underlying hypoxic condition, and evaluation for co-infection are important. Diagnosis can be established by calculating the score

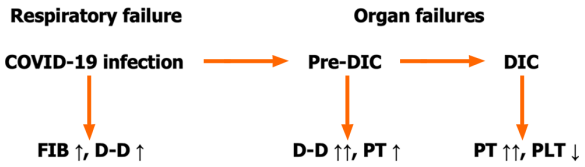

Figure 2 Coagulopathy in coronavirus disease 2019 patients. D-D: D-dimer; DIC: Disseminated intravascular coagulation; FIB: Fibrinogen; PLT: Platelet; PT: Prothrombin time; COVID-19: Coronavirus disease 2019.

from the guide of the International Society on Thrombosis and Haemostasis (ISTH; Table 1)[38].

Bacterial superinfections should be treated aggressively. LMWHs prevent VTE and can change the course of DIC by reducing thrombin formation. Long-term antiplatelet therapy should often be discontinued in DIC patients unless agents are definitely required (recent acute coronary syndrome or stent implantation). Antiplatelet therapy should be individualized in DIC patients. Healing process in DIC depends on endogenous fibrinolysis, which breaks down the thrombus. Blood product support should be considered based on septic coagulopathy occurring in bleeding in DIC in those with COVID-19. In patients with DIC, it is recommended to administer platelet suspension when the platelet count is < 50 × 10^9/L, PT/PTT prolongation, fresh frozen plasma if INR > 1.8, and fibrinogen concentrate or cryoprecipitate when the fibrinogen level is < 1.5 g/L.

MANAGEMENT

Similar to other coagulopathies, the treatment of the underlying condition is the mainstay. In patients with COVID-19 infection, coagulopathy occurs on approximately day 7. Markers indicating coagulopathy (platelet, PT, aPTT, fibrinogen, D-dimer) should be monitored. The American Society of Chest Physicians recommends that patients who developed VTE in the setting of COVID-19 should be anticoagulated for 3 to 6 months[39].

LMWH should be started if there is no contraindication, including in non-critical patients who are at risk of hospitalization. The recommended treatment for prophylaxis is LMWH (enoxaparin) that is preferred to standard heparin. LMWH causes thrombocytopenia less frequently. Oral anticoagulants are not routinely recommended for prophylaxis. LMWHs can be administered intravenously or subcutaneously. When evaluated in terms of drug interactions, they have a lower side effect potential than oral anticoagulants. LMWHs have shorter half-lives[30]. The use of fondaparinux is recommended in case of heparin-induced thrombocytopenia.

Should the patient be admitted to hospital due to an acute thrombotic event in the setting of COVID-19, the use of heparins (LMWH or UFH) should be preferred over a DOAC, with weight-based therapeutic-dose LMWH at twice daily dosing as the preferred agent. For obese patients, the use of weight-adjusted LMWH is recommended. For patients on IV UFH, weight-adjusted and nomogram-based monitoring with anti-Xa levels should be preferred over APTT monitoring [40].

A novel predictive model based on one dimensional convolutional neural networks (1D CNN) was designed to use clinical variables in predicting the survival outcome of COVID-19 patients. The authors of this 1D CNN disclosed that heparin treatment significantly influenced the survival outcome[41].

ISTH COVID-19 Antithrombotic Guidelines do not recommend antiplatelet therapy added routinely in critically ill COVID-19 patients[38]. Nonetheless, addition of antiplatelet agents can be considered in critically ill patients at low bleeding risk, not on therapeutic anticoagulation, and receiving gastric acid suppression[40]. This regimen may include low-dose aspirin or a P2Y12 inhibitor besides standard low-dose heparin prophylaxis, unless the patient has to receive therapeutic anticoagulation. Low-dose aspirin, clopidogrel and other P2Y12 inhibitors were compared with each other in the REMAP-CAP study in critically ill COVID-19 patients as add-on therapies and disclosed no benefit in improving survival. On the other hand, a significant improvement was reported in the secondary outcome of all-cause mortality until discharge[42].

Dipyridamole

Dipyridamole has been approved for use to prevent stroke, among other indications as an antiplatelet drug, which may help improve the clinical outcomes of COVID-19 treatment[43]. Dipyridamole has been suggested to have beneficial effects in the treatment of NETs-evoked digital ischemia[44]. It is generally safe, affordable, and available worldwide. 75 mg twice a day oral administration can be used for its antiplatelet and anti-inflammatory effects, as it reduces the replication of the SARS-CoV-2 virus and antiviral load, in the early stages of the disease / inflammation period. Research disclosed that it is recommended for the first 14 days and may cause hypotension.

Aspirin

All intracellular thrombotic pathways which are essential for viral replication, and resultant inflammatory responses, hypercoagulability, and platelet activation are affected by aspirin treatment. In this way, aspirin is a useful adjunctive treatment of COVID-19. Moreover, Tantry *et al*[45] cited that inhaled formulation with its rapid effects may enhance direct delivery to the lung, which is the key organ damaged in COVID-19 during the critical initial course of the disease, whereas the 150-325 mg/day can be used for long-term treatment to prevent thrombotic event occurrences.

Table 1 International Society on Thrombosis and Haemostasis criteria (> 5 points is indicative of disseminated intravascular coagulation)

Variable	Values	Points
Platelets (× 10^9/L)	> 100	0
	50-100	1
	< 50	2
D-dimer/fibrin degradation products	None	0
	Moderate increase	2
	Severe increase	3
PT	< 3 seconds	0
	3-6 seconds	1
	> 6 seconds	2
Fibrinogen (g/L)	> 1	0
	< 1	1

PT: Prothrombin time.

Administration of 100 mg aspirin in COVID-19 patients reduces the lung-damaging effect of the disease, but there is scarcity of research data. There are reports that patients with multisystem inflammatory syndrome in children (MIS-C) and cardiac involvement associated with COVID-19 benefited from aspirin treatment[46,47]. Medical management of MIS-C and cardiac sequelae have included supportive care, intravenous immunoglobulins, and corticosteroids, as well as immunomodulators, monoclonal antibodies, aspirin, and therapeutic anticoagulation, which have prevented serious outcomes in the majority of pediatric patients[48]. In a cohort study of adult patients with COVID-19, aspirin use at least 7 days before hospitalization or within 24 hours of hospitalization was associated with lower rates of mechanical ventilation (36% *vs* 48%) and ICU admission (39% *vs* 51%)[49].

Thrombolytic therapy

It is given in cases of STEMI on ECG, acute ischemic stroke, and massive PE leading to hemodynamic compromise (systolic blood pressure < 90 mmHg or obstructive shock findings).

Mechanical prophylaxis

In cases where pharmacological prophylaxis is not appropriate, intermittent pneumatic compression devices or compression stockings can be used. It can also be applied as an adjunct to treatment in patients with limited mobility[30].

CONCLUSION

COVID-19 infection can lead to serious conditions. Growing awareness of the medical community on the prothrombotic effect in COVID-19 stimulates more comprehensive diagnostic studies for thrombotic complications. Early administration of antithrombotic drugs will have a beneficial effect in both the prevention and treatment of thrombotic events, especially in non-ambulatory patients. Prophylactic dose anticoagulation is associated with good efficacy and safety in those with COVID-19, including portal vein and splenic artery thromboses.

FOOTNOTES

Author contributions: Karcioglu O and Akman C contribute equally to this study as co-first authors. Karcioglu O, Akman C, and Ozturk GA designed the research study; Karcioglu O, Akman C, and Ozturk GA contributed to original draft preparation, and data curation; Karcioglu O, Akman C, and Ozturk GA analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

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