Hematology profile and Biomarker for COVID 19

Diagnosis and Prognosis

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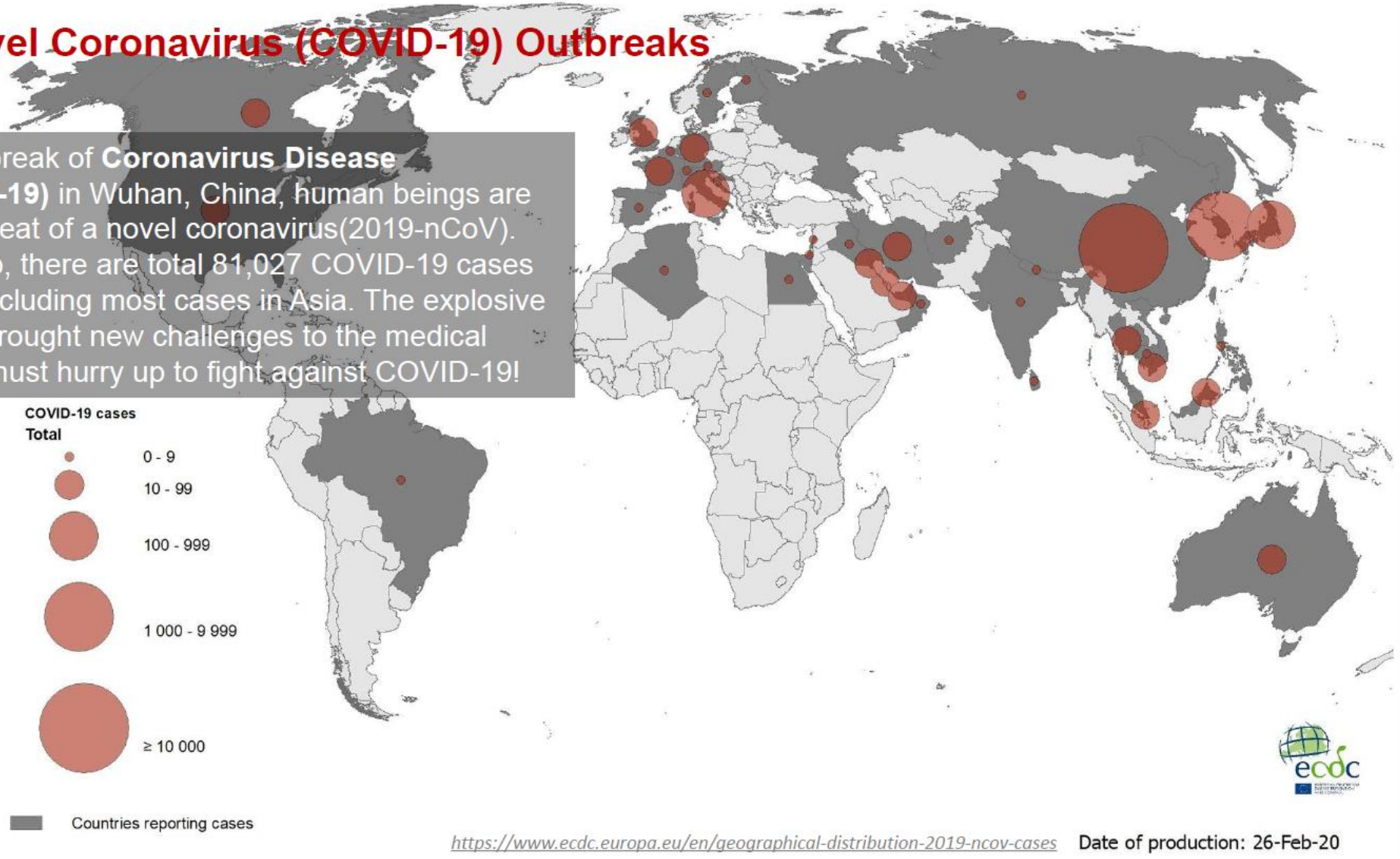
Novel Coronavirus (COVID-19) Outbreaks

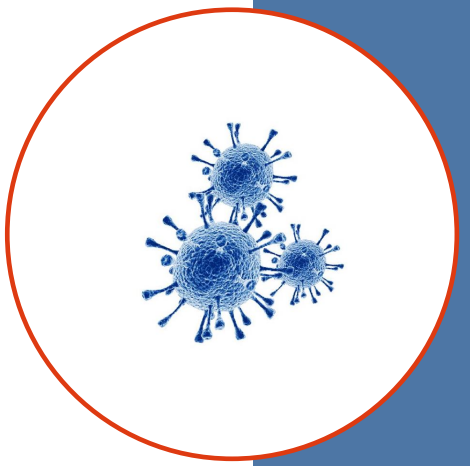
With the outbreak of **Coronavirus Disease 2019(COVID-19)** in Wuhan, China, human beings are facing the threat of a novel coronavirus(2019-nCoV). Until 26th Feb, there are total 81,027 COVID-19 cases worldwide, including most cases in Asia. The explosive growth has brought new challenges to the medical system, we must hurry up to fight against COVID-19!



https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases Date of production: 26-Feb-20

Overview

- COVID-19 is a systemic infection with a significant impact on the hematopoietic system and hemostasis.
- Lymphopenia may be considered as a cardinal laboratory finding, with prognostic potential.
- Neutrophil/lymphocyte ratio may also have prognostic value in determining severe cases.
- Blood hypercoagulability is common among hospitalized COVID-19 patients. Elevated D-Dimer levels are consistently reported, whereas their gradual increase during disease course is particularly associated with disease worsening.



Routine blood test support COVID-19 management

Blood test for COVID-19

A. WBC: normal or increased (24-30% of 73 patients)[3,4]

B. Lymphocyte count and percentage : decreased(63% of 41 patients)[3]

C. CRP: increased (86% of 73 patients)[4]

D. Eosinophil count: decreased[5]

CBC results from COVID-19 patients & healthy people[5]

	COVID-19 patients (median)	Healthy (median)
Case number	38 patients	120 healthy check-ups
Lymphocyte(10^9/L)	0.87	2.13
Lymphocyte (%)	19.5	33.7
Eosinophil (10^9/L)	0.0061	0.1417
Eosinophil(%)	0.13	2.16
CRP(mg/L)	61.8	<10

- **Most patients showed decreased Lymphocyte count, increased CRP and decreased Eosinophil count.**
- **CBC test is primary method to screen suspected COVID-19.**
- **Routine blood test is fast and fully automated analyzing method to avoid cross contamination, low cost.**

3. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020 Jan 24.
4. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Jan 30.
5. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res. 2020 Feb 6.

Incubation period, usually ranging from 1 to 14 days, of the disease (non-specific symptoms)

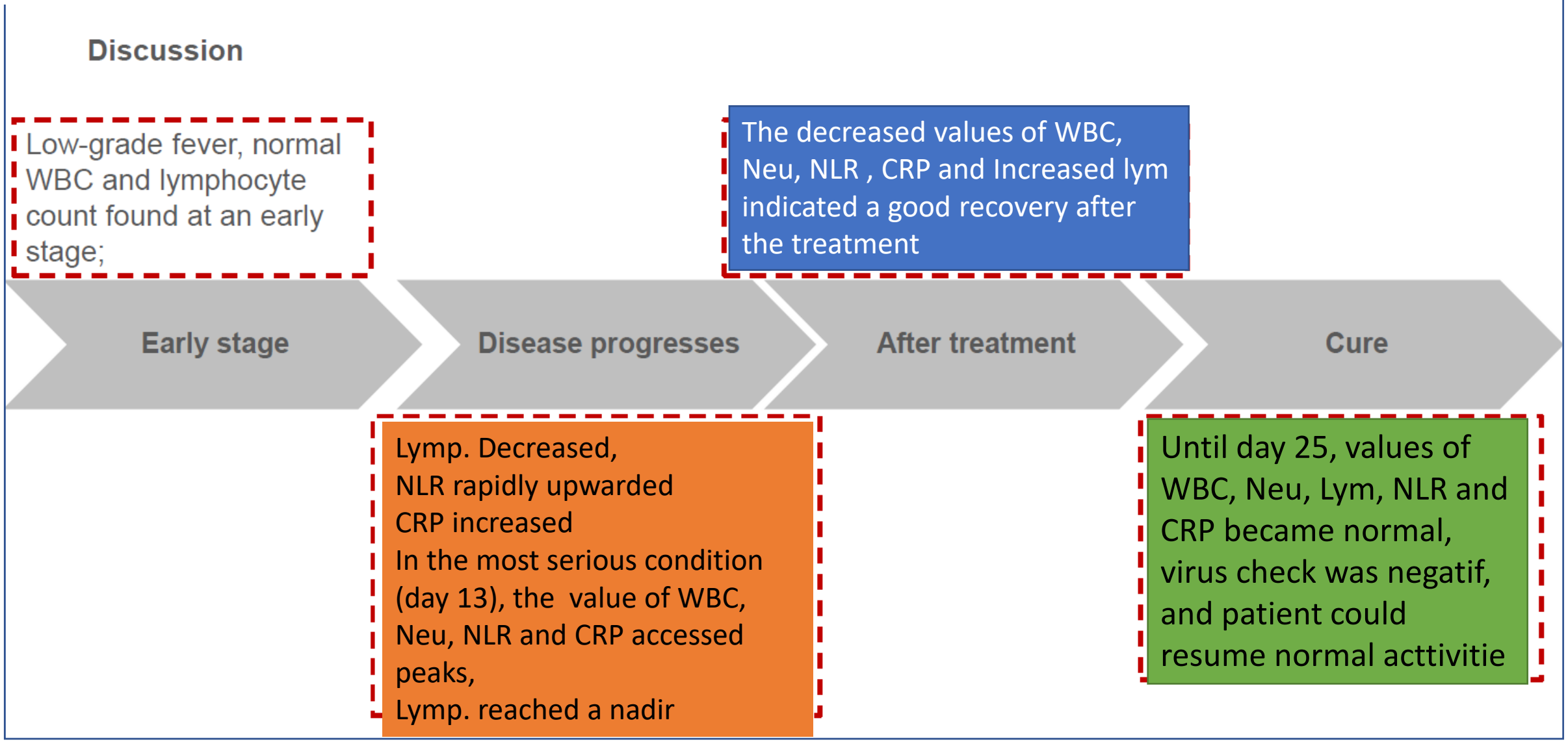
- Peripheral blood leukocyte, lymphocyte counts are normal or slightly reduced.

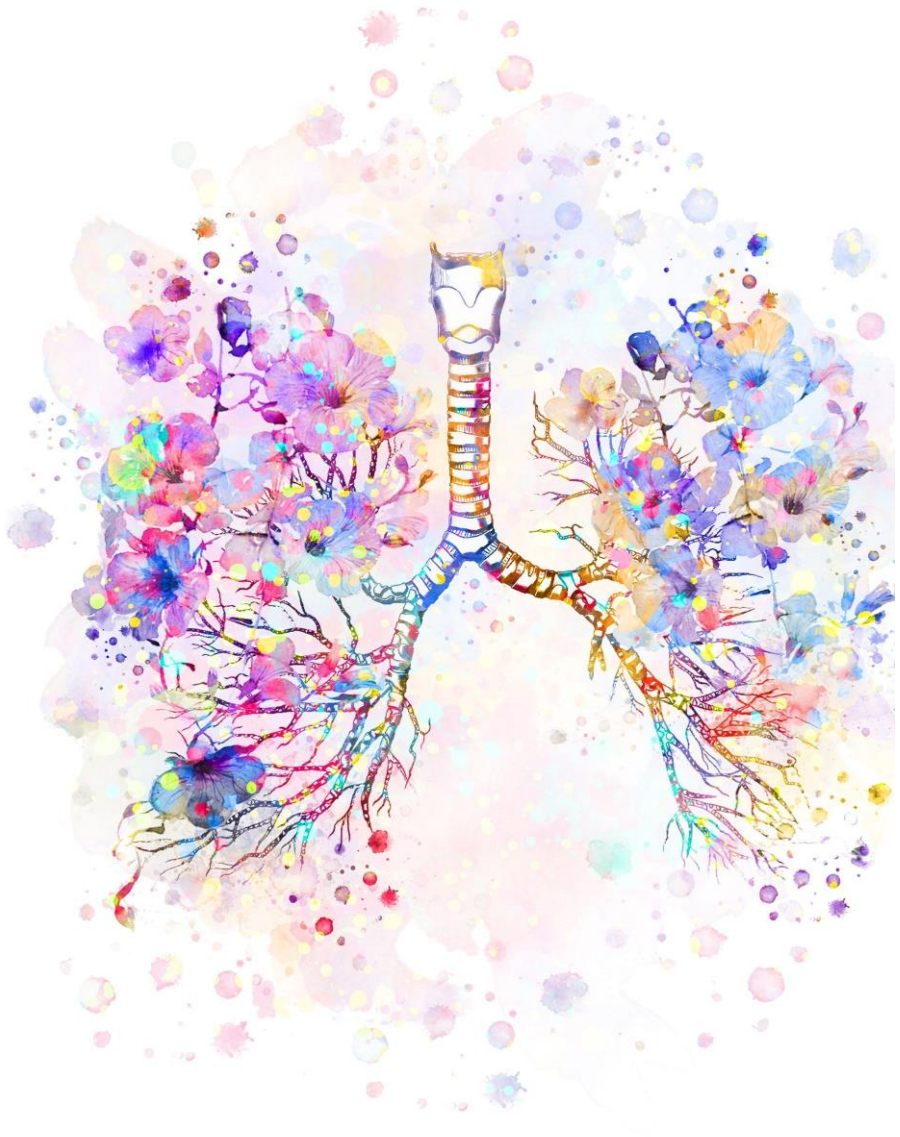
Viremia, Approximately 7 to 14 days from the onset of the initial symptoms

- Increase of inflammatory mediators and cytokines, “cytokine storm”.
- Significant lymphopenia

Terpos, Evangelos, et al. *American Journal of Hematology. 2020.*

LABORATORY OVERVIEW IN COVID 19





Pathophysiology
Lymphopenia in COVID - 19

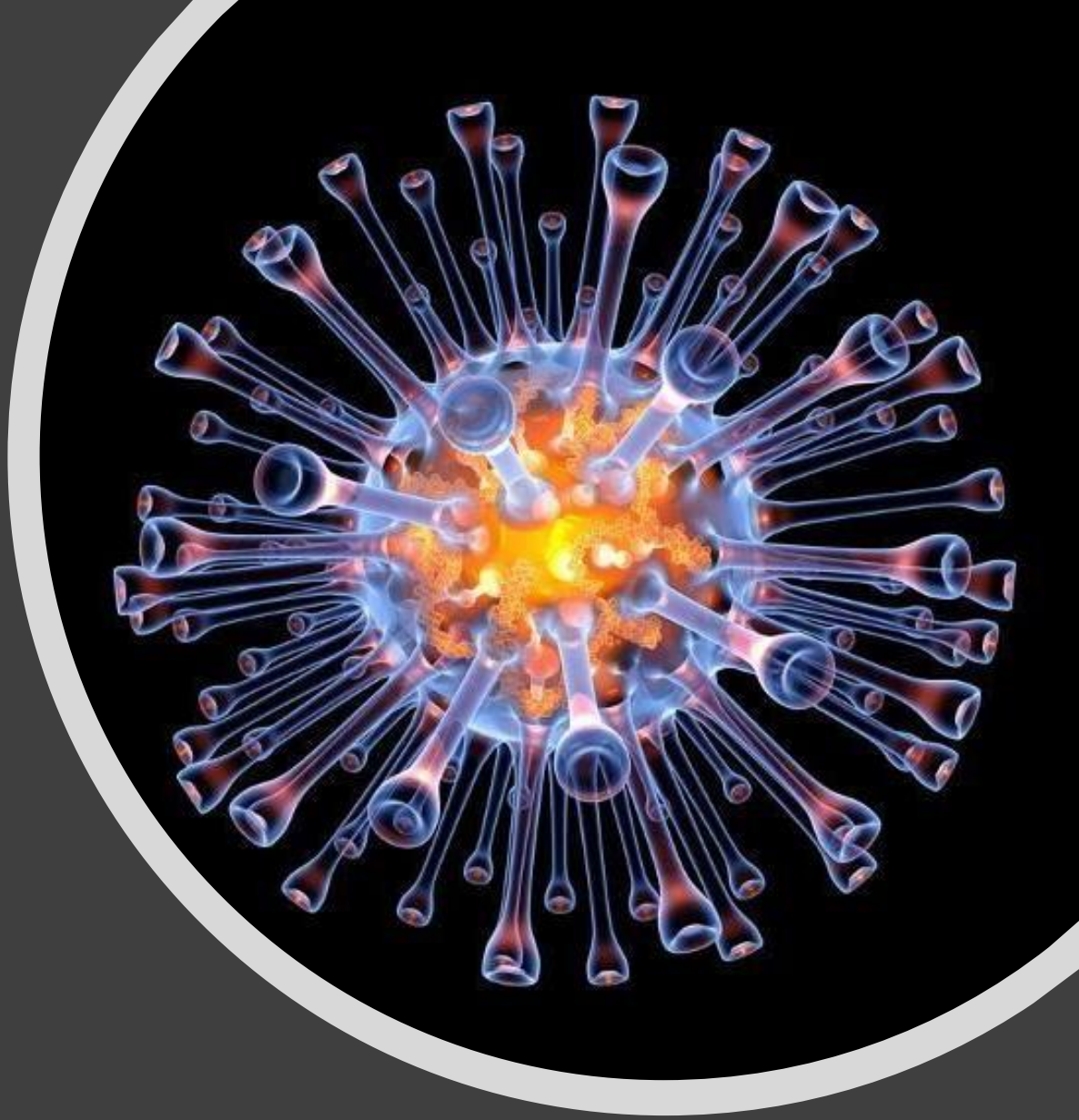
Several factors may contribute to COVID-19 associated lymphopenia :

- **Lymphocytes express the ACE2 receptor on their surface**; thus SARS-CoV-2 may directly infect those cells and ultimately lead to their lysis.
- ***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

Terpos, Evangelos, et al. *American Journal of Hematology. 2020.*

Pathophysiology Lymphopenia in COVID - 19

- Substantial cytokine activation may be also associated with atrophy of lymphoid organs, including the spleen, and further impairs lymphocyte turnover.



Terpos, Evangelos, et al. *American Journal of Hematology. 2020.*

Clinical and Laboratory Profile

	Frequency (%) or median value							
Study	Guan, et al	Chen J, et al	Huang C, et al	Young, et al	Wang D, et al	Mo, et al	Xu, et al	Arentz M, et al
Subject	1099	249	41	18	138	155	62	21
Location	China	Shanghai	Wuhan	Singapure	Wuhan	Wuhan	Zhejiang	Washington
Clinical Findings								
Fever	43,4	87,1	98	72	98,6	81,3	77	52,4
Cough	67,8	36,5	76	83	59,4	62,6	81	47,6
Cold	4,8	6,8	-	6	-	-	-	-
Sore throat	13,9	6,4	-	61	17,4	-	-	-
Fatique	38,1	15,7	44	-	69,6	73,2	52	-
Headache	13,6	11,2	8	-	6,5	9,8	34	-
Dyspnea	18,7	7,6	55	11	31,2	32,3	3	76,2
Diarrhea	3,8	3,2	3	17	10,1	4,5	8	-

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Subject	1099	249	41	18	138	155	62	21
Location	China	Shanghai	Wuhan	Singapore	Wuhan	Wuhan	Zhejiang	Washington
Laboratory Findings								
Leukosit (/mm^3)	4.700	4.710 (3.800-5.860)	6.200 (4.100-10.500)	4.600 (1.700-6.300)	4.500 (3.300-6.200)	4.360 (3.300-6.030)	4.700 (3.500-5.800)	9.365 (2.890-16.900)
Limfosit absolut (/mm^3) ↓	1.000	1.120 (790-1.490)	800 (600-1.100)	1.200 (800-1.700)	800 (600-1.100)	900 (660-1.100)	1000 (800-1.500)	889 (200-2.390)
Platelet (/mm^3)	168.000	-	164.000	-	163.000	170.000	176.000	215.000
ALT (U/L) ↑	21,3%	23(15-33)	32(21-50)	-	24(16-40)	23(16-38)	22(14-34)	273(14-4.4432)
AST (U/L) ↑	22,2%	25(20-33)	34(24-48)	-	31(24-51)	32(24-48)	26(20-32)	108(11-1.414)
Creatinin Serum (mg/dL) ↑	1,6%	-	↑10%	-	0,8 (0,67-0,98)	0,8 (0,67-0,98)	0,81 (0,67-0,94)	1,45(0,1-4,5)
Bilirubin total (mmol/L) ↑	10,5%	-	11,7 (9,5-13,9)	-	9,8(8,4-14,1)	-	-	0,6 mg/dL (0.2-1.1)

Clinical and Laboratory Profile

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Subject	1099	249	41	18	138	155	62	21
Location	China	Shanghai	Wuhan	Singapore	Wuhan	Wuhan	Zhejiang	Washington
Laboratory Findings								
LED (mm/jam)	-	54(33-90)	-	-	-	25(14-47)	-	-
CRP (mg/L)	↑60,7%≥ 10 mg/L	-	16,3 (0,9-97,5)	-	-	33(16-74)	-	-
PCT ≥ 0,5 ng/mL	5,5%	-	8%	-	35,5% ≥ 0,05 ng/mL	0.05 (0.05-0.09)	0.04 (0.03-0.06)	1.8 (0.12-9.56)
Laktat (mmol/L)	-	1,4(1,1-2,1)	-	-	-	-	-	1.8(0.8-4.9)
IL-6 (pg/mL)	-	-	-	-	-	45 (17-96)	-	-
LDH (U/L)	↑41,0%	229 (195-291)	↑73% > 245	512 (285-796)	261 (182-403)	277 (195-404)	205 (184-260,5)	-
D-dimer	↑46,4%	-	0,5 mg/L (0,3-1,3)	-	203 ng/mL	191 ng/mL	0,2 mg/L	-
Hs Trop I	-	-	↑12%	-	6,4 pg/mL (2,8-18,5)	-	-	↑14%

Hematologic parameters in patients with COVID-19 infection

		Non-ICU patients (n = 58)		ICU patients (n = 9)			Overall (n = 67)	
		Median (IQR)	No. (%)	Median (IQR)	No. (%)	*P* value	Median (IQR)	No. (%)
Demographic characteristics at admission	Age (years)	41 (32-53)		54 (47-62)		.02	42 (35-54)	
	Ethnicity					.65		
	Chinese		52 (89.7)		8 (88.9)			60 (89.6)
	Malays		3 (5.2)		0 (0.0)			3 (4.5)
	Indians		1 (1.7)		0 (0.0)			1 (1.5)
	Others		2 (3.5)		1 (11.1)			3 (4.5)
	Gender					.72		
	Males		31 (53.5)		6 (66.7)			37 (55.2)
	Females		27 (48.6)		3 (33.3)			30 (44.8)

Am J Hematol. 2020;1–4.

		Non-ICU patients (n = 58)		ICU patients (n = 9)			Overall (n = 67)	
		Median (IQR)	No. (%)	Median (IQR)	No. (%)	*P* value	Median (IQR)	No. (%)
Blood profile at admission	Hb (g/dL)[a]	14.2 (12.9 - 15.2)		13.2 (12.5-14)		.07	14 (12.9-15.2)	
	WBC ($\times 10^9$/L)[a]	4.7 (4.0 - 5.8)		5.1 (3.5-8.2)		.87	4.7 (3.9-5.8)	
	WBC ($\times 10^9$/L)[a]					.36		
	<2		1 (1.8)		0 (0.0)			1 (1.5)
	2-4		14 (25.0)		4 (44.4)			18 (27.7)
	>4		41 (73.2)		5 (55.6)			46 (70.8)
	ALC ($\times 10^9$/L)[a]	1.3 (0.9 - 1.7)		0.5 (0.48-0.8)		.0002	1.2 (0.8-1.6)	
	ALC ($\times 10^9$/L)[a]					<.001		
	<0.5		1 (1.8)		4 (44.4)			5 (7.7)
	0.5-1.0		16 (28.6)		3 (33.3)			19 (29.2)
	>1		39 (69.6)		2 (22.2)			41 (63.1)
	AMC ($\times 10^9$/L)[a]	0.5 (0.4 - 0.6)		0.3 (0.2-0.5)		.12	0.5 (0.3-0.6)	
	AMC ($\times 10^9$/L)[a]					.19		
	≤0.3		11 (19.6)		4 (44.4)			15 (23.1)
	>0.3		45 (80.4)		5 (55.6)			50 (76.9)
	ANC ($\times 10^9$/L)[a]	2.6 (2.1 - 3.8)		4.2 (2.1-6.9)		.17	2.6 (2.1-4.1)	
	ANC ($\times 10^9$/L)[a]					.99		
	<0.5		0 (0.0)		0 (0.0)			0 (0.0)
	0.5-1.0		2 (3.6)		0 (0.0)			2 (3.1)
	>1		54 (96.4)		9 (100.0)			63 (96.9)

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Hematologic parameters in patients with COVID-19 infection

	Non-ICU patients (n = 58)		ICU patients (n = 9)			Overall (n = 67)	
	Median (IQR)	No. (%)	Median (IQR)	No. (%)	*P* value	Median (IQR)	No. (%)
Platelets ($\times 10^9$/L)[a]	201 (157-263)		217 (154-301)		.81	201 (155-263)	
Platelets ($\times 10^9$/L)[a]					.67		
<100		0 (0.0)		0 (0.0)			0 (0.0)
100-150		12 (21.4)		1 (11.1)			13 (20.0)
>150		44 (78.6)		8 (88.9)			52 (80.0)
LDH (U/L)[b]	401 (352-513)		1684 (1053-2051)		.003	446 (364-595)	
LDH (U/L)[b]					.005		
≤550		21 (80.8)		0 (0.0)			21 (70.0)
>550		5 (19.2)		4 (100.0)			9 (30.0)

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Hematologic parameters in patients with COVID-19 infection

		Non-ICU patients (n = 58)		ICU patients (n = 9)			Overall (n = 67)	
		Median (IQR)	No. (%)	Median (IQR)	No. (%)	*P* value	Median (IQR)	No. (%)
Blood profile during Inpatient stay	Nadir Hb (g/dL)	13.6 (12.7-15.1)		11.1 (10.2-11.9)		<.001	13.3 (12.2-15)	
	Nadir ALC ($\times 10^9$/L)	1.2 (0.8-1.6)		0.4 (0.3-0.5)		<.001	1.0 (0.8-1.5)	
	Nadir ALC ($\times 10^9$/L)					<.001		
	<0.5		1 (1.7)		7 (77.8)			8 (11.9)
	0.5-1.0		23 (39.7)		2 (22.2)			25 (37.3)
	>1		34 (58.6)		0 (0.0)			34 (50.8)
	Nadir AMC ($\times 10^9$/L)	0.4 (0.3-0.5)		0.2 (0.19-0.23)		<.001	0.4 (0.3-0.5)	

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	Non-ICU patients (n = 58)		ICU patients (n = 9)			Overall (n = 67)	
	Median (IQR)	No. (%)	Median (IQR)	No. (%)	*P* value	Median (IQR)	No. (%)
Nadir AMC ($\times 10^9$/L)					<.001		
≤0.3		14 (24.1)		8 (88.9)			22 (32.8)
>0.3		44 (75.9)		1 (11.1)			45 (67.2)
Nadir Platelets ($\times 10^9$/L)	192 (150-261)		154 (131-216)		.15	185 (148-259)	
Nadir Platelets ($\times 10^9$/L)					.69		
<100		0 (0.0)		0 (0.0)			0 (0.0)
100-150		15 (25.9)		3 (33.3)			18 (26.9)
>150		43 (74.1)		6 (66.7)			49 (73.1)
Peak ANC ($\times 10^9$/L)	3.5 (2.6-4.4)		11.6 (9.3-13.8)		<.001	3.8 (2.7-5.0)	
Peak ANC ($\times 10^9$/L)							
<0.5		0 (0.0)		0 (0.0)			0 (0.0)
0.5-1.0		0 (0.0)		0 (0.0)			0 (0.0)
>1		58 (100.0)		9 (100.0)			67 (100.0)
Peak LDH (U/L)[c]	451 (367-629)		1081 (752-1460)		<.001	470 (386-684)	
Peak LDH (U/L)[c]							
≤550		35 (66.0)		0 (0.0)	<.001		35 (56.5)
>550		18 (34.0)		9 (100.0)			27 (43.6)

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Prognosis

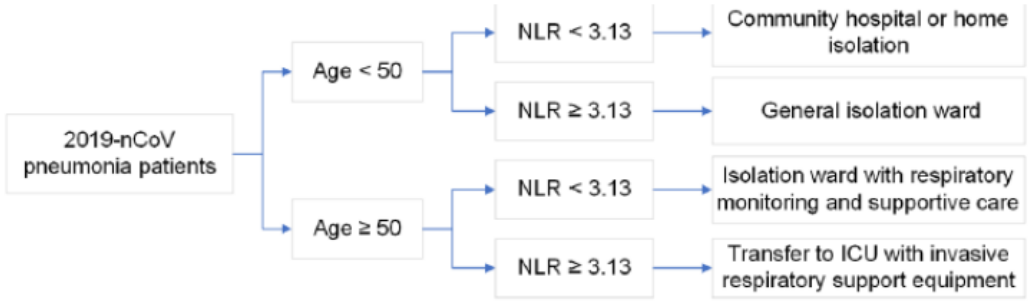
Wu et al retrospectively analyzed possible risk factors for developing ARDS and death among 201 patients with COVID-19 pneumonia in Wuhan, China.

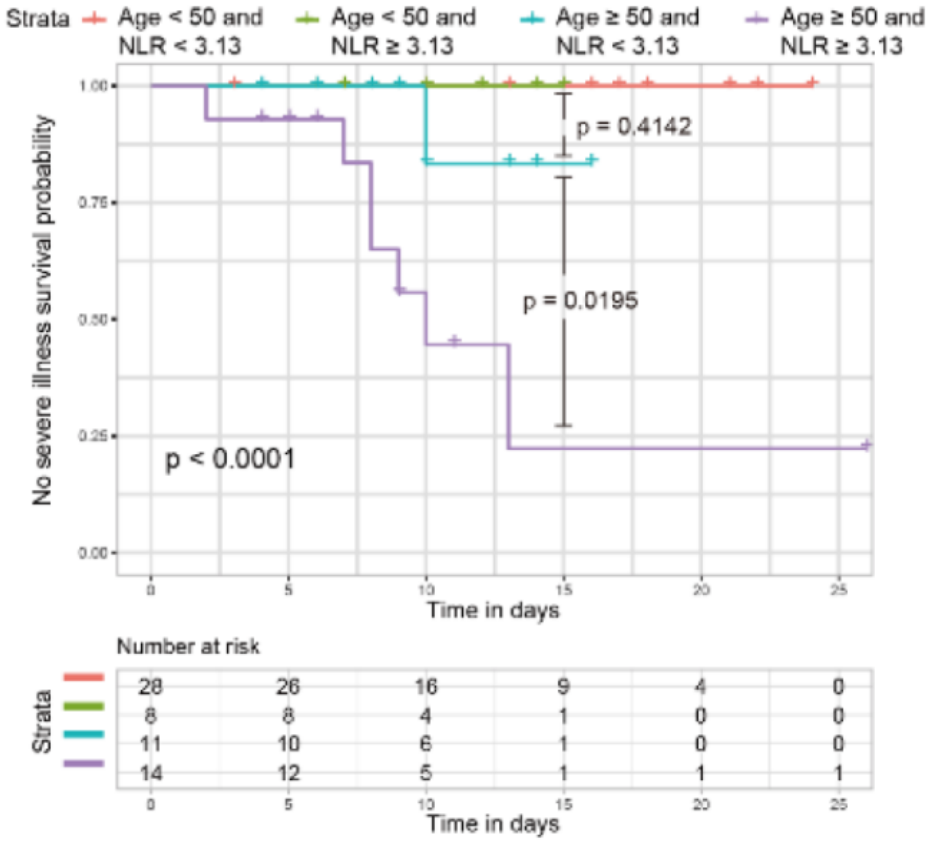
- Increased risk of ARDS during the disease course was significantly associated with increased neutrophils ($p<0.001$), decreased lymphocytes ($p<0.001$) in a bivariate Cox regression analysis.
- Increased neutrophils ($p=0.03$) were associated with increased risk of death.

Wu C, Chen X, Cai Y, *et al. JAMA Intern Med* 2020 Mar 13.

A new prognosis indicator - NLR

- **NLR** is **N**eutrophil to **L**ymphocyte count **R**atio, it's calculated from CBC result, easy-to-use parameter.
- Study[6] in Beijing showed that cut-off value of NLR is 3.13, sensitivity is 0.875 and specificity is 0.717.
- Patients should be transferred to ICU with age >50 and NLR>3.13. If NLR<3.13 and age<50, the patients could isolate at home or community hospital.



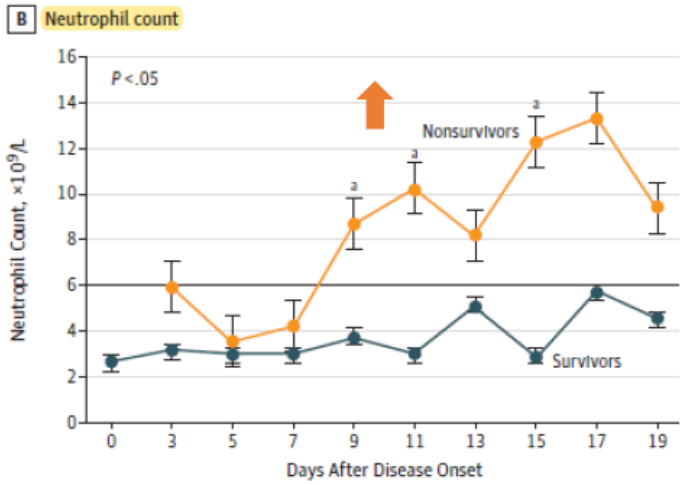


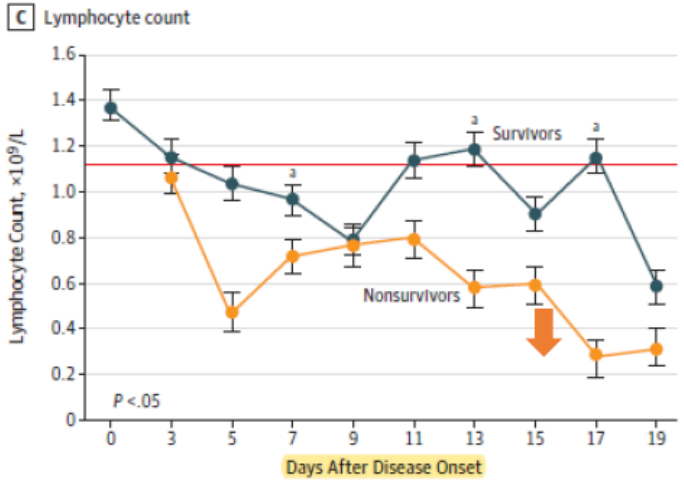
Conclusion: NLR is meaningful parameters for prognosis and risk stratification management, which would be helpful to alleviate insufficient medical resources.

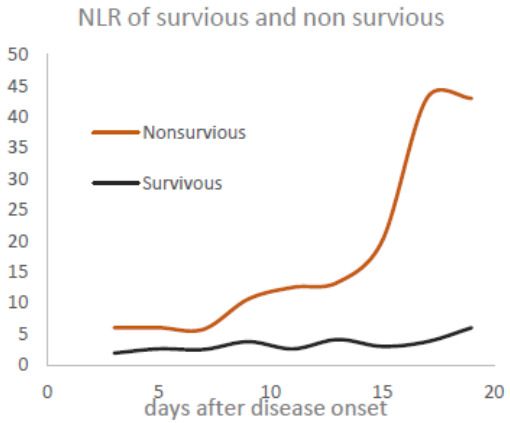
6. Neutrophil-to-Lymphocyte Ratio Predicts Severe Illness Patients with 2019 Novel Coronavirus in the Early Stage. medRxiv 2020.Feb.10
Note: This article is a preprint and has not been peer-reviewed.

A new prognosis indicator - NLR

- Progressive lymphocytopenia is commonly found in severe cases.
- 5 out of 138 patients were in severe illness with Neu# ↑ and a Lym# ↓ , ultimately, death[7].
- Neu# ↑ and Lym# ↓ is a progressive increased NLR result.







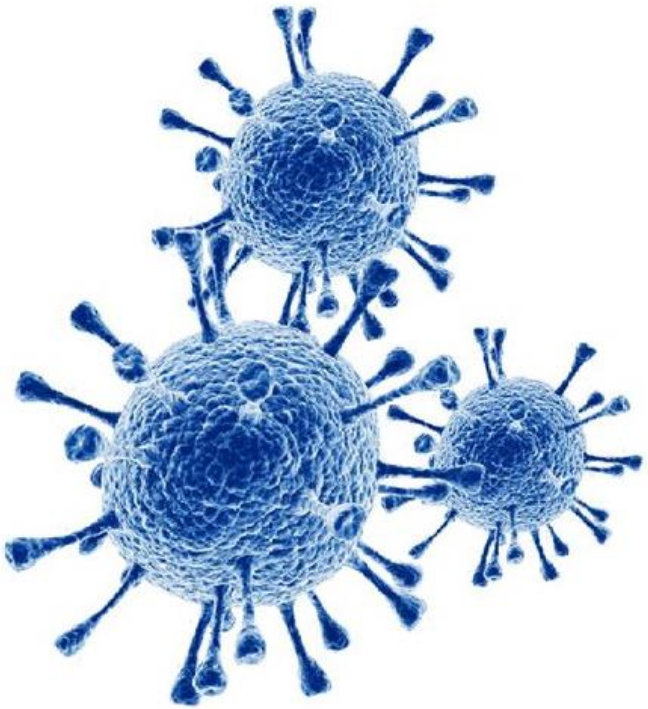
7. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. Jama 2020

Biomarkers

Severe cases showed a more marked increase compared with the non-severe ones :

- CRP : 81.5% versus 56.4%
- Procalcitonin : 13.7% versus 3.7%
- LDH : 58.1% versus 37.2%

- Higher CRP, has been linked to unfavorable aspects of COVID-19 disease, such as ARDS with increased risk of death.
- Increased procalcitonin values were associated with a nearly 5-fold higher risk of severe infection.



Guan WJ, Ni ZY, Hu Y, *et al. N Engl J Med* 2020 Feb 28.

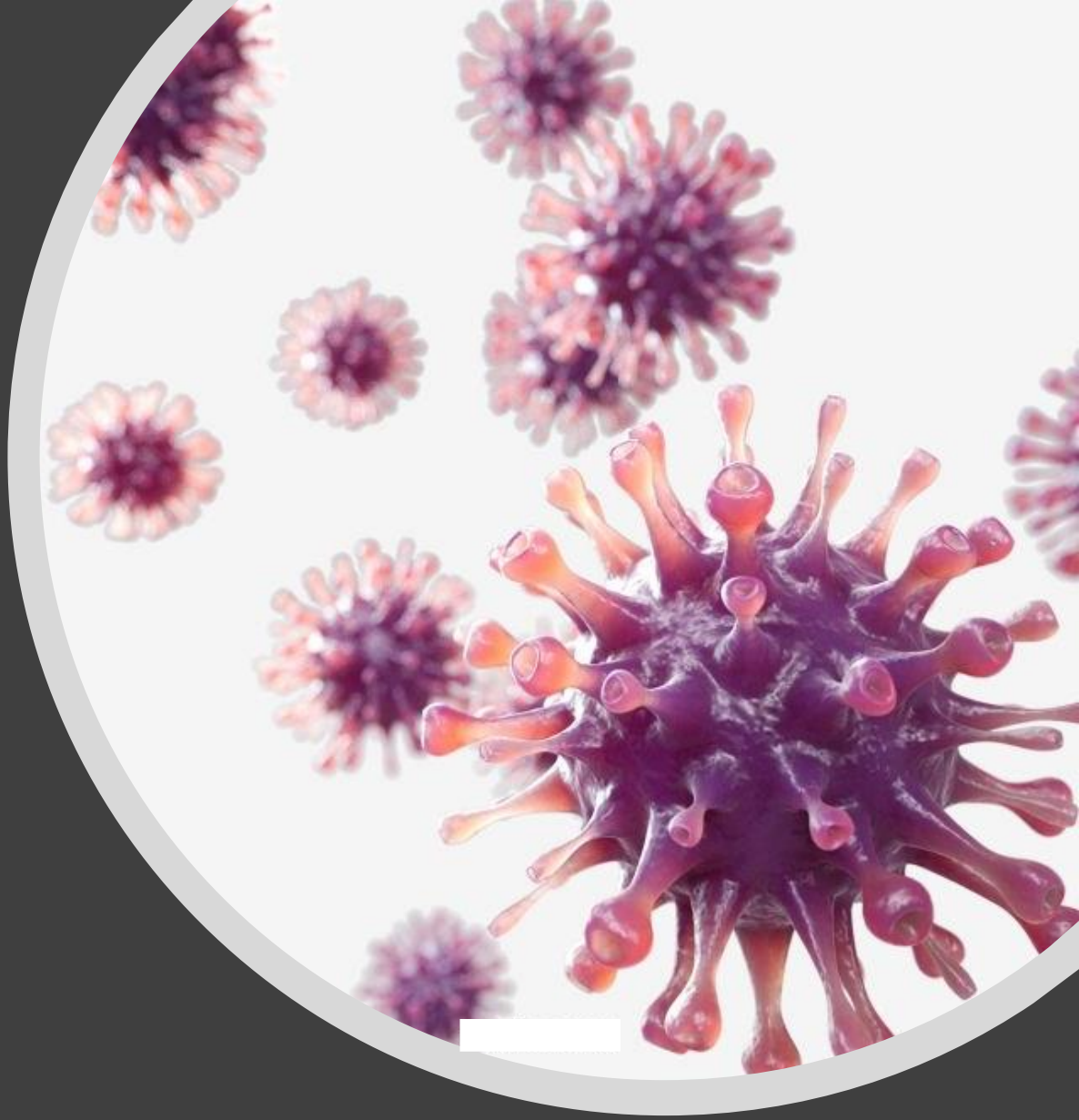
Routine blood test support COVID-19 management

- **Routine CBC test** is primary screening method for COVID-19 disease.
- **CBC test + CRP + NLR support COVID-19 prognosis.**
  - CRP, an inflammation response protein, plays an active role in COVID-19 screening and prognosis.
  - **NLR is meaningful parameters for prognosis and risk stratification management, which is intended to alleviate insufficient medical resources.**
  - **NLR & CRP is great of prognostic value, which can be used for treatment monitoring.**

CBC test + CRP test + NLR prognosis = support COVID-19 management

Conclusion

- COVID-19 disease has prominent manifestations from the hematopoietic system and is often associated with a major blood hypercoagulability.
- Careful evaluation of laboratory indices at baseline and during the disease course can assist clinicians in formulating a tailored treatment approach and promptly provide intensive care to those who are in greater need.



TERIMA KASIH