The Association Between D-dimer Levels and long COVID

Maryam Nayyerabadi[1], Patrick Prud'homme[2], Thao Huynh[2], Pierre-Olivier Hétu[3], Johanne Poudrier[1], Emilia Liana Falcone[1]

[1]: Montreal Clinical Research Institute (IRCM), [2]: Impact-Quebec COVID-19 (IQ-19), [3]:Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM)

Introduction

- The WHO defines long COVID or post-COVID-19 conditions (PCC) as the presence of at least 1 symptom in individuals with a probable or confirmed history of SARS-CoV-2 infection, at least 3 months from the onset of COVID-19, that cannot be explained by an alternative diagnosis.
- Studies have suggested that PCC may be partly caused by hypercoagulability and the formation of microclots.
- Vascular damage from viral invasion, hypoxia, or inflammation causes coagulation and micro thrombosis while complement system activation can amplify hypercoagulation.
- Individuals with PCC have been shown to have amyloid deposits (microclots) that are more resistant to fibrinolysis and supported by persistent thrombin generation abnormalities post-infection.
- The resulting hypercoagulopathy can lead to complications like vasculitis, pulmonary embolism, cardiac injury and stroke.
- One manifestation of hypercoagulability during the acute COVID-19 phase, especially in ICU-admitted patients, is an elevated D-dimer level.
- D-dimer is a fibrin degradation product of fibrin and its plasma levels increase during coagulation activation and fibrinolysis. Clinically, D-dimer measurement is employed to exclude the diagnosis of venous thromboembolism (VTE).

Aims

Our aims were: 1) to investigate the frequency and evolution of elevated D-Dimer levels in 2 Quebec cohorts of patients with PCC, 2) determine whether elevated D-Dimer levels correlated increased thromboembolic events, and 3) evaluate whether elevated D-dimer levels were associated with increased markers of systemic inflammation.

Methods

- **Included prospective cohorts:**
  - 167 participants from IPCO (IRCM Post-COVID-19) Research Clinic Protocol
  - 114 participants from IQ-19 (IMPACT QUEBEC SARS-CoV-2)

- **Participant Selection:**
  - IPCO Inclusion criteria: Adults (≥ 18 years) residing in Québec with a history of previous SARS-CoV2 infection (confirmed by molecular testing or had symptoms of COVID-19 while residing with an individual who tested positive for COVID-19)
  - IPCO Exclusion criteria: Known pregnancy at time of enrollment.
  - IQ-19 Inclusion criteria: Adults (≥ 18 years) residing in Québec with a history of previous SARS-CoV2 infection exhibiting persistent cardio-pulmonary symptoms (chest pain, dyspnea, syncope, palpitations).

- **Data Collection Period:**
  - IPCO: February 12th, 2021 to March 10th, 2022.
  - IQ-19: May 1st, 2021 to December 31st, 2021.

- **Baseline and Follow-up Assessments:**
  - Baseline: demographics, medical history, acute COVID-19 severity and complications, symptom evaluation, vital signs, physical exam, laboratory tests.
  - Follow-up: interval clinical evaluation, symptom evaluation, vital signs, physical exam, laboratory tests.

- **Laboratory Tests:**
  - CBC, CRP, troponin, NT-pro-BNP (only IQ-19), GFR, INR, PT (only IQ-19), PTT (only IQ-19), D-dimer, panel of 71 cytokines/chemokines (Eve technologies, only IPCO)
  - Follow-up imaging for patients with elevated D-dimer levels: CT angiograms, VQ scans, lower extremity doppler.

- **Data Analysis:**
  - Primary analysis: D-dimer levels using site-specific reference ranges.
  - Sensitivity analysis: Age-adjusted D-dimer values.
  - Correlation analysis between levels of blood D-Dimers, clinical markers of inflammation and cytokines/chemokines.

Results

Figure 1. Longitudinal D-dimer measurements of patients with elevated values on inclusion (IPCO cohort)

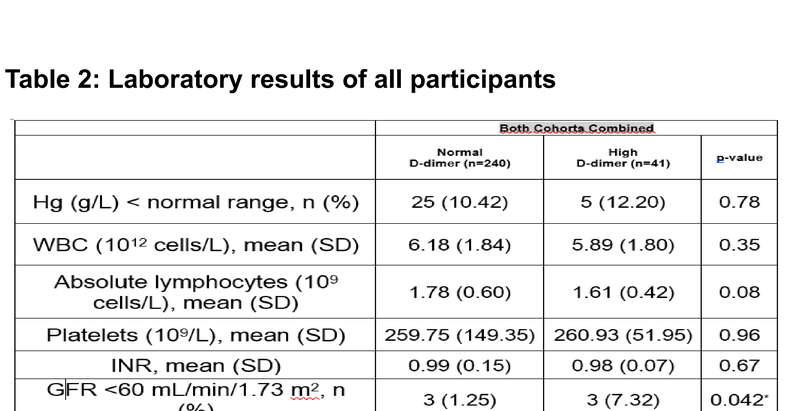

Table 1. Demographic and clinical characteristics of all participants.

SD=standard deviation, BMI=body mass index, WHO=World Health Organization

	Normal D-dimer (n=240)	High D-dimer (n=41)	p-value		Normal D-dimer (n=240)	High D-dimer (n=41)	p-value
Sex, female, n (%)	158 (65.83)	31 (75.61)	0.28	Current pregnancy, n (%)	0 (0.00)	0 (0.00)	>0.99
Age, mean (SD)	47.59 (12.34)	47.74 (12.42)	0.94	Autoimmune disease, n (%)	15 (6.25)	4 (9.76)	0.49
History of smoking, n (%)	73 (30.42)	15 (36.59)	0.46	Liver disease, n (%)	5 (2.08)	0 (0.00)	>0.99
BMI ≥30, n (%)	72 (30.00)	10 (24.39)	0.57	Kidney disease, n (%)	11 (4.58)	3 (7.32)	0.43
WHO severity score ≥4 during acute SARS-CoV-2, n (%)	32 (13.33)	14 (34.15)	0.002**	Thromboembolic disease in the past 6 months, n (%)	0 (0.00)	2 (4.88)	0.022*
History of neoplasm, n (%)	6 (2.50)	2 (4.88)	0.32	On anticoagulant, n (%)	3 (1.25)	0 (0.00)	>0.99
Trauma or surgery in the past 6 months, n (%)	0 (0.00)	0 (0.00)	>0.99	On antiplatelet agent, n (%)	5 (2.08)	2 (4.88)	0.27
Active infection, n (%)	8 (3.33)	5 (12.20)	0.026*	On oral contraceptive, hormone replacement therapy, n (%)	23 (9.58)	1 (2.44)	0.22

Table 2: Laboratory results of all participants

	Both Cohorts Combined		
	Normal D-dimer (n=240)	High D-dimer (n=41)	p-value
Hg (g/L) < normal range, n (%)	25 (10.42)	5 (12.20)	0.78
WBC (10^{12} cells/L), mean (SD)	6.18 (1.84)	5.89 (1.80)	0.35
Absolute lymphocytes (10^9 cells/L), mean (SD)	1.78 (0.60)	1.61 (0.42)	0.08
Platelets (10^9/L), mean (SD)	259.75 (149.35)	260.93 (51.95)	0.96
INR, mean (SD)	0.99 (0.15)	0.98 (0.07)	0.67
GFR <60 mL/min/1.73 m^2, n (%)	3 (1.25)	3 (7.32)	0.042*
CRP (mg/L) >10, n (%)	14 (5.83)	3 (7.32)	0.72
Troponin (ng/mL) >normal range, n (%)[2]	1 (0.42)	1 (2.44)	0.27

Table 3: Age-adjustment levels, two-fold increased levels, clinical presentations, imaging and outcome of participants with high D-dimer level

	IPCO Cohort	IQ-19 Cohort	Both Cohorts Combined
D-dimer higher than age-adjusted cut-off point, n (%)	25(83.33)	11 (100)	36(87.80)
D-dimer higher than 2 X normal range, n (%)	7(23.33)	1(9.09)	8(19.51)
Acute VTE symptoms at time of study visit, n (%)[1]	0(0)	0(0)	0(0)
Patients having undergone imaging for VTE ≥4 weeks after COVID-19 diagnosis, n (%)[2]	9(30)	1(9.09)	10(24.39)
Patients diagnosed with VTE ≥4 weeks after COVID-19 diagnosis, n (%)	0(0)	0(0)	0(0)

- **There was no significant correlation between D-dimer levels and the levels of any of the 71 plasma cytokines and chemokines measured.**

Conclusions

- 18 % of patients with PCC had elevated D-Dimer levels on inclusion in the IPCO cohort, vs. 9.6% of patients in the IQ-19 cohort. These frequencies are comparable to previous studies[4,6].
- D-dimer levels in patients with PCC can fluctuate significantly over time and do not necessarily correlate with PCC symptom severity or VTE symptoms.
- Elevated D-Dimer levels in our cohorts were not associated with thromboembolic events, suggesting that another process such as viral persistence may be contributing to D-Dimer elevations. Standard clinical VTE guidelines should continue to guide the management of patients with PCC.
- Elevated D-Dimer levels were not associated increased levels of evaluated markers of systemic inflammation, suggesting that further studies are needed to better understand the mechanistic underpinnings of D-dimer elevations in patients with PCC.

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