CANCERWEEK
ΟΛΕΣ ΟΙ ΕΞΕΛΙΞΕΙΣ ΓΥΡΩ ΑΠΟ ΤΟΝ ΚΑΡΚΙΝΟ

Αιματολογικές διαταραχές της λοίμωξης COVID-19

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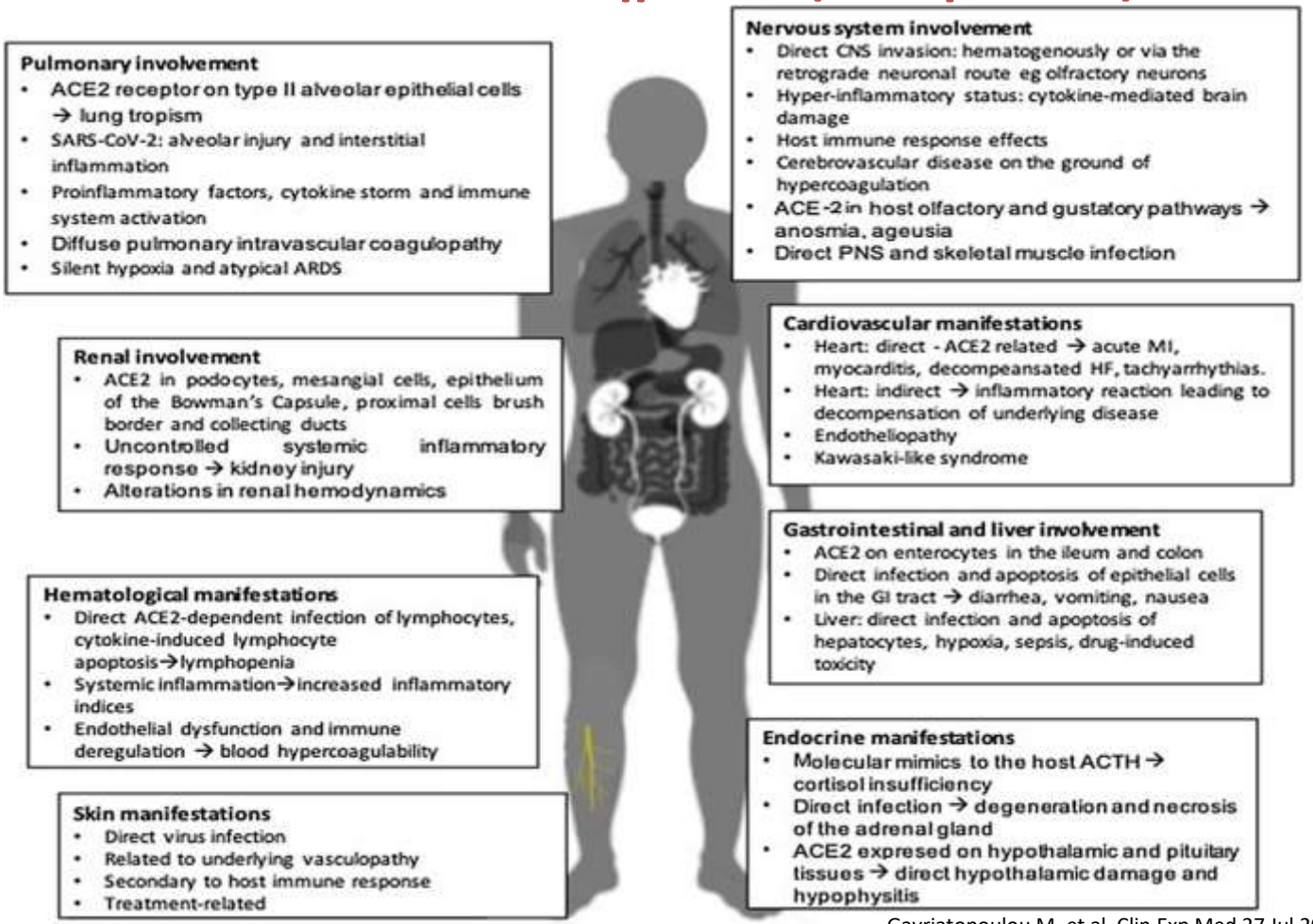
Δήλωση συμφερόντων

Δηλώνω ότι **δεν έχω** (προσωπικά ή ως μέλος εργασιακής /ερευνητικής ομάδας ή μέλος της οικογένειάς μου) οποιοδήποτε *οικονομικό ή άλλου είδους όφελος* από τις εταιρείες /επιχειρήσεις που διοργανώνουν/χρηματοδοτούν την άνω εκδήλωση, κατά τη διάρκεια των τελευταίων 4 ετών.

COVID-19 – Συστηματικές εκδηλώσεις



Gavriatopoulou M, et al. Clin Exp Med 27 Jul 2020 [epub ahead of print]

Αιματολογικές Διαταραχές στη λοίμωξη COVID-19

Λεμφοπενία

First author (year)	Sample size	Main findings
Guan (2020)	1099	**Lymphocytopenia was present in 83.2% of patients on admission**. 92.6% (50/54) of patients with the composite primary endpoint (**admission to an intensive care unit, use of mechanical ventilation, or death**) presented with lymphocytopenia vs. 82.5% (681/825) of patients without the primary endpoint (p=0.056). **Severe cases** presented lymphocytopenia more frequently (96.1%, 147/153) vs. non-severe cases (80.4%, 584/726); p<0.001
Huang (2020)	41	85% (11/13) of patients **needing ICU care** presented low lymphocyte count vs. 54% (15/28) of patients that did not need ICU care (p=0.045).
Wang (2020)	138	**ICU cases presented with lower lymphocyte count** (median:0.8, IQR: 0.5-0.9) vs. non-ICU cases (median: 0.9, IQR: 0.6-1.2); p=0.03. Longitudinal decrease was noted in **non-survivors**.
Wu (2020)	201	**Lower lymphocyte count was associated with ARDS development** (HR=0.37, 95%CI: 0.21-0.63, p<0.001 in the incremental model)
Bhatraju (2020)	24 ICU patients	Lymphocytopenia was common (**75%** of patients), with a median lymphocyte count of 720 per mm^3 (IQR: 520 to 1375).

Terpos E, Ntanasis-Stathopoulos I et al. Am J Hematol. 2020 Jul;95(7):834-847.

Λεμφοπενία στην COVID-19 -Αιτιολογία

- **Lymphocytes express the ACE2 receptor** [1] thus SARS-CoV-2 may directly infect those cells and ultimately lead to their lysis.
- The **cytokine storm** is characterized by markedly increased levels of interleukins (mostly IL-6, IL-2, IL-7, granulocyte colony stimulating factor, interferon-γ inducible protein 10, MCP-1, MIP1-a) and tumor necrosis factor (TNF)-alpha, which may promote **lymphocyte apoptosis**. [2,3]
- Substantial cytokine activation may be also associated with **atrophy of lymphoid organs**, including the spleen, and further impairs lymphocyte turnover.[4]
- Coexisting **lactic acid acidosis**, which may be more prominent among cancer patients who are at increased risk for complications from COVID-19,[5] may also **inhibit lymphocyte proliferation.**[6]

1. Xu H et al. Int J Oral Sci 2020 24; **12**(1)**:** 8.
2. Singh S et al. PLoS One 2014; **9**(5)**:** e98020.
3. Liao YC et al. J Immunol 2002 ; **169**(8)**:** 4288-4297.
4. Chan JF et al. Clin Infect Dis 2020 Mar 26.
5. You B et al. Lancet Oncol 2020 Mar 25.
6. Fischer K et al. Blood **109**(9)**:** 3812-3819.

Θρομβοπενία

First author (year)	Sample size	Main findings
Guan (2020)	1099	**Thrombocytopenia was present in 36.2% of patients on admission**. **Severe cases** presented thrombocytopenia more frequently (57.7%, 90/156) vs. non-severe cases (31.6%, 225/713); p<0.001
Wang (2020)	138	No significant difference (p=0.78) was noted in platelet count between ICU cases (median:142, IQR: 119-202) vs. non-ICU cases (median: 165, IQR: 125-188); p=0.78.
Wu (2020)	201	Platelet counts **did not differ between patients with ARDS** vs. those without ARDS (difference: -4.00, 95%CI: −27.00 to +20.00, p=0.73). Accordingly, no significant difference was noted in dead vs. alive ARDS patients (p=0.10).
Fan (2020)	69	Low platelets were not associated with ICU care either at admission (p=0.67) or as a nadir during hospital stay (p=0.69)
Yang (2020)	52 critically ill patients	Platelet count noted in non-survivors was 191 (63) and 164 (74) in survivors; no statistical tests were presented.
Zhou (2020)	191	**Median platelet count was lower in non-survivors (165.5, IQR: 107.0–229.0) vs. survivors** (220.0, IQR: 168.0–271.0), p<0.0001
Lippi (2020)	9 published studies	Platelet count was significantly **lower in patients with more severe COVID-19** (WMD -31×10^9/L, 95% CI, -35 to -29×10^9/L), with very high heterogeneity

Terpos E, Ntanasis-Stathopoulos I et al. Am J Hematol. 2020 Jul;95(7):834-847.

Κυτταροκίνες Φλεγμονής

- **More severe cases** showed a more marked increase compared with the non-severe ones (81.5% versus 56.4% for **CRP**, 13.7% versus 3.7% for **procalcitonin** and 58.1% versus 37.2% for **LDH**).
- In a retrospective cohort study including 191 patients with COVID-19 from Wuhan, China, **non-survivors**, as compared with survivors, presented more often with high **LDH** ($p<0.0001$), high **procalcitonin** ($p<0.0001$), increased serum **ferritin** levels ($p=0.0008$) and elevated **IL-6** ($p<0.0001$).
- Higher **CRP** has been linked to unfavorable aspects of COVID-19 disease, such as **ARDS development, higher troponin-T levels and myocardial injury, and death**.
- A meta-analysis of four published studies showed that increased **procalcitonin** values were associated with a nearly 5-fold higher risk of severe infection (OR=4.76; 95% CI: 2.74-8.29, I^2=34%) .
- Wu et al. showed that higher serum **ferritin** was associated with **ARDS** development (HR=3.53, 95%CI: 1.52-8.16, p=0.003)

Terpos E, Ntanasis-Stathopoulos I et al. Am J Hematol. 2020 Jul;95(7):834-847.

Διαταραχές Πηκτικότητας

Elevated D-dimers

First author (year)	Sample size	Main findings
Guan (2020)	1099	Patients with the composite primary endpoint (**admission to an intensive care unit, use of mechanical ventilation, or death) presented with elevated D-dimer** more frequently: 69.4% (34/49) vs. 44.2% (226/511; p=0.001). Accordingly, **severe cases** presented elevated D-dimer more frequently (59.6%, 65/109) vs. non-severe cases (43.2%, 195/451); p=0.002
Wang (2020)	138	**ICU cases presented with higher D-dimer level** (median:414, IQR: 191-1324) vs. non-ICU cases (median: 166, IQR: 101-285); p<0.001. Longitudinal increase was noted in non-survivors.
Wu (2020)	201	Higher D-dimer level was associated with **ARDS development** (HR=1.03, 95%CI: 1.01-1.04, p<0.001) and **poor survival** (HR=1.02, 95%CI: 1.01-1.04, p=0.002) in the incremental models.
Zhou (2020)	191	Higher D-dimer was associated with **higher odds of death** (OR=18.42, 95%CI: 2.64–128.55; p=0.0033)
Lippi (2020)	553 (4 published studies)	**D-dimer values were considerably higher in COVID-19 patients with severe disease than in those without (WMD= 2.97mg/L; 95% CI: 2.47–3.46 mg/L).**

Terpos E, Ntanasis-Stathopoulos I et al. Am J Hematol. 2020 Jul;95(7):834-847.

Διαταραχές Πηκτικότητας – Αντιπηκτικό Λύκου

Table 1. Demographic and Clinical Characteristics and Laboratory Findings in 35 Patients with Covid-19 and a Prolonged aPTT.*

Characteristic or Finding	Value in Patients (N=35)	Reference Range
Mean age (95% CI) — yr	56.6 (18.6–83.4)	—
Male sex — no. (%)	24 (69)	—
Taking oral anticoagulant at admission — no.	0	—
Thrombosis status — no. (%)		
Arterial	0	—
Venous, confirmed	1 (3)	—
Venous, suspected	1 (3)	—
Mean (95% CI) values on coagulation assay		
aPTT — sec	35.5 (30.0–54.6)	21–29
PT — sec	11.8 (10.2–14.1)	8.8–11.7
aPTT 50:50 — sec	32.6 (29.0–38.0)	21–29
Factor VIII level — IU/dl	199 (100–369)	52–153
Factor IX level — IU/dl	125 (62–205)	58–138
Factor XI level — IU/dl	81 (37–144)	58–148
Factor XII level — IU/dl	55 (26–100)	52–164
Anti–factor Xa heparin activity on heparin assay — no. (%)		
<0.05 IU/ml	7 (20)	—
0.05–0.19 IU/ml	7 (20)	—
0.20–0.40 IU/ml	14 (40)	—
0.41–0.50 IU/ml	5 (14)	—
>0.50 IU/ml	2 (6)	—
LA test result†		
Positive — no./total no. (%)	31/34 (91)	—
DRVVT — no.	7	—
LA-sensitive aPTT — no.	6	—
Both tests positive — no.	18	—
Negative — no./total no. (%)	3/34 (9)‡	—

* The abbreviation aPTT denotes activated partial-thromboplastin time, CI confidence interval, DRVVT dilute Russell's viper-venom time, LA lupus anticoagulant, and PT prothrombin time.
† Assays for lupus anticoagulant were performed with 34 of the specimens.
‡ The 3 specimens that were negative for lupus anticoagulant had levels of factor XII that were deemed sufficient to prolong the aPTT.

Bowles L. et al. N Engl J Med 2020 May 5; doi: 10.1056/NEJMc2013656

Αιματολογικά Ευρήματα σε Νοσηλευόμενους Ασθενείς

	Normal range	Non-ICU patients (n=223)	ICU patients (n=77)	P
Age (years)	NA	66 (53-76)	62 (53-70)	<0.040
PT (sec)	<13.6 sec	14.0 (13.3-15.0)	14.6 (13.8-15.7)	0.002
Fibrinogen (g/L)	1.8 – 4.0	5.9 (4.7-7.0)	6.9 (6.0-7.7)	<0.0001
D-dimer (ng/mL)	<500 for age under 60 years	1228 (650-2031)	2168 (1074-4219)	<0.0001
Antithrombin (%)	80 - 120	96 (84-107)	87 (75-99)	0.0001
Protein C (%)	70 - 130	97 (79-112)	89 (72-100)	0.005
Red blood cells (x10^9/L)	4.0 - 5.2	4.3 (4.0-4.8)	4.2 (3.5-4.6)	0.028
Hemoglobin (g/dL)	12.0 - 16.0	12.6 (11.3-13.7)	11.9 (10.1-13.2)	0.005
Hematocrit (%)	35.0 - 47.0	37.2 (34.2-40.3)	34.8 (30-38.7)	0.002
Platelets (x10^9/L)	150 - 400	240 (176-307)	211 (154-261)	0.004
White blood cells (x10^9/L)	4.0 - 10.0	6.7 (5.1-8.8)	7.9 (6.1-10.8)	0.007
Neutrophils (x10^9/L)	1.5 - 7.0	5.0 (3.4-6.7)	6.6 (4.9-9.6)	0.0001
Lymphocytes (x10^9/L)	1.5 - 4.0	1.04 (0.70-1.49)	0.74 (0.52-1.10)	0.0001
Monocytes (x10^9/L)	0.1 - 1.0	0.49 (0.30-0.69)	0.31 (0.20-0.48)	<0.0001
Eosinophils (x10^9/L)	0.03 - 0.7	0.02 (0-0.07)	0.01 (0-0.05)	0.126
Basophils (x10^9/L)	<0.1	0.01 (0.01-0.02)	0.01 (0.01-0.02)	0.290

Gerotziafas Γ, et al. Thrombosis & Hemostasis 2020 (in revision)

COMPASS-COVID-19 risk assessment model (RAM) for prediction to ICU admission

Predictors	OR (95%CI)	p
Obesity (BMI≥30 versus BMI<30 kg/m^2	6.56 (2.98-14.46)	<0.001
Gender Male versus female	2.59 (1.29-5.21)	0.007
DIC ISTH score ≥5 versus <5	2.58 (1.07-6.21)	0.034
Lymphocytes (x10^9/L) <1 versus ≥1	2.21 (1.17-4.19)	0.015
Hemoglobin (g/dL) <11 versus ≥11	2.25 (1.13-4.48)	0.021

COMPASS-COVID-19 RAM	
Predictors for risk of worsening disease	Score
Obesity (BMI>30)	19
Male gender	10
DIC-ISTH score ≥5	9
Lymphocytes <10^9/L	8
Hemoglobin <11 g/dL	8
Total ≥ 18 : high risk for worsening disease	– –

Validation of the COMPASS-COVID-19 risk assessment model

The validation cohort included 120 patients stratified at the C-group (n=89) and the W-group (n=31).

The score at 18 points cut-off value identified as high risk for disease worsening 90% of patients at the W-group and 38% of the patients at the C-group.

The sensitivity and the specificity of the score were 94% and 58% respectively and the negative and positive predictive values were 96% and 45% respectively.

Gerotziafas G, et al. Thromb Haemost. 2020; in revision

ISTH score for overt DIC

Factors	Points	ISTH Overt DIC
Platelet counts	3	–
	2	$<50 \times 10^9$/L
	1	$\geq 50, <100 \times 10^9$/L
FDP	3	Strong increase
	2	Moderate increase
	1	–
Prothrombin time[a]	2	≥6 seconds
	1	≥3, <6 seconds
Fibrinogen	1	<100 g/mL
SIRS score	1	–
Points required to be criteria positive		5 points

Wada H et al. doi: 10.1111/jth.12155.

VTE risk – Padua Prediction Score

Active cancer (metastases and/or chemoradiotherapy in the previous 6 months)	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Bedrest for ≥3 days	3
Thrombophilia	3
Recent (≤1 month) trauma and/or surgery	2
Elderly age (≥70 years)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥30 kg/m^2)	1
Ongoing hormonal treatment	1

Barbar, et al. Journal of Thrombosis and Haemostasis: JTH 2010, 8 (11): 2450-7

VTE risk – Padua Prediction Score

	Padua Prediction Score <4 (n=619)	Padua Prediction Score ≥4 (n=407)	OR (95% CI)*	p value*
High bleeding risk†	7 (1%)	44 (11%)	8·51 (3·74–19·35)	<0·0001
Intensive care unit admission	5 (1%)	47 (12%)	12·82 (5·00–32·91)	<0·0001
Mechanical ventilation	6 (1%)	57 (14%)	13·17 (5·56–31·19)	<0·0001
Mortality	0 (0%)	14 (3%)	–	–
Age, years	42 (33–55)	52 (40–64)	–	<0·0001
≥70‡	19 (3%) of 559	56 (15%) of 384	4·85 (2·83–8·31)	<0·0001

Data are n (%) or median (IQR). *Adjusted by age. †Bleeding risk was evaluated according to a previous study.[7] ‡A threshold of 70 years was selected on the basis of the Padua Prediction Score and age data were not available for all patients.

Table: Bleeding score, outcomes, and age of patients with COVID-19 with high and low risk of venous thromboembolism according to the Padua Prediction Score

Wang T et al. Lancet Haematol. 2020 May;7(5):e362-e363.

Full Length Article

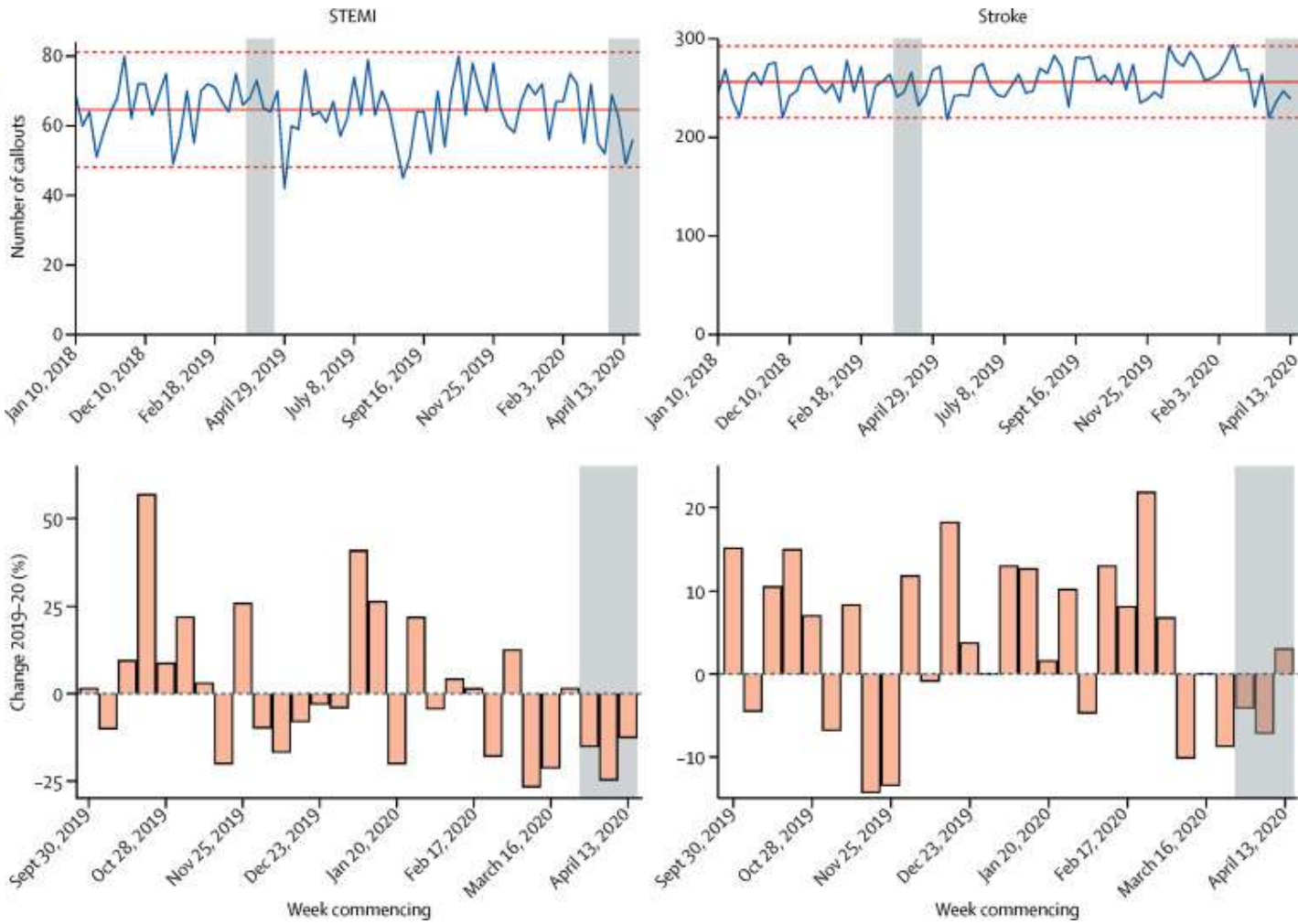
Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy

Corrado Lodigiani[a,b,*], Giacomo Iapichino[c], Luca Carenzo[c], Maurizio Cecconi[b,c], Paola Ferrazzi[a], Tim Sebastian[d], Nils Kucher[d], Jan-Dirk Studt[e], Clara Sacco[a], Bertuzzi Alexia[f], Maria Teresa Sandri[g], Stefano Barco[d,h], on behalf of the Humanitas COVID-19 Task Force

Table 3
Venous and arterial thromboembolic events in hospitalized COVID-19 patients.

	Intensive care unit			General ward			Total		
Thromboembolic events	n	% of closed cases (n = 48)	% of imaging tests performed*	n	% of closed cases (n = 314)	% of imaging tests performed*	n	% of closed cases (n = 362)	% of imaging tests performed
At least one thromboembolic event	8	16.7% (95%CI 8.7%–29.6%)	–	20	6.4% (95%CI 4.2%–9.6%)	–	28	7.7% (95%CI 5.4%–11.0%)	–
VTE	4	8.3%	22%	12	3.8%	46%	16	4.4%	36%
PE (± DVT)	2	4.2%	25%	8	2.5%	36%	10	2.8%	33%
Isolated pDVT	1	2.1%	7%	3	1.0%	44%	4	1.1%	21%
Isolated dDVT	0	–	–	1	0.3%	13%	1	0.3%	13%
Catheter-related DVT	1	2.1%	50%	0	–	–	1	0.3%	50%
Ischemic stroke	3	6.3%	–	6	1.9%	–	9	2.5%	–
ACS/MI	1	2.1%	–	3	1.0%	–	4	1.1%	–

Emergency ambulance services for heart attack and stroke during UK's COVID-19 lockdown



Holmes JL, et al. Lancet 2020 May 23;395(10237):e93-e94

Θρομβωτικά επεισόδια σε ασθενείς με SARS-CoV-2 Αιτιολογία

Coagulopathy

- Severely infected COVID-19 patients might be at risk of thromboembolic events from COVID-associated coagulopathy.
- Hospitalized COVID-19 patients have been reported to have increased coagulation activity, marked by increased D-dimer concentrations.
- Patients with both cerebrovascular disease and SARS-CoV-2 had higher D-dimer levels than SARS-CoV-2 patients without cerebrovascular disease (6.9 mg/L vs 0.5 mg/L, $P < .001$).

Lodigiani C, et al. Throm Res. 2020 Jul;191:9-14.
Guan WJ, et al. N Engl J Med 2020; 382(18);1708–1729.
Zhou F, et al. Lancet 2020; 395(10229):1054–1062.

Θρομβωτικά επεισόδια σε ασθενείς με SARS-CoV-2
Αιτιολογία (2)

Antiphospholipid antibodies

- Lupus anticoagulants and prolonged aPTT are frequently found in hospitalized COVID-19 patients, in whom the prevalence of lupus anticoagulant is 45% to 91%.
- A case series reported the finding of antiphospholipid antibodies in 3 critically ill COVID-19 patients with bilateral cerebral infarcts in multiple vascular territories.
- This case series suggested an **acquired antiphospholipid syndrome** was the underlying etiology, but unlike in the reported series of large-artery strokes in 5 young patients, these patients with antiphospholipid antibodies were over 60 years of age.
- Since their clinical significance is not yet known, these laboratory tests **should not be routinely checked in COVID-19 patients without thrombosis.**

Bowles L. et al. N Engl J Med 2020 May 5; doi: 10.1056/NEJMc2013656
Zhou F, et al. Lancet 2020; 395(10229):1054–1062.

Θρομβωτικά επεισόδια σε ασθενείς με SARS-CoV-2
Αιτιολογία (3)

Vasculitis

- Postmortem histologic analysis of 3 COVID-19 patients revealed lymphocytic endotheliitis within the endothelial cells of multiple organs, including the lungs, heart, kidneys, small intestine, and liver.
- Endotheliitis can cause microcirculatory vasoconstriction and endothelial dysfunction with consequent ischemia and apoptosis.
- Direct viral infection of endothelial cells via ACE-2 receptors, along with the host inflammatory response, may contribute to the wide spectrum of clinical sequalae of COVID-19.
- Histopathologic analysis of the central nervous system is needed to determine if SARS-CoV-2-related central nervous system vasculitis can occur due to lymphocytic endotheliitis.

Varga Z, et al. Lancet 2020; 395(10234):1417–1418.

Θρομβοπροφύλαξη στην COVID-19

All in-patients should have VTE risk assessment : on admission and if condition changes
All in-patients should have LMWH prophylaxis with enoxaparin, irrespective of mobility, unless contraindicated.
Choose the dose of prophylactic LMWH according to body weight and renal function.
Mild prolongation of PT and/or APTT only, if due to COVID coagulopathy, is NOT a contraindication to LMWH prophylaxis.
Do not administer prophylactic LMWH if platelets < 25 or Clauss fibrinogen < 0.8g/l or active bleeding occurring.
If there is an unexplained 50% fall in platelet count in the absence of worsening coagulopathy, consider HIT (Heparin Induced Thrombocytopenia). Carry out a 4Ts score and seek haematology advice.
Do not give additional prophylactic LMWH to patients continuing oral anticoagulation prescribed prior to admission.

NHS Guidance on Covid Coagulopathy. Version 2.4 01/05/2020

Συμπεράσματα

- Λεμφοπενία και θρομβοπενία αποτελούν συχνές διαταραχές της γενικής αίματος στη λοίμωξη COVID-19 και σχετίζονται με σοβαρή μορφή της νόσου και αυξημένη θνητότητα
- Υπερπηκτικότητα χαρακτηρίζει τις σοβαρές μορφές της νόσου
- Θρομβώσεις και ΔΕΠ αποτελούν επιπλοκές της COVID-19
- Οι **LMWH** αποτελούν “standard of care” για τους νοσηλευόμενους ασθενείς με COVID-19

Ευχαριστώ για την προσοχή σας