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Subsegmental Thrombus in COVID-19 Pneumonia: Immunothrombosis or Pulmonary Embolism? Data Analysis of Hospitalised Patients With Coronavirus Disease

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Received 23 May 2020; received in revised form 9 August 2020; accepted 11 August 2020; online published-ahead-of-print xxx

**Background**

The new coronavirus disease (SARS-CoV-2) has caused more than 350,000 deaths worldwide. Thrombotic complications due to considerable inflammation, cytokine-mediated microvascular damage and pulmonary immunothrombosis formation seem to have emerged as an important issue in people infected with COVID-19.

**Methods**

This study reviewed consecutive symptomatic patients with proven COVID-19 infection admitted to Acibadem University Hospital in Istanbul, Turkey (15 March–25 May 2020). The primary outcome was any venous thromboembolic (VTE) complication. The secondary outcome was the incidence of subsegmental pulmonary embolism with or without deep vein thrombosis (DVT), which represented immunothrombosis development.

**Results**

The mean age was 55.7±17.4 years (range, 29–84); 224 (63.6%) were men. Of those patients, 12 (3.4%) died, 273 (77.5%) were discharged alive and 67 (19.1%) were still hospitalised as of 25 May 2020. Venous thromboembolic events occurred in 58 patients with a cumulative rate of 16.4% during the study period. The surprising discovery was that DVT was not identified in 20 (86.9%) of the 23 patients with subsegmental pulmonary embolism, which corroborated the pulmonary immunothrombosis theory.

**Conclusions**

The high incidence of VTE events suggests an important role of COVID-19-induced coagulopathy. Thus, repeated assessment and optimised treatment are necessary to reduce the occurrence of VTE and prevent fatal pulmonary embolism events. Further studies are needed to investigate the molecular mechanism of this immunothrombosis development.

**Keywords**

COVID-19 • Anticoagulation • Deep vein thrombosis • Immunothrombosis • Pulmonary embolism • Venous thromboembolism

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Please cite this article in press as: Dumantepe M, et al. Subsegmental Thrombus in COVID-19 Pneumonia: Immunothrombosis or Pulmonary Embolism? Data Analysis of Hospitalised Patients With Coronavirus Disease. Heart, Lung and Circulation (2020), https://doi.org/10.1016/j.hlc.2020.08.003
Introduction

The coronavirus disease of 2019 (COVID-19) is a viral illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). It has been extensively reported and now considered a pandemic by the World Health Organization (WHO) [1,2]. COVID-19 infection has a number of important thrombotic and cardiovascular complications, and people with previous cardiovascular disease are at higher risk of mortality from COVID-19 infection [3]. Cytokine-mediated microvascular damage, hypoxia, systemic inflammation, microangiopathy, coagulation pathway activation, and eventual immunothrombosis development have been described as key features of severe COVID-19 [4]. Recent reports have recommended that haemostatic abnormalities – including arterial and venous thrombotic events, myocardial or cerebral infarction – may occur in COVID-19 patients [5]. Furthermore, elevated D-dimer level, thrombocytopenia and prolonged prothrombin time are very frequent in COVID-19-related deaths [4,5].

COVID-19 infection is related to high morbidity and mortality, mainly due to respiratory failure, with microvascular hyaline membrane and pulmonary immunothrombosis formation presumably playing a crucial role. Histopathology of pulmonary immunothrombosis consists of diffuse alveolar damage, hyaline membrane activated pneumocytes, microvascular thromboemboli, capillary congestion, and protein-enriched interstitial oedema [6].

In patients with COVID-19 pneumonia, presenting with disease progression or worsening of respiratory symptoms and significant elevation of D-Dimer levels, more attention should be paid to the occurrence of potential pulmonary embolism (PE) with or without deep venous thrombosis (DVT). Therefore, a contrast-enhanced computed tomography (CT) scan should be performed to detect superimposed acute high-risk PE. In addition, in cases of venous thromboembolism (VTE) suspicion, strict anticoagulation prophylaxis, close laboratory monitoring and interventional treatment, if necessary, are recommended. This study reported the incidence of VTE in COVID-19 patients admitted to the Acibadem University Hospital in Istanbul, Turkey (15 March–25 May 2020), and analysed the occurrence of subsegmental PE rates with or without DVT, which represent pulmonary immunothrombosis formation.

Methods

Patient Population

This retrospective study included symptomatic VTE patients with laboratory-proven COVID-19 infection who had been admitted to Acibadem University Hospital. COVID-19 was confirmed by reverse transcription polymerase chain reaction (RT-PCR) test on a nose/throat swab or sputum sample positive for SARS-CoV-2. The primary outcome was an objectively confirmed diagnosis of VTE events, including DVT and PE. The secondary outcome was the frequency of subsegmental PE with or without DVT. Diagnosis of VTE traditionally relies upon assessment of physical exam findings and imaging with duplex ultrasonography (DUS) for DVT or with CT pulmonary angiography (CTPA) for PE. The cumulative incidence of the composite outcome for DVT and PE complications was separately calculated.

Patient data were retrospectively reviewed from the day of admission to the hospital until hospital discharge, death, transfer to another hospital, or end of data collection. The data collection of demographics, clinical and laboratory findings, treatment methods, and outcome data were recorded. Written informed consent was obtained according to the guidelines of the Institutional Review Board, the local Ethics Committee and the Turkish Ministry of Health, which approved the study.

COVID-19 and Thromboembolic Risk Stratification

Recent publications show that critically ill COVID-19 patients may have many thrombotic risk factors once combined with other infections (bacteria, virus, fungi, etc.), prolonged immobility, obesity, or other comorbidities [7]. Increased occurrence of dehydration, hypotension or sedation in relatively bedridden ICU patients may lead to immobilisation. Furthermore, gastrointestinal complications, which may cause significant dehydration, insufficient fluid volume and haemoconcentration, increase blood viscosity and venous stasis [8]. In addition to that, central venous catheterisation may cause vascular endothelial injury in critically ill COVID-19 patients who need mechanical ventilation, especially with high positive end-expiratory pressure. The combination of these factors may lead to a hypercoagulable state, VTE or even high-risk fatal PE [9].

Statistical Analysis

Statistical analysis was performed with Graphpad Instat software (version 3.1 for Mac; GraphPad Software Inc., La Jolla, CA, USA). Comparisons between continuous variables were performed using Student’s t-test when distribution was normal. Comparison between categorical variables was performed using Pearson’s Chi-squared test or Fisher’s exact test. Discrete variables were reported as numbers with percentages, and continuous data as mean and standard deviation. The rate of VTE events was accompanied by 95% confidence interval (95% CI) and defined as patients diagnosed with a VTE event or discharged or dead. For all analyses, a p-value of <0.05 was considered to represent a statistically significant difference.

Results

This study reviewed symptomatic patients with laboratory proven COVID pneumonia and admitted to the hospital between 15 March–25 May 2020. Of those patients, 12 (3.4%) died, 273 (77.5%) were discharged alive and 67 (19.1%) were still in the hospital on 25 May 2020. Mean age was 55.7±17.4 years (range, 29–84); 224 (63.6%) were men. The baseline characteristics are reported in Table 1. The mean length of...
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Table 1 Baseline clinical and demographic data.

| Characteristic                      | N=352 (Mean±SD or Range) |
|-------------------------------------|--------------------------|
| Age, years (range, 29–84)           | 55.7±17.4                |
| Gender, male:female                 | 224:128                  |
| Body mass index, kg/m² (range, 19–33) | 26.3±2.4               |
| ‘Coagulopathy during admission, n (%): | 51 (14.4%)             |
| Therapeutic anticoagulation at admission, n (%) | 35 (9.9%)          |
| Mean reported symptom duration, days | 4.1±1.2                 |
| Comorbidities, n (%)                | 13 (3.6%)                |
| Active cancer or ongoing treatment  | 91 (25.8%)               |
| Hypertension                        | 59 (16.7%)               |
| Hypercholesterolaemia               | 10 (2.8%)                |
| Recent major surgery                | 64 (18.1%)               |
| Diabetes                            | 26 (7.3%)                |
| History of cancer                   | 28 (7.9%)                |
| Coronary artery disease             | 34 (9.6%)                |
| Chronic obstructive pulmonary disease | 105 (29.8%)           |
| Tobacco use                         | 6 (1.7%)                 |
| Heparin or renal insufficiency      | 10 (2.8%)                |
| Prior venous thromboembolism        | 50 (14.2%)               |
| Troponin I >0.40 ng/mL at presentation | 1.380±230 (range, 670–7240) |
| Mean D-Dimer level, ng/mL           | 1.380±230 (range, 670–7240) |
| Mean fibrinogen level, g/L          | 5.4±1.5 (range, 3.1–7.2) |

Data are numbers of patients, with percentages or ranges in parentheses. Data are expressed mean±standard deviation.

*Defined as spontaneous prolongation of the prothrombin time (PT) >3 s or activated partial thromboplastin time (APTT) >5 s.

hospital stay was 14.9±3.2 days (range, 10–33). DVT was not identified in 20 (86.9%) of the 23 subsegmental PE patients and, in contrast to recent study findings, most of the subsegmental PE cases were diagnosed on the general ward. The distribution of VTE events in COVID-19 patients is reported in Table 2. Mean reported symptom duration was 4.1±1.2 days and 67% of thromboembolic events were diagnosed within the first 24 hours of admission. The mean value of fibrinogen level at admission was 5.4±1.5 g/L (range, 3.1–7.2) and the mean D-dimer value was 1,380±230 ng/mL (range, 670–7,240). Forty-eight (48) (82.7%) patients who had VTE were not receiving any anticoagulant treatment before admission.

Treatment of Venous Thromboembolism

A total of 127 (46.1%) patients admitted to general wards received initial in-hospital thromboprophylaxis with low-molecular-weight heparin (LMWH) or direct anticoagulants (Rivaroxaban, Xarelto®; Bayer Pharma). A prophylactic dosage was used in 105 (82.6%) patients, and 22 (17.3%) received therapeutic dose anticoagulation, including 15 who continued ambulatory treatment for prior VTE or cardiac arrhythmia.

Interventional Treatment of VTE

Twenty-one (21) laboratory proven COVID-19-infected patients with lower extremity DVT were identified. Of the 21 patients with an episode of acute DVT, eight had distal DVT, defined as infrapopliteal thrombosis of the deep venous system, and 13 had COVID-19 in conjunction with iliofemoral DVT, defined as proximal DVT. Thirteen (13) patients who had iliofemoral DVT underwent pharmaco-mechanical thrombectomy with an 8-French Angiojet Zelante percutaneous thrombectomy catheter (Boston Scientific, Marlborough, MA, USA). Complete recanalisation was achieved in 10 patients (77%), and partial recanalisation was achieved in three (23%). The operative data and adjunctive treatments details are reported in Table 3.

During the study period, four COVID-19 pneumonia patients in conjunction with high-risk PE were treated with EKOS™ Acoustic Pulse Thrombolysis (APT) (Boston Scientific). For the remaining 10 intermediate low-risk and 23 low-risk (subsegmental) PE patients, first-line treatment was based on parenteral anticoagulation with LMWH in the absence of contraindication (Enoxaparin 100 IU/kg, twice daily). A 52-year-old patient’s CT scan showed the presence of a bilateral filling defect associated with extensive ground-glass opacifications involving both lung parenchyma (Figure 1). The mean troponin level was 1.38±0.21 ng/dL and the mean pro-B-type natriuretic peptide (pro-BNP) level was 1,945±437 pg/mL for the high-risk PE patients. All patients underwent treatment for bilateral PE and the mean tPA dose was 18.6±1.6 mg. The mean infusion time was 14.5±3.7 hours (range, 11–21). Symptomatic improvement was observed among all surviving patients. The treatment

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infection with severe acute respiratory distress syndrome—associated COVID-19. Globally, on 6 May 2020, there had been 3,557,235 confirmed cases of COVID-19, including 245,150 deaths, reported to the WHO [10]. Most people infected with the COVID-19 virus experience mild to moderate respiratory disease and recover without special treatment. Older people and those with underlying chronic medical problems, such as cardiovascular disease, diabetes, chronic respiratory disease, and cancer, are more likely to develop serious illness [8–10]. Recent observations suggest that acute respiratory failure in COVID-19 is not only driven by the development of respiratory distress syndrome alone, and microvascular thromboembolic complications seem to have emerged as an important issue in patients with COVID-19. It has been postulated that the high mortality observed among COVID-19 patients may be partly due to unrecognised PE and pulmonary in situ thrombosis.

Although, the coagulation system may be activated by many different viruses, COVID-19 infection may be a trigger, especially for VTE. Several pathogenetic mechanisms are involved in VTE, including: endothelial dysfunction, characterised by increased levels of von Willebrand factor; systemic inflammation, by Toll-like receptor activation; and a procoagulatory state, by tissue factor pathway activation [11]. High plasma levels of proinflammatory cytokines were observed in a subgroup of patients with severe COVID-19 infection [12]. The notion that direct activation of the coagulation cascade is caused by a cytokine storm is reasonable. Severe hypoxaemia develops in some patients with COVID-19. Thrombus formation under hypoxic conditions is facilitated both in animal and human models of thrombosis. The vascular response to hypoxia is primarily controlled by hypoxia-inducible transcription factors, whose target genes include several factors that regulate thrombus formation [13].

In the recent autopsy study by Wichmann et al., a high incidence of DVT (58%) was found in patients who died of COVID-19 [14]. They also reported that one-third of the patients had a pulmonary embolism as the direct cause of death. Moreover, diffuse alveolar damage and pulmonary immunothrombosis formation was demonstrated by histology in eight patients (67%). As demonstrated by histopathological studies, pulmonary immunothrombosis formation consists of diffuse alveolar damage, hyaline membrane activated pneumocytes, microvascular thromboemboli and capillary congestion, which all play an important role in respiratory failure and mortality [6,14].

Since the COVID-19 outbreak started, many publications have reported a high incidence of thrombotic complications, including venous and arterial thrombosis [2,3,5,13]. The current results indicate that thromboembolic complications may play an important role in the clinical presentation of COVID-19 infection and already present at the time of initial hospital admission. Although many publications have reported a lower incidence of VTE during COVID-19 infection, it can be hypothesised that the cases were underdiagnosed due to the lack of specific imaging tests being performed. It was found that 67% of thromboembolic events were

### Discussion

Acute respiratory failure and systemic coagulopathy are critical aspects of the morbidity and mortality characterising outcome and adverse events of high-risk PE patients are reported in Table 4. The right: left ventricular (RV:LV) ratio decreased from 1.19±0.12 to 0.87±0.13 at follow-up (p<0.001). The mean RV end-diastolic diameter was reduced from 52.1±4.5 to 39.7±2.6 mm.

There were no systemic bleeding complications for the remaining patients during EKOSTM Acoustic Pulse thrombolysis, but two patients suffered minor access-site bleeding without requiring transfusion or interruption of the procedure. In the high-risk PE group, one patient died from refractory shock and cardiac arrest-related multiorgan failure. Another patient died with PE recurrence 11 days after discharge, despite adequate anticoagulation. The remaining patients with high-risk PE survived, with a mean length of hospital stay of 13.8±4.1 days (range, 11–29).

### Table 3  Operative data and adjunctive treatments of deep vein thrombosis patients.

| Number of Patients | N=13 |
|--------------------|------|
| Mean reported symptom duration, days | 4.1±1.7 |
| Affected limb, left:right | 8:5 |
| Involved venous segments |  |
| Iliac or femoral or popliteal | 3 (23%) |
| Iliac of femoral plus VCI thrombosis | 2 (15%) |
| Iliac or femoral only | 6 (47%) |
| Femoral or popliteal only | 2 (15%) |
| Treatment approach |  |
| PMT | 11 |
| PMT plus CDT | 2 |
| Mean Angiojet device activation time, minutes | 8.1±1.4 (range, 5–11) |
| Mean Angiojet device passes | 2.7±1.1 (range, 2–5) |
| Averaged aspirated fluid (mL) | 750±145 (range, 450–965) |
| Additional procedures |  |
| Common iliac vein stenting | 2 |
| External iliac vein stenting | 1 |
| Balloon angioplasty | 7 |
| Thrombus clearance grade |  |
| Complete (>95% reduction) | 10 (77%) |
| Partial (50–95% reduction) | 3 (23%) |
| Minimal (<50% reduction) | 0 |
| Minor haemorrhage | 2 |
| Major haemorrhage | 0 |
| In-hospital mortality | 0 |

Data are presented as means±standard deviation.
Abbreviations: CDT, catheter-directed thrombolysis; PMT, pharmacomechanical thrombectomy; VCI, vena cava inferior.

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diagnosed within the first 24 hours of admission and were not preventable by in-hospital thromboprophylaxis. Most of the complications reported in other studies occurred in patients admitted to the ICU, even though patients were receiving routine thrombosis prophylaxis. Conversely, in the current patient cohort, most of the subsegmental PE were diagnosed at the general ward setting. Furthermore, the current data analysis highlights that 86.9% of the low-risk (subsegmental) PE were not related with lower extremity DVT. It is believed that the early onset and relatively short time to diagnose VTE events along with this data corroborate the immunothrombosis formation theory.

In a recent study of 191 patients with COVID-19, 50% of those who died had coagulopathy, compared with 7% of survivors. D-dimer levels >1,000 µg/L were associated with a fatal outcome [15]. Similarly, Tang et al. investigated the prognostic factors for mortality of severely infected COVID-19 patients and they found that prolonged prothrombin time, older age and elevated D-dimer levels were associated with higher mortality. Another study concluded that administration of LMWH was associated with lower mortality [16]. It would be interesting to see whether the authors could retrospectively re-analyse their study cohort to find out how many COVID-19 patients were screened for DVT by DUS or screened for PE with CTPA, as in the current study, and assess whether VTE was more frequent among subjects who did not receive LMWH compared with anticoagulated patients. Anticoagulation is crucial for VTE prophylaxis; however, some patients with COVID-19 with high risk of VTE also have a high risk of bleeding due to abnormal coagulation. For these patients, anticoagulation dose and period should be adjusted. Additionally, elastic compression stockings or an intermittent pneumatic compression device should be utilised, especially for immobilised patients.

A recently updated analysis from Klok et al. showed that symptomatic VTEs, which mainly comprised PE, were diagnosed in 27% of COVID-19 patients who received thromboprophylaxis [17]. In addition to that, the prevalence of thrombotic complications was 25% with VTE assessment, according to a Chinese study [18]. All of these values revealed that higher than expected rates of symptomatic VTE events were observed in most of the studies with COVID-19-infected patients.

It is believed that the major weakness of recent studies that reported a lower rate of VTE is that they did not perform systematic DUS and contrast-enhanced CT scans; therefore, they may have underestimated the frequency of VTEs, especially subsegmental PE. The diagnosis of VTE is a challenging situation in patients with COVID-19. Symptoms of PE are often superposed with symptoms of COVID-19 pneumonia; therefore, mild symptoms may be overlooked in a patient with dyspnoea and other respiratory symptoms.

Figure 1 (A and B) Computed tomography pulmonary angiography demonstrates bilateral filling defects in the pulmonary arteries (white arrows); (C and D) Bilateral peripheral extensive ground glass opacities involving lung parenchyma with predominant consolidation in the posterior basal segment of the right lower lobe.
manifestations. On the other hand, diagnosis of DVT in the lower extremity with compression DUS is not always easy to perform in severe COVID-19 patients, especially when physicians primarily focus on respiratory status and do not systematically assess lower extremities for the symptoms of DVT. If the haemodynamic and respiratory conditions suddenly worsen in COVID-19 patients and there are signs of massive or high-risk PE – such as hypotension, RV dysfunction or cardiogenic shock – catheter-directed thrombolytic therapy should be urgently initiated [19]. In critically ill COVID-19 patients with circulatory collapse or cardiopulmonary arrest, extracorporeal membrane oxygenation may be considered in combination with surgical embolec- tomy or catheter-directed treatment as survival treatment options [20,21].

A research letter from Leonard-Lorant et al. reported that of 106 pulmonary CTPA performed for COVID-19 patients over a one-month period, 32 patients (30%) had acute PE [22]. This rate of PE is considerably higher than usually experienced in critically ill patients in the ICU without COVID-19 infection. Furthermore, in another study published from another centre in France, researchers were able to diagnose PE by CTPA in 23% of COVID-19 patients [23]. Active intrapulmonary infusion of thrombolytic drugs has been performed in patients with a high risk of PE and demonstrated good safety and efficiency [24,25]. The current results compare favourably, with complete lysis in 87.5% of the treated patients, with a mean of 14.5 hours thrombolysis time. Despite the fact that most of the patients with COVID-19 have coagulation disorders, there were no major haemorrhagic complications in the APT treatment group. A 39% reduction in the mean pulmonary artery pressure, indicating a reduced RV overload, was obtained with APT. These findings are consistent with other studies, which show that pulmonary artery pressure reduction using catheter-directed thrombolytic treatment is associated with resolution in RV dysfunction [25].

Current radiology guidelines suggest a low-dose, non-contrast chest CT scan to assess the pulmonary status of COVID-19 patients [26,27]. However, many publications have shown that microangiopathy and coagulopathy may occur during COVID-19 infection. Furthermore, these patients have frequent risk factors for pulmonary embolus such as mechanical ventilation, immobility or ICU admission. Therefore, the use of contrast-enhanced CT rather than routine non-contrast CT may be considered for high-risk patients. CTPA may be used for COVID-19 patients with severe clinical features, to evaluate the lung parenchyma and other thromboembolic complications that may result in respiratory distress. The results of the analysis by Barco et al. recommend that a lower threshold of suspicion to perform diagnostic VTE studies may be reasonable, even in the very early phases of COVID-19 infection [28]. The current results showed frequent VTE in patients with COVID-19 infection. Most of the patients with subsegmental PE were diagnosed from the general ward and they had no proven DVT or significant VTE risk factors such as prolonged immobilisation or advanced age. Important clinical markers were available that may explain or be associated with pulmonary embolism, including D-dimer and Pro-BNP.

The main limitations of this study were the relatively small patient population and the retrospective nature. Future prospective studies with larger patient populations may be needed.

### Conclusion

Thrombotic risk assessment and VTE prevention are substantial components of the comprehensive treatment of COVID-19 infection. This treatment approach, which consists of effective anticoagulation, is essential to prevent complications of VTE during COVID-19 infection. Repeated diagnostic assessments and an optimised treatment algorithm are necessary to reduce the occurrence of VTE and prevent fatal high-risk PE in COVID-19 patients. Although the patients had COVID-19 infection, interventional treatment modalities demonstrated safe, promising and reproducible results. In addition, important considerations for the preventive and therapeutic use of antithrombotic agents should be kept in mind to mitigate the thrombotic events in these high-risk patients.

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Table 4  Treatment outcome and adverse events of high-risk pulmonary embolus patients.

| Number of Patients | N=4 |
|--------------------|-----|
| Cardiac troponin level, ng/dL | 1.38±0.21 |
| Pro-BNP level, pg/mL | 1.945±437 |
| Thrombolytic dose, tPA, mg | 18.6±1.6 mg (range, 16–26) |
| Thrombolytic infusion, hours | 14.5± 3.7 (range, 11–21) |
| Mean pulmonary artery pressure, mmHg | 42.6±3.7 |
| Pretreatment | 21.8±2.5+ |
| Miller Index score | 22.1±3.1 |
| Pretreatment | 10.5±1.6+ |
| RV/LV ratio | 1.19±0.12 |
| Pretreatment | 0.87±0.13+ |
| Hospital stay, days | 13.8±4.1 (range, 11–29) |
| Major bleeding | 0 |
| Minor bleeding | 2 |
| 30-d mortality, total | 2 |

Data are presented as means±standard deviation (range). Abbreviations; PAP, pulmonary artery pressure; RV, right ventricle; LV, left ventricle. *p<0.001 preintervention versus postintervention within groups.
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Acknowledgements

Disclosure statement: All authors declare that there is no funding and conflict of interest to be disclosed. The authors also warrant that the article is their original work, has not been previously published and is not under consideration for publication elsewhere.

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HLC3223_proof ■ 8 September 2020 ■ 7/7