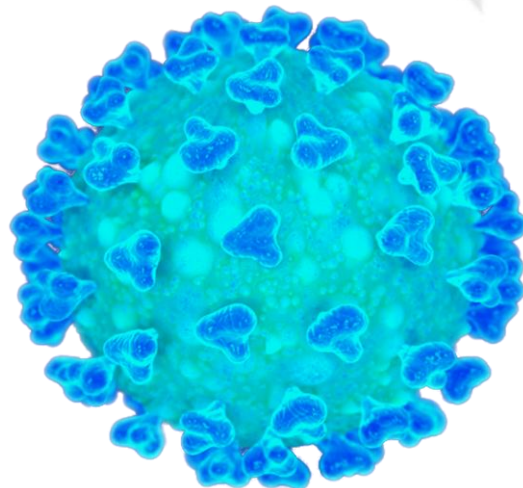


# Thromboembolic risk and anticoagulant therapy in COVID-19 patients

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# Introduction

- ❑ COVID-19 ,caused by (SARS-CoV2) has contributed to significant mortality in several countries with the number of infected cases increasing exponentially worldwide.
- ❑ Emerging data, alongside recent clinical experience, have suggested a high prevalence of venous thromboembolism (VTE) in patients with COVID-19.
- ❑ Development of coagulopathy is one of the key and persistent features which is associated with poor outcomes.

# Introduction

- ❑ The incidence of venous thromboembolism among COVID-19 patients in Intensive Care Unit appears to be somewhat higher compared to that reported in other studies including such patients with other disease conditions
- ❑ Thrombotic complications are common among patients admitted to intensive care unit(ICU) for COVID -19 (reported in 9.5%-47%) particularly pulmonary embolism

# Introduction

- ❑ There are 11 studies that reported on VTE rates in patients diagnosed with COVID-19
- ❑ All 11 were observational reports at high risk for selection bias, and eight of 11 were retrospective
- ❑ In a relevant review of 4 studies the rate of VTE in ICU patients without thromboprophylaxis ranged from 13% to 31% [4].
- ❑ In another meta-analysis of 7 studies including 1,783 ICU patients the mean rate of VTE diagnosis was 12.7%

# Introduction

- ❑ Pulmonary embolism is the most common thrombotic manifestation of COVID-19.
- ❑ Other thromboembolic events reported with lesser extent in COVID 19 include Arterial thrombosis, Myocardial infarction, Ischemic strokes, and Microvascular thrombosis.
- ❑ Thromboembolic complications can occur despite preventive measures

# VTE Prevalence and Incidence

Source	Follow-up Duration	Patients Still Admitted at Study End	Isolated Leg DVT	Isolated Proximal Leg DVT	PE ± DVT	Proximal PE ± DVT	Major Bleeding	Mortality
Cui et al <sup>4</sup>	NR	NR	20/81 (25%)	NR	NR	NR	NR	8/81 (10%)
Klok et al <sup>6,7</sup>	Median, 14 days	65/184 (35%)	1/184 (0.5%)	1/184 (0.5%)	65/184 (35%)	46/184 (25%)	NR	41/184 (22%)
Helms et al <sup>5</sup>	Mean, 9.6 days	100/150 (67%)	3/150 (2.0%)	NR	25/150 (17%)	22/150 (15%)	4/150 (2.7%)	13/150 (8.7%)
Ranucci et al <sup>25</sup>	NR	3/16 (19%)	0	0	0	0	NR	7/16 (44%)
Spiezia et al <sup>12</sup>	NR	NR	5/22 (23%)	NR	NR	NR	NR	NR
Llitjos et al <sup>8</sup>	NR	7/26 (27%)	14/26 (54%) <sup>a</sup>	NR	6/26 (23%) <sup>b</sup>	NR	NR	3/26 (12%)
Lodigiani et al <sup>9</sup>	Median, 18 days	13/61 (21%)	1/61 (1.6%)	Unclear <sup>c</sup>	2/61 (3.3%)	NR	NR	NR <sup>d</sup>
Poissy et al <sup>11</sup>	NR	22/107 (21%)	2/107 (1.9%)	NR	22/107 (21%)	Unclear	NR	15/107 (14%)
Thomas et al <sup>13</sup>	Median, 8 days	28/62 (45%)	0	0	5/62 (8.1%)	4/62 (6.5%)	NR	10/62 (16%)
Middeldorp et al <sup>10</sup>	Median, 15 days	NR <sup>e</sup>	23/75 (31%)	14/75 (19%)	11/75 (15%)	10/75 (13%)	NR	NR <sup>f</sup>
Xu et al <sup>14</sup>	NR	NR	3/15 (20%)	NR	NR	NR	NR	NR



# Pathophysiology of COVID-19 coagulopathy

- ❑ The mechanism for this is likely multifactorial
- Hospitalized COVID-19 patients share similar strong clinical intrinsic and extrinsic risk factors for VTE.
- In fact, it could be argued that the lungs of patients with COVID-19 exhibit all components of **Virchow's triad**: hypercoagulable state, endothelial injury, and stasis of blood flow

# Pathophysiology of COVID-19 coagulopathy

## A hypercoagulable state.

- Triggered by High plasma levels of several proinflammatory cytokines (IL-2, IL-7, granulocyte colony-stimulating factor, IP10, MCP1, MIP1A, and tumor necrosis factor- $\alpha$ )
- **Significant endothelial injury**
- As evidenced by reports of significantly elevated vonWillebrand factor and Factor VIII levels.
- **Stasis of blood flow** :high PEEP,fluid restriction



# Why actions

- ✓ Prevention of thrombosis and microthrombosis in COVID-19 may have huge benefit for patient health and use of scarce health resources
- ✓ The diagnosis of VTE using standardized objective testing is problematic in these patients
- ✓ Investigational therapies for severely ill COVID-19 patients may carry an increased risk for VTE or have drug drug interactions
- ✓ Anticoagulant therapy might improve prognosis

# Laboratory testing for risk stratification

- A VTE risk assessment should be completed for all patients admitted to hospital as per local hospital policy and national guidance.

# Laboratory testing for risk stratification

- Both ISTH-IG and ASH are the only societies that recommend monitoring D-dimer, PTT, platelet count, and fibrinogen levels for risk stratification of critical care
- . ISTH-IG also recommends obtaining D-dimer, PTT, platelet count, and fibrinogen for all patients who present with COVID-19 infection to help guide which patients may require admission.

# Laboratory testing for risk stratification

- Following thresholds for admission to the hospital: D-dimer markedly raised three- to fourfold, prothrombin time prolonged, platelet count  $< 100 \times 10^9$ , and fibrinogen  $< 2.0$  g/L
- Monitoring of parameters after admission may be helpful as more aggressive critical care treatment is warranted and experimental therapies should be considered if parameters worsen.

# Laboratory testing for risk stratification

- For patients in the ICU, trend CBC, PT, PTT and fibrinogen daily (or whenever labs are being drawn if less frequent)
- Trend D-dimer daily (or whenever labs are being drawn if less frequent) if baseline or subsequent >1000 ng/mL)
- **Routine Doppler ultrasonography of the lower extremities or is not recommended**

# Recommendations for venous thromboembolic prophylaxis

- ❖ VTE prophylaxis in non-ICU hospitalized COVID-19 patients:
  - A universal strategy of routine thromboprophylaxis with standard-dose UFH or LMWH should be used after careful assessment of bleed risk, with LMWH as the preferred agent
  - VTE prophylaxis recommendations should be modified based on extremes of body weight, severe thrombocytopenia (i.e. platelet counts of  $50,000 \times 10^9$  per liter or  $25,000 \times 10^9$  per liter) or deteriorating renal function



# Recommendations for venous thromboembolic prophylaxis

- UFH preferred in patients at high bleeding risk and in renal failure (creatinine clearance < 30 mL/min). or needing imminent procedures
- In history of heparin-induced thrombocytopenia, use fondaparinux .
- **Abnormal PT or APTT is not a contraindication**
- When anticoagulants are contraindicated or unavailable, use mechanical thromboprophylaxis (e.g. pneumatic compression devices)

# Dose of thromboprophylaxis

- None of the major societies recommend therapeutic anticoagulation for prevention of thrombotic complications.
- For most , standard prophylactic anticoagulation dose is recommended
- Heparin 5000 units bd or tds s/c, Enoxaparin 40mg od s/c, dalteparin 5000 u daily
- The SCC-ISTH mentions that intermediate LMWH dosing can be considered in in non-critically ill hospitalized patients.

# prophylaxis in ICU hospitalized COVID-19 patients

- Routine thromboprophylaxis with prophylactic-dose UFH or LMWH should be used after careful assessment of bleed risk
- LMWH or UFH over anticoagulant thromboprophylaxis with fondaparinux or a DOAC.
- Intermediate LMWH dosing can be considered in high risk critically ill patients(SCC-ISTH,ACC)

# Duration

- Extended post-discharge thromboprophylaxis should be considered for all hospitalized patients with COVID-19 that meet high VTE risk criteria.
- The duration of post-discharge thromboprophylaxis can be approximately 14 days at least , and up to 30 -45 days
- Either LMWH or a DOAC (i.e., rivaroxaban or abixiban can be used for extended-duration thromboprophylaxis

## ❖ High VTE risk criteria

- advanced age, stay in the ICU, cancer, a prior history of VTE, thrombophilia, severe immobility, an elevated D-dimer ( $>2$  times ULN), and an IMPROVE VTE score of 4 or more.
- None of guidelines recommended aspirin for post-discharge thromboprophylaxis.

# Oral anticouglant

- Some DOACs are approved for in-hospital prophylaxis, these agents should be considered with caution in COVID-19 patients in whom co-administration of immunosuppressant, antiviral and other experimental therapies may potentiate or interfere with DOAC therapy such as sarilumab (Kevzara).
- Apixaban 2.5 mg , rivaroxaban 10 mg ,betrixaban 80-160 mg



# Pt already on anticoagulant

❑ Patients on warfarin (target INR 2.5)\* OR direct oral anticoagulant agent (DOAC) such as dabigatran, apixaban, rivaroxaban, edoxaban for stroke prevention in AF or previous VTE could be switched to a LMWH (ISTH recommendation) as below:

1. Therapeutic dose tinzaparin 175 units/kg (unless contraindicated) and CrCl >30 mL/min
2. Therapeutic dose enoxaparin (if not contraindicated) if CrCl 15-30 mL/min (adjusted to CrCl) or they can continue anticoagulation 3

# Pt already on anticoagulant

- For CrCl <15 mL/min, use enoxaparin 1mg/kg od or 0.5mg/kg bd, rounded to nearest 10mg dose, with anti-Xa monitoring based on a pragmatic approach to minimise blood sampling and patient contact.
- NOTE: Once INR is below the lower end of their target range, start treatment dose LMWH
- .

# Pt already on anticoagulant

- ❑ Patients on warfarin (target INR  $>3.5$ )\* AND/OR metallic heart valve (discuss with Cardiology), switch to:
  - Tinzaparin/enoxaparin as above
  - Monitor peak anti-Xa levels (4 hours after 5th dose and discuss with Haematology Consultant). Aim for anti-Xa levels at the higher end of the therapeutic range.

# Acute thrombosis diagnosis

- ❑ The diagnostic assessment of suspected VTE in hospitalized COVID-19 patients is challenging
- ❑ Imaging studies may be difficult to perform
- ❑ The value of the clinical pre-probability WELLS score is unclear
- ❑ The frequent finding of an elevated D-dimer

❖ **SO**

- clinical assessment with a low threshold for further investigation is recommended

# Acute thrombosis diagnosis

- Practitioners should use standard-of-care objective testing (i.e., CTPA, V/Q scan, MRI venography, Doppler ultrasonography) to diagnose VTE based on clinical index of suspicion.
- A pragmatic approach (i.e., point-of-care bedside ultrasonography or echocardiography) can also be combined with standard-of-care objective testing.

# Acute thrombosis diagnosis

## ❖ Concern for DVT:

- Obtain venous Doppler study, if possible, to evaluate asymmetric limb pain or edema.
- If patient is unable to get US due to concern of staff exposure to COVID-19, and clinical suspicion for DVT is high, it would be suggested to treat pt with full dose anticoagulation (unless contraindicated) over obtaining any diagnostics testing.



# Acute thrombosis diagnosis

❖ **Concern for PE:** This is a challenge .

1. Consider PE in the case of:

- ✓ Marked increase/rising D dimer from priors AND
- ✓ Acute worsening of oxygenation, blood pressure, tachycardia with imaging findings NOT consistent with worsening COVID-19.

# Acute thrombosis diagnosis

- During the COVID pandemic, standard diagnostic evaluation (CTA, ECHO) may not be possible.
  - If possible, obtain US and if + DVT, treat with full dose anticoagulation or
  - If possible, obtain point of care ECHO and if evidence of acute, otherwise unexplained right heart strain, or intra-cardiac thrombous, treat with full dose anticoagulation.

# Acute thrombosis diagnosis

- If patient unable to get US or ECHO due to concern of staff exposure to COVID-19 and clinical suspicion for PE remains high, it would be suggested to treat pt with full dose anticoagulation (unless contraindicated) over obtaining any diagnostics testing.

# Acute thrombosis management

## ❖ Anticoagulation therapy

- ✓ Standard regimens for patients without COVID-19 patients should be used.
- ✓ Initially parenteral therapy are preferred over oral anticoagulant therapy.
- ✓ LMWH or fondaparinux over UFH
- ✓ UFH might be preferred over LMWH or fondaparinux in patients at high bleeding risk (including those with severe renal failure), or in those with overt or imminent hemodynamic decompensation due to PE

# Acute thrombosis management

## ❖ Thrombolysis

- Consider if clinical indication such as STEMI, acute ischemic stroke, or high risk massive PE with hemodynamic instability
- empiric thrombolysis is not recommended unless cardiac arrest (evidence in echo)
- Peripheral thrombolysis recommended over catheter-directed thrombolysis.

# Discharge on

- ☐ Treatment should be for a minimum duration of three months. Longer durations may be required based on clinical assessment.
- ☐ DOACs can be considered if patients are sufficiently well to take oral medication or may be switched to a DOAC as their condition improves, if no invasive procedures are anticipated and they are not on interacting medications



# Withholding anticoagulation

- ❑ It is reasonable to consider the indication of anticoagulation and risk of bleeding for adjusting dose or discontinuation of anticoagulation.
- ❑ Of note, the ISTH-IG, ACF, and ASH mention that abnormal PT or PTT is not a contraindication to thromboprophylaxis
- ❑ Most of the major societal guidelines and recommendations (ISTH-IG, ACF, CDC, and ASH) advise holding anticoagulation in patients who are actively bleeding or severely thrombocytopenic

# Withholding anticoagulation

- ❑ ASH mentions that therapeutic anticoagulation should be held if platelet count  $< 30\text{--}50 \times 10^9/\text{L}$  or fibrinogen  $< 1.0 \text{ g/L}$ , and prophylactic anticoagulation should be held only if platelet count  $< 25 \times 10^9/\text{L}$  or fibrinogen  $< 0.5 \text{ g/L}$
- ❑ Assess bleeding risk against usual criteria, and contraindication of LMWH

# Monitoring of anticoagulation

- ❖ Monitoring of patients with prolonged PTT levels receiving therapeutic anticoagulation
- The ACF is the only society to recommend monitoring anti-Xa levels in patients with prolonged baseline PTT levels receiving therapeutic anticoagulation with UFH.

# Monitoring of anticoagulation

## ❖ Monitoring of patients receiving LMWH

- None of the guidelines recommend or mentions routine monitoring for LMWH anticoagulation, with the exception of ISTH-IG which advises monitoring in patients with severe renal impairment receiving LMWH prophylactic anticoagulation.

# Monitoring of anticoagulation

## ❖ Monitoring of patients receiving therapeutic anticoagulation

- CDC: Per standard of care for patients without COVID-19
- None of the societal guidelines and recommendations make specific monitoring recommendations for patients receiving therapeutic anticoagulation with the exception of the ACF and ACCP which both recommend monitoring anti-Xa levels to monitor UFH due to baseline abnormalities in PTT

# Bleeding and coagulopathy management

## ❖ Bleeding Risk Factors

- Remember to consider bleeding risks when introducing thromboprophylaxis. •
- ✓ Active bleeding (or within 3 months prior to admission)
- ✓ Acquired bleeding disorders
- ✓ Uncontrolled hypertension
- ✓ Concurrent use of anticoagulants
- ✓ Acute stroke



# Bleeding Risk Factors (cont)

- ✓ Thrombocytopenia (platelet counts  $<50 \times 10^9/L$ , checked on admission) – if platelets below 30-50x10<sup>9</sup>/L, consider standard dose anticoagulant prophylaxis in the absence of additional bleeding risk factors and monitor platelet count daily
- ✓ Uncontrolled inherited bleeding disorders (such as haemophilia)
- ✓ Trauma patient\*
- ✓ Neurosurgery, spinal surgery, or eye surgery\*
- ✓ For at least 4-6 hours after surgery

# Bleeding Risk Factors (cont)

- ✓ LP/epidural/spinal anesthesia within the previous 4-6 hours or expected within the next 12 hours
- ✓ Other procedures with high bleeding risk\*
- ✓ PT (prothrombin time) >6 seconds above upper limit of normal (ULN) or APTT (activated partial thromboplastin >6 seconds above ULN and NOT due to coagulopathy
- ✓ CrCl <30mL/min, haematological disorder affecting platelet function (e.g. myelodysplasia (MDS)); platelets >1000x10<sup>9</sup>/L in(MPN)

# DIC score

Parameter	Score
<b>Platelet count</b>	
>100 x 10 <sup>9</sup> /L	0
50-100 x 10 <sup>9</sup> /L	1
<50 x 10 <sup>9</sup> /L	2
<b>D-dimer</b>	
No increase	0
Moderate increase (1-10 times upper limit of normal)	2
Strong increase (>10 times upper limit of normal)	3
<b>Fibrinogen</b>	
>1.0 g/L	0
≤1.0 g/L	1
<b>Prothrombin time prolongation</b>	
<3s	0
3-6s	1
>6s	2
<b>Overt Disseminated Intravascular Coagulation probable (repeat score daily)</b>	≥ 5
DIC not present. Repeat score in 1-2 days	0-4
If a patient on ITU, repeat score daily regardless of score	

**Patient admitted with suspected/confirmed COVID-19 infection and coagulopathy**

**No evidence of bleeding**

Monitor FBC clotting screen (includes fibrinogen) daily. Repeat D-dimer every 1-2 days if clinical deterioration

Thromboprophylaxis with LMWH unless platelets  $<30 \times 10^9/L$ , in which case IPC is essential

If fibrinogen  $\leq 1g/L$  give cryoprecipitate 15mL/kg; adjust dose for fluid overload risk

Do not correct other coagulopathies, but consider vitamin K (phytomenadione) PO/IV 10mg for 1-3 days if PT  $> 6$  seconds above ULN and review

If APTT  $> 6$  seconds above ULN, discuss with Haematology Consultant

**Minor bleeding**

Local haemostatic measures. **AVOID tranexamic acid.** Support platelets if  $<50 \times 10^9/L$

**Clinically relevant non-major bleeding**

If PT/APTT  $> 1.5$  times normal

Consider fresh frozen plasma (FFP) 12-15mL/kg (pragmatically 1 unit every 20kg, 4 units in an adult)

+/- Cryoprecipitate 15mL/kg (two 5 unit pools) or fibrinogen concentrate 3-4g

Maintain fibrinogen  $> 1.5g/L$

Support platelets if  $<50 \times 10^9/L$

Consider surgical, endoscopic or radiological intervention

Prothrombin complex concentrate (PCC) such as Octaplex and Recombinant Factor VIIa (rVIIa) e.g. Novoseven are contraindicated in patients with DIC

**AVOID systemic tranexamic acid**

**Major haemorrhage**

Manage as per WSH protocol for major haemorrhage and discuss with a Haematology Consultant Haematologist

## Pharmacological thromboprophylaxis in patients with coagulopathy

- ❑ Coagulopathy should not prevent the prescribing and administration of pharmacological thromboprophylaxis, unless there is evidence of active bleeding.

# Remember

- ✓ Routine thromboprophylaxis should be used in hospitalized pt with COVID 19
- ✓ Anticoagulant therapy might improve prognosis
- ✓ Aspirin is not recommended for post-discharge thromboprophylaxis.
- ✓ Abnormal PT or PTT is not a contraindication to thromboprophylaxis
- ✓ Clinical assessment with a low threshold for further investigation is recommended



- ❑ There are significant similarities and differences surrounding the major societal recommendations and guidelines regarding risk stratification and management of COVID-19-associated coagulopathy
- ❑ Research on COVID 19 is emerging rapidly. As such, this guidelines are fluid and will be updated regularly.

