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STRATEGI PEMERIKSAAN LAB COVID-19

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Diskusi Online : Diagnostik Lab Covid 19

Sabtu, 11 April 2020

Topik Bahasan

- 1. Modalitas Lab COVID-19
- 2. Fungsi Pemeriksaan Lab COVID-19
- *3. Awareness & Pitfall*
- 4. Protokol Lab COVID-19

1. Modalitas Lab COVID-19

- Hematologi : Darah Lengkap/CBC,hemostasis PPT,APTT, D-Dimer
- Kimia Klinik : LFT, RFT, AGD dll
- Sero-Imunologi : CRP, Feritin, Ab
- Molekuler : PCR (termasuk TCM)

2.Fungsi Pemeriksaan Lab COVID-19

2.1. Skrining
2.2. Diagnosis
2.3. Pemantauan
2.4. Surveilens

Parameter Minimal Dasar: CBC & CRP

Secara Umum[1] :

- WBC Normal atau menurun (pada awal penyakit)
- Limfosit absolut (Lym#) dan persentase ↓= ALC (PENTING)
- Trombosit ↓ (pada kasus berat)
- Eosinofil ↓ (pada kasus berat)
- CRP ↑ (penting serial)

Parameter[2]	Non ICU	ICU
WBC (x 10^6/L)		
<2000	1,8 %	0 %
2000-4000	25 %	44,4%
>4000	73,2 %	55,6 %
Abs Lymph Count (ALC) (x10^6/L)		
<500	**1,8%**	**44,4%**
500 – 1000	28,6%	33,3%
>1000	**69,6%**	**22,2 %**

[1] Webinar Mindray 19 Maret 2020. HEMATALK on COVID-19

[2] Fan et al, 2020. Hematologic parameters in patients with COVID-19 infection. Am J Hematol. 2020;1–4. DOI: 10.1002/ajh.25774

Parameter Hematologi Dasar

Parameter	All Patients	Nonsevere	Severe
Hb median (g/dL)	13,4	13,5	12,8
WBC median (per mm^3)	4.700	4.900	3.700
>10.000/mm^3	5,9 %	4,8 %	11,4 %
<4.000/mm^3	33,7 %	28,1 %	61,1 %
Lymphocyte Count (ALC) median (per mm^3) **<1500/mm^3**	1000 **83,2 %**	1000 **80,4 %**	800 **96,1 %**
Trombosit median (per mm^3)	168.000	172.000	137.500
<150.000	36,2 %	31,6 %	57,7 %

Guan et al, 2020. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Feb 28. doi: 10.1056/NEJMoa2002032

Parameter Laboratorium Lain

Parameter	All Patients	Nonsevere	Severe
CRP ≥ 10mg/L	**60,7 %**	**56,4 %**	**81,5 %**
Procalcitonin ≥ 0,5 ng/mL	5,5 %	3,7 %	13,7 %
LDH ≥ 250 U/L	**41 %**	**37,2 %**	**58,1 %**
AST >40 U/L	22,2 %	18,2 %	39,4 %
ALT >40 U/L	21,3 %	19,8 %	28,1 %
Bilirubin Total >17,1 µmol/L	10,5 %	9,9 %	13,3 %
Creatine Kinase ≥ 200 U/L	13,7 %	12,5 %	19 %
Creatinine 1,5 mg/dL	1,6 %	1,0 %	4,3 %
D-Dimer ≥ 0,5 mg/L	**46,4 %**	**43,2 %**	**59,6 %**

Guan et al, 2020. Clinical Characteristics of Coronavirus Disease 2019 in China. doi: 10.1056/NEJMoa2002032

Neutrophil – Lymphocyte Ratio (NLR)

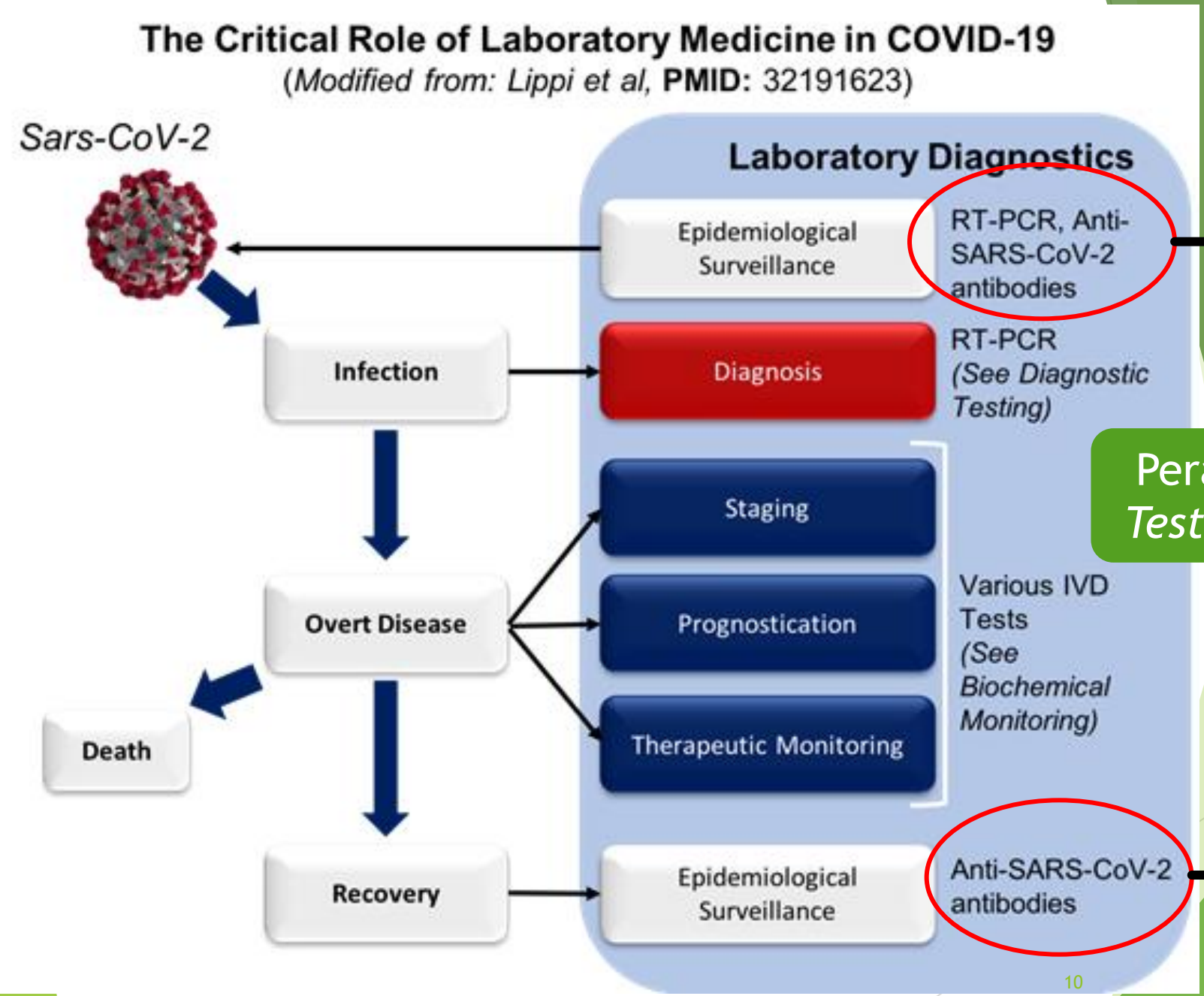
- *Cut-off* 3,13
- Limfopenia absolut terjadi pada kasus berat
- NLR ≥ 3,13 dan usia ≥ 50 tahun → risiko meningkat 50% untuk terjadi keparahan penyakit
- Saran penanganan berdasarkan NLR dan usia:

NLR	USIA	SARAN
< 3,13	< 50 tahun	Tidak ada risiko, isolasi rumah
≥ 3,13	< 50 tahun	Risiko rendah, rawat inap
< 3,13	≥ 50 tahun	Risiko sedang, rawat inap dengan monitoring respirasi
≥ 3,13	≥ 50 tahun	Risiko tinggi, ICU

Liu et al, 2020. Neutrophil-to-Lymphocyte Ratio Predicts Severe Illness Patients with 2019 Novel Coronavirus in the Early Stage. DOI: 10.1101/2020.02.10.20021584

3. *Awareness/Pitfalls*

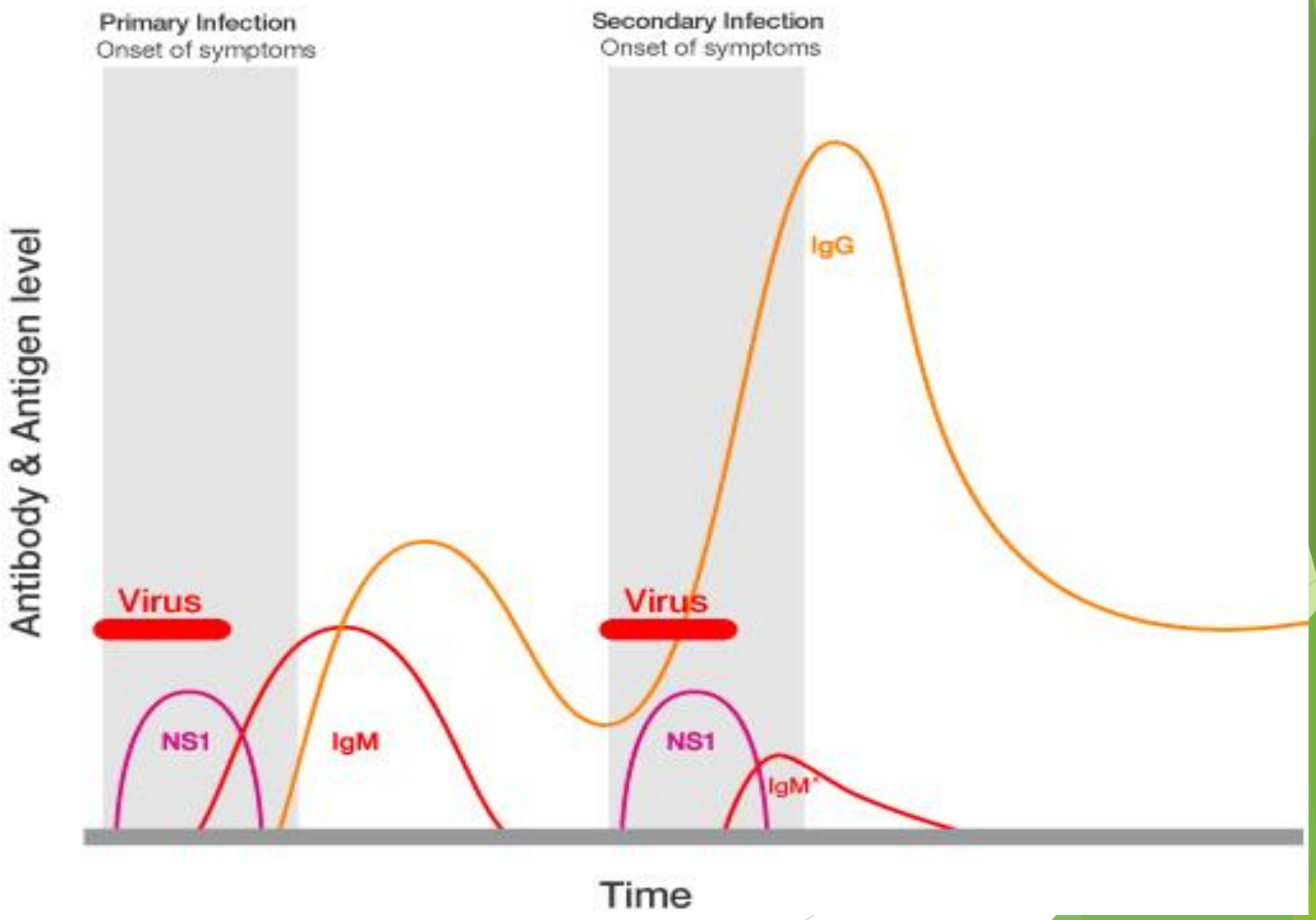
- Preanalitik
- Interpretasi Darah Lengkap/CBC (virus vs bakteri)
- Interpretasi Rapid test Antibodi
- Interpretasi Molekuler (PCR dan TCM)
- Pelaporan Rapid test dan molekuler terkontrol
- Hipotesis respons imun bervariasi
- Hati2 dalam interpretasi kombinasi antibodi n molekuler
- Perhatikan Validitas semua modalitas lab



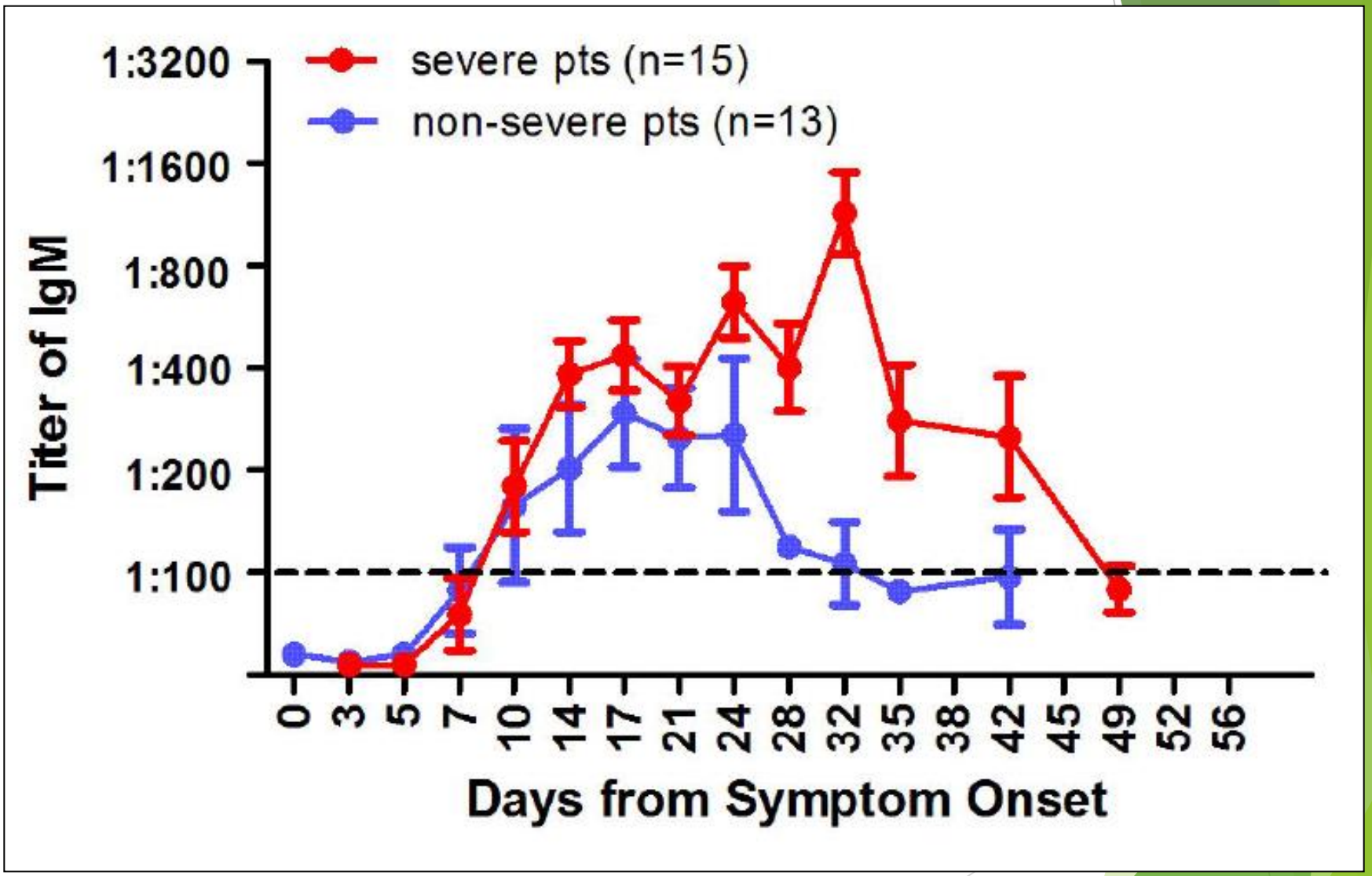
https://www.ifcc.org/ifcc-news/2020-03-26-ifcc-information-guide-on-covid-19/

ANALOGI

Respons Imun Infeksi Virus Dengue (IVD)

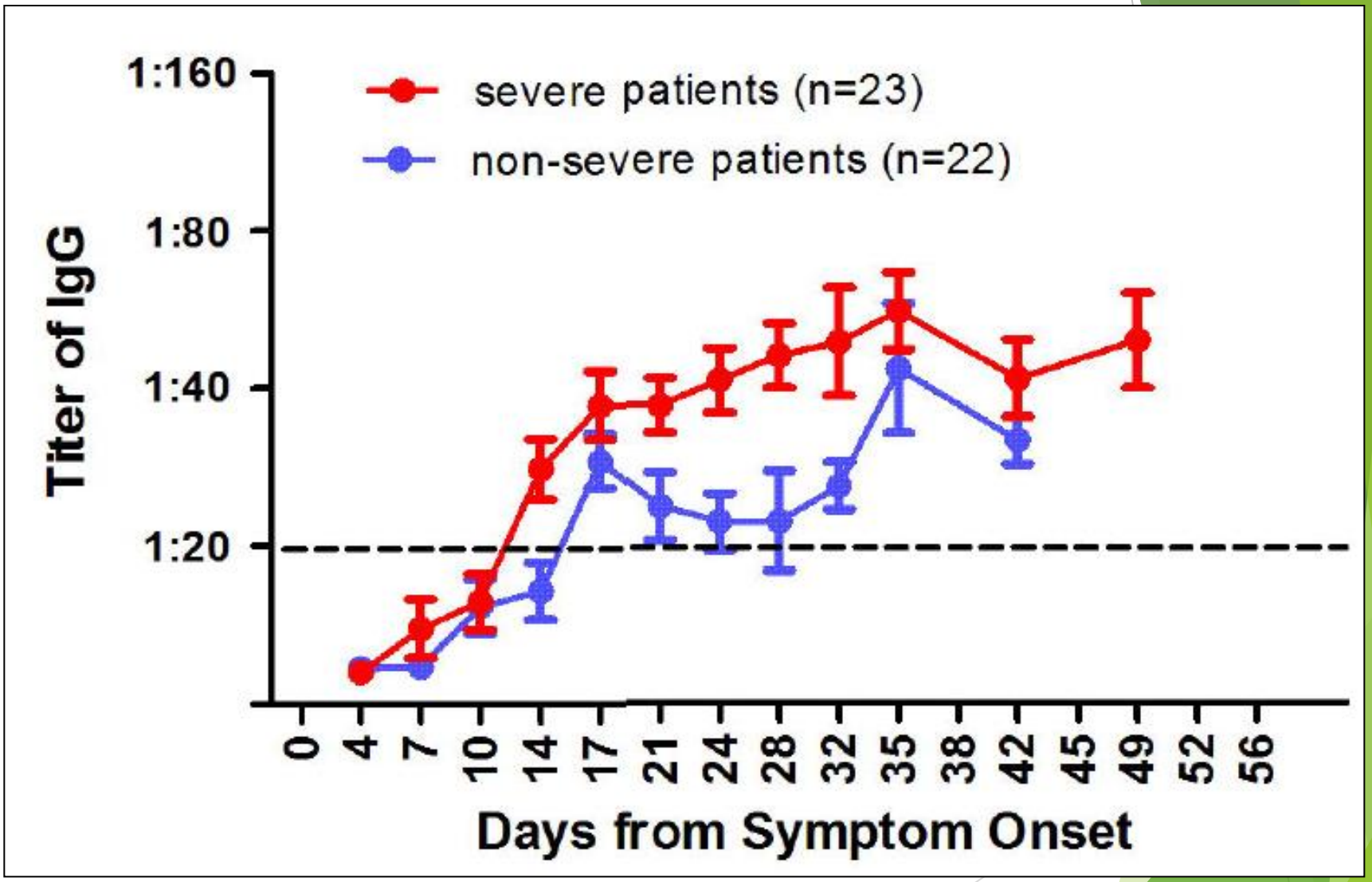


Dynamic Titers of IgM Antibodies to SARS-CoV-2



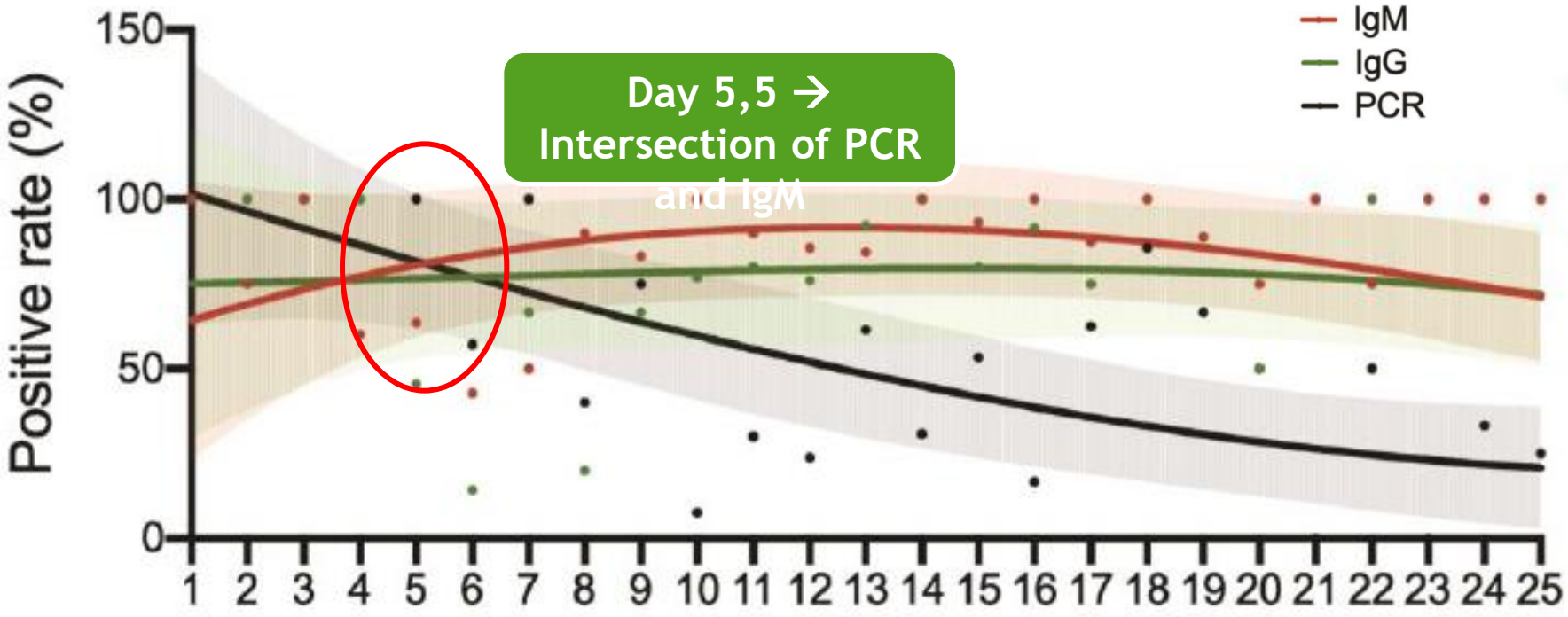
Tan et al, 2020. **Viral Kinetics and Antibody Responses in Patients with COVID-19.** https://doi.org/10.1101/2020.03.24.20042382.

Dynamic Titers of IgG Antibodies to SARS-CoV-2



Tan et al, 2020. **Viral Kinetics and Antibody Responses in Patients with COVID-19.** https://doi.org/10.1101/2020.03.24.20042382.

Kinetik PCR, IgM & IgG Anti SARS-CoV-2



Guo et al, 2020. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). Clin Infect Dis. 2020 Mar 21. pii: ciaa310. doi: 10.1093/cid/ciaa310

Article

Virological assessment of hospitalized patients with COVID-2019

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Roman Wölfel[1,6], Victor M. Corman[2,6], Wolfgang Guggemos[3,6], Michael Seilmaier[3], Sabine Zange[1], Marcel A. Müller[2], Daniela Niemeyer[2], Terry C. Jones[2,4], Patrick Vollmar[1], Camilla Rothe[5], Michael Hoelscher[5], Tobias Bleicker[2], Sebastian Brünink[2], Julia Schneider[2], Rosina Ehmann[1], Katrin Zwirglmaier[1], Christian Drosten[2,7]✉ & Clemens Wendtner[3,7]✉

Coronavirus disease 2019 (COVID-19) is an acute respiratory tract infection that emerged in late 2019[1,2]. Initial outbreaks in China involved 13.8% cases with severe, and 6.1% with critical courses[3]. This severe presentation corresponds to the usage of a virus receptor that is expressed predominantly in the lung[2,4]. By causing an early onset of severe symptoms, this same receptor tropism is thought to have determined pathogenicity, but also aided the control, of severe acute respiratory syndrome (SARS) in 2003[5]. However, there are reports of COVID-19 cases with mild upper respiratory tract symptoms, suggesting the potential for pre- or oligosymptomatic transmission[6–8]. There is an urgent need for information on body site-specific virus replication, immunity, and infectivity. Here we provide a detailed virological analysis of nine cases, providing proof of active virus replication in upper respiratory tract tissues. Pharyngeal virus shedding was very high during the first week of symptoms (peak at 7.11×10^8 RNA copies per throat swab, day 4). Infectious virus was readily isolated from throat- and lung-derived samples, but not from stool samples, in spite of high virus RNA concentration. Blood and urine never yielded virus. Active replication in the throat was confirmed by viral replicative RNA intermediates in throat samples. Sequence-distinct virus populations were consistently detected in throat and lung samples from the same patient, proving independent replication. Shedding of viral RNA from sputum outlasted the end of symptoms. Seroconversion occurred after 7 days in 50% of patients (14 days in all), but was not followed by a rapid decline in viral load. COVID-19 can present as a mild upper respiratory tract illness. Active virus replication in the upper respiratory tract puts the prospects of COVID-19 containment in perspective.

DE GRUYTER

Clin Chem Lab Med 2020; aop

Letter to the Editor

Giuseppe Lippi* and Mario Plebani

Laboratory abnormalities in patients with COVID-2019 infection

https://doi.org/10.1515/cclm-2020-0198
Received for publication February 24, 2020

Keywords: coronavirus; COVID-19; laboratory medicine; laboratory tests; prognosis.

reverse-transcription polymerase chain reaction (rRT-PCR) enables direct virus identification, whilst detection of anti-COVID-19 antibodies by means of fully-automated immunoassays is the mainstay of serological surveillance [5]. Nevertheless, the role of laboratory diagnostics

Viral Kinetics and antibody Responses in Patients with Covid-19
Wenting Tan, Yanqiu Lu, Juan Zhang, et al, 2020
https://doi.org/10.1101/2020.03.24.20042382.

Advice on the use of point-of-care immunodiagnostic tests for COVID-19

Scientific Brief

8 April 2020

In response to the growing COVID-19 pandemic and shortages of laboratory-based molecular testing capacity and reagents, multiple diagnostic test manufacturers have developed and begun selling rapid and easy-to-use devices to facilitate testing outside of laboratory settings. These simple test kits are based either on detection of proteins from the COVID-19 virus in respiratory samples (e.g. sputum, throat swab) or detection, in blood or serum, of human antibodies generated in response to infection.

WHO applauds the efforts of test developers to innovate and respond to the needs of the population.

However, before these tests can be recommended, they must be validated in the appropriate populations and settings. Inadequate tests may miss patients with active infection or falsely categorize patients as having the disease when they do not, further hampering disease control efforts. **At present, based on current evidence, WHO recommends the use of these new point-of-care immunodiagnostic tests only in research settings. They should not be used in any other setting, including for clinical decision-making, until evidence supporting use for specific indications is available.**

With the limited data now available, **WHO does not currently recommend the use of antigen-detecting rapid diagnostic tests for patient care, although research into their performance and potential diagnostic utility is highly encouraged.**

Based on current data, **WHO does not recommend the use of antibody-detecting rapid diagnostic tests for patient care but encourages the continuation of work to establish their usefulness in disease surveillance and epidemiologic research.**

Next steps

- Molecular (e.g. PCR) testing of respiratory tract samples is the recommended method for the identification and laboratory confirmation of COVID-19 cases. COVID-19 molecular diagnostic products are being evaluated for quality and safety through the WHO Prequalification Emergency Use Listing Procedures and through a collaboration with the Foundation for Innovative New Diagnostics (FIND). WHO guidance documents for detection of COVID-19 have been published: WHO Guidance on Laboratory testing for COVID-19 in suspected human cases. In addition, guidance on how testing might be rationalized when lack of reagents or testing capacity necessitates prioritization of certain populations or individuals for testing is also available.

4.Protokol Lab COVID-19

4.1. Skrining
4.2. Diagnosis
4.3. Pemantauan
4.4. Surveilens

4.1). Skrining

a). Pemeriksaan laboratorium

i). Hematologi :

(1). Jumlah Leukosit (< 4000/uL)

(2). Netrofil (> 2500/uL)

(3). Hitung limfosit absolut/ALC (< 1500/uL)

(ii). Neutrofil Limfosit Ratio/NLR (>3.13)

(iii). CRP >10 mg/L

(iv). Pemeriksaan molekuler (TCM, *Real Time* PCR), misal GeneXpert, Abbott, Roche, Bioneer, Standard Biosensor, Genbody Standard Q, dll

4.2). Diagnosis

a). Klinis

b). Pemeriksaan laboratorium

i). Hematologi:

(1). Jumlah Leukosit (< 4000/uL)

(2). Netrofil (> 2500/uL)

(3). Hitung limfosit absolut /ALC (< 1500/uL)

ii). Neutrofil Limfosit Ratio/NLR (>3.13)

iii). CRP >10 mg/L

iv). Kombinasi *rapid test antibody* dengan PCR (konvensional/TCM/*Real Time*)

Contoh hasil DL (CBC) pasien terkonfirmasi COVID-19

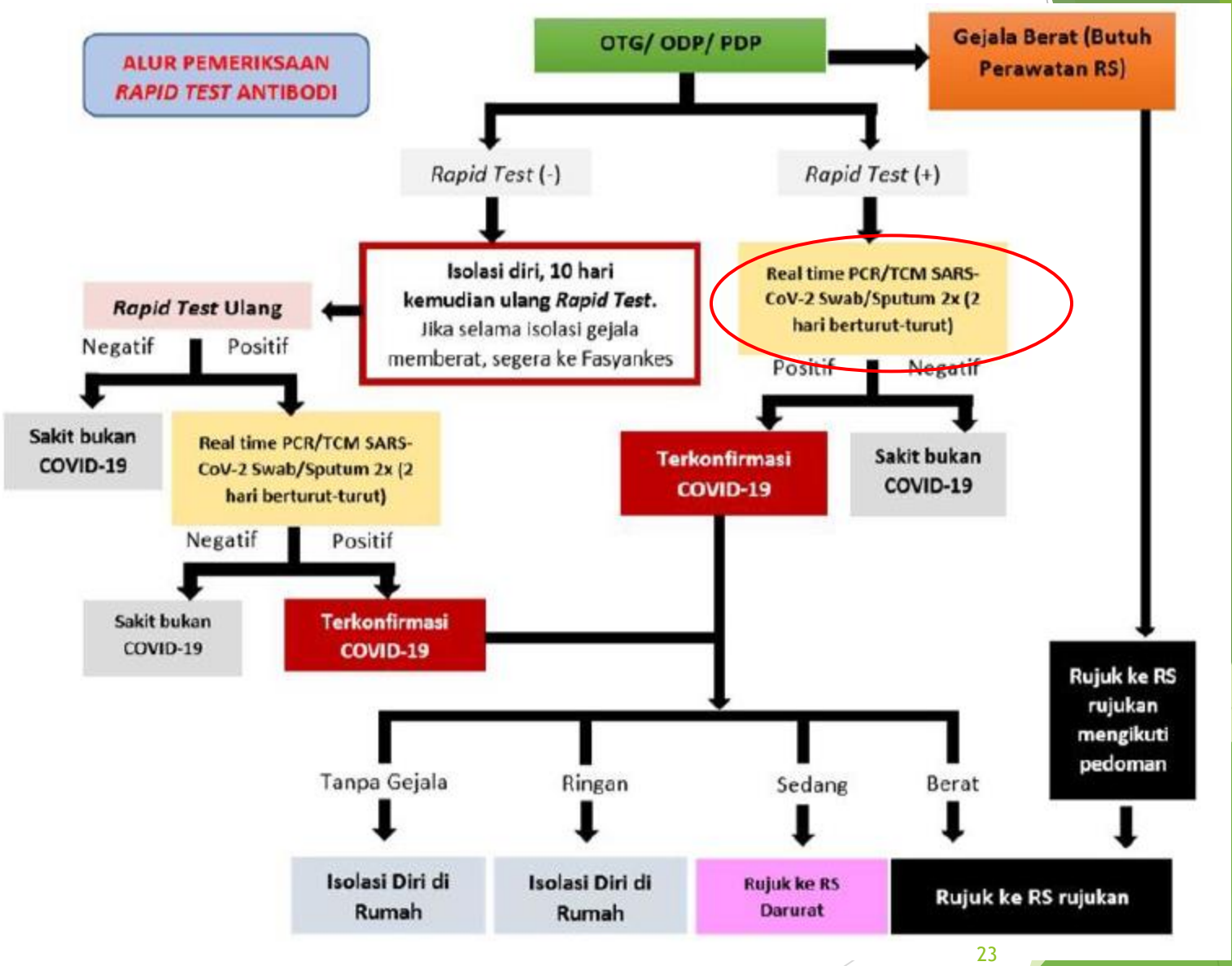
PARAMETERS			NILAI RUJUKAN
HGB	12.2	[g/dL]	L 13,3 - 16,6
			P 11,0 - 14,7
RBC	4.15	[10^6/uL]	3,69 - 5,46
HCT	35.1	[%]	L 41,3 - 52,1
			P 35,2 - 46,7
MCV	84.6 -	[fL]	86,7 - 102,3
MCH	29.4	[pg]	27,1 - 32,4
MCHC	34.8	[g/dL]	29,7 - 33,1
RDW-SD	40.5	[fL]	41,2 - 53,6
RDW-CV	13.0	[%]	12,2 - 14,8
NRBC%	0.0	[%]	
NRBC#	0.00	[10^3/uL]	
WBC	8.91	[10^3/uL]	3,37 - 10
EO%	0.3	[%]	0,6 - 5,4
BASO%	0.1	[%]	0,3 - 1,4
NEUT%	86.6 +	[%]	39,8 - 70,5
LYMPH%	5.9 -	[%]	23,1 - 49,9
MONO%	7.1	[%]	4,3 - 10,0
EO#	0.03	[10^3/uL]	0 - 0,5
BASO#	0.01	[10^3/uL]	0 - 0,15
NEUT#	7.71 +	[10^3/uL]	1,26 - 7,3
LYMPH#	0.53 -	[10^3/uL]	0,8 - 4,0
MONO#	0.63	[10^3/uL]	0,1 - 0,8
IG%	1.0	[%]	
IG#	0.09	[10^3/uL]	
PLT	318	[10^3/uL]	150 - 450
PDW	8.7 -	[fL]	9,6 - 15,2
MPV	9.1	[fL]	9,2 - 12,0
P-LCR	17.2	[%]	19,7 - 42,4
PCT	0.29	[%]	0,19 - 0,39
IPF		[%]	1,1 - 6,1

PARAMETERS			NILAI RUJUKAN
HGB	13.2	[g/dL]	L 13,3 - 16,6
			P 11,0 - 14,7
RBC	4.48	[10^6/uL]	3,69 - 5,46
HCT	38.2	[%]	L 41,3 - 52,1
			P 35,2 - 46,7
MCV	85.3 -	[fL]	86,7 - 102,3
MCH	29.5	[pg]	27,1 - 32,4
MCHC	34.6	[g/dL]	29,7 - 33,1
RDW-SD	41.1	[fL]	41,2 - 53,6
RDW-CV	13.2	[%]	12,2 - 14,8
NRBC%	0.0	[%]	
NRBC#	0.00	[10^3/uL]	
WBC	15.17 +	[10^3/uL]	3,37 - 10
EO%	0.9	[%]	0,6 - 5,4
BASO%	0.2	[%]	0,3 - 1,4
NEUT%	84.7 +	[%]	39,8 - 70,5
LYMPH%	7.0 -	[%]	23,1 - 49,9
MONO%	7.2	[%]	4,3 - 10,0
EO#	0.13	[10^3/uL]	0 - 0,5
BASO#	0.03	[10^3/uL]	0 - 0,15
NEUT#	12.86 +	[10^3/uL]	1,26 - 7,3
LYMPH#	1.06	[10^3/uL]	0,8 - 4,0
MONO#	1.09	[10^3/uL]	0,1 - 0,8
IG%	1.3	[%]	
IG#	0.19	[10^3/uL]	
PLT	373 *	[10^3/uL]	150 - 450
PDW	11.7 *	[fL]	9,6 - 15,2
MPV	10.5 *	[fL]	9,2 - 12,0
P-LCR	28.9 *	[%]	19,7 - 42,4
PCT	0.39 *	[%]	0,19 - 0,39
IPF		[%]	1,1 - 6,1

NLR =

NLR = 12,1

Alur Pemeriksaan Menggunakan *Rapid Test* Antibodi



Kemenkes RI. Maret 2020. *Pedoman Pencegahan dan Pengendalian Infeksi Revisi Ke-4 Coronavirus Disease (COVID-19) hal. 79*

4.3). Pemantauan

a). Serial 1-3 hari tergantung klinis

b). Pemeriksaan laboratorium

i). Hematologi:

(1). Jumlah Leukosit

(2). Neutrofil

(3). Hitung Limfosit absolut/ALC

(4). Neutrofil Lymphocyte Ratio/NLR

(5). Jumlah Trombosit

ii). CRP mg/L atau mg/dL, Prokalsitonin

iii). Feritin (*acute phase reactant*)

iv). Analisa gas darah

v). Elektrolit

vi). Pemeriksaan tambahan

(1). Hemostasis: PT, APTT, D-dimer

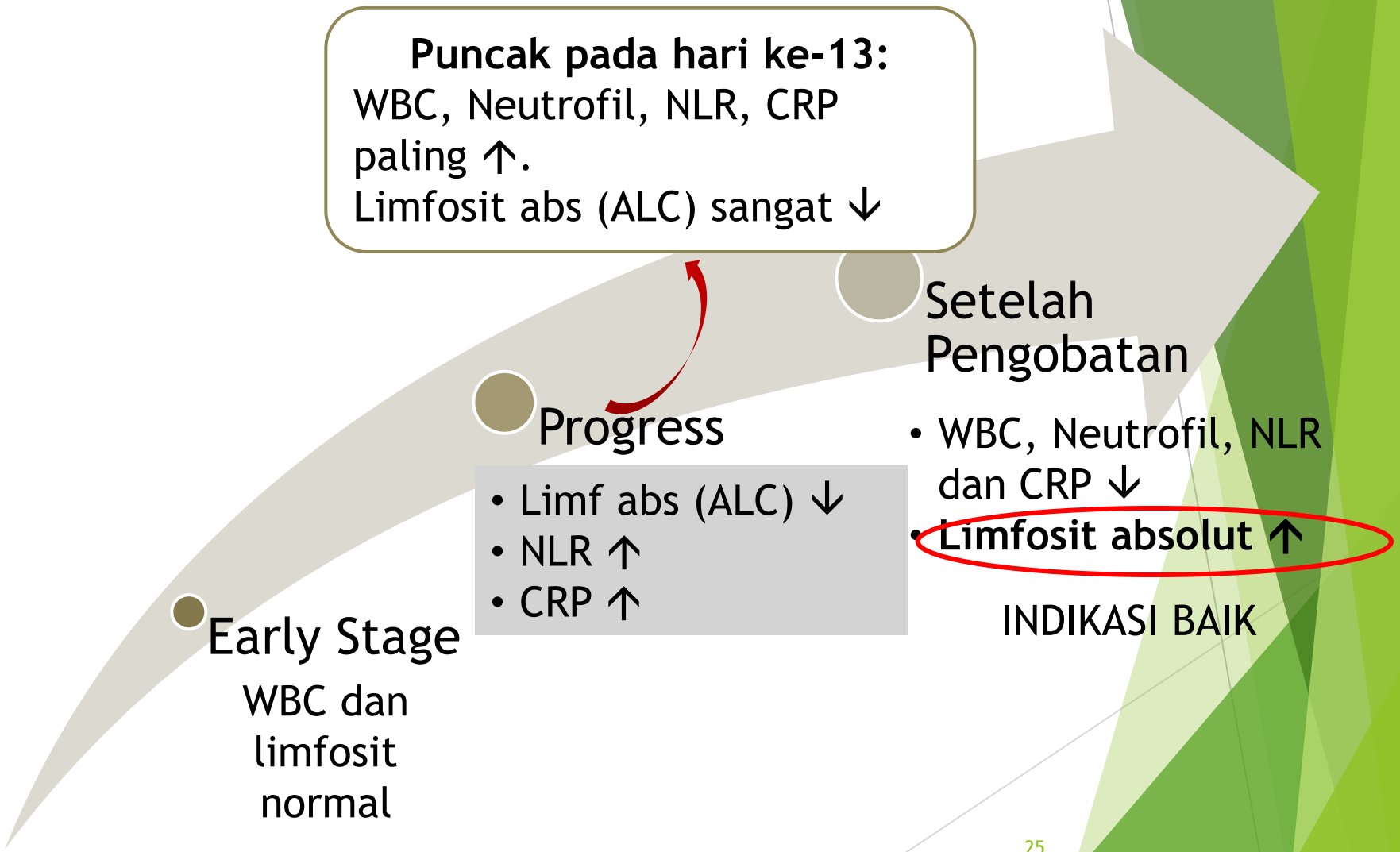
(2). Fungsi ginjal: ureum, kreatinin

(3). Fungsi hati: ALT, AST, LDH

(4). Pemeriksaan lainnya sesuai komorbid, misal glukosa darah untuk pasien DM

(viii). PCR (konvensional/TCM/*Real Time*)

Infeksi COVID-19



Webinar Mindray 19 Maret 2020. HEMATALK on COVID-19

Prediktor Derajat Keparahan Penyakit

Parameter	Nilai Cut-Off	Sensitivitas	Spesifisitas
Usia	44	75 %	70 %
CRP (mg/L)	14,22	83 %	58 %
NLR	5,87	64 %	81 %
Serum Urea Nitrogen (mmol/L)	4,54	78 %	57 %
LED (mm/jam)	26	74	61

Kadar CRP meningkat dalam 4-6 jam kondisi inflamasi dan berlipat ganda setiap jamnya[2]
Nilai dapat mencapai 100 – 1000 kali normal

Song et al, 2020. COVID-19 early warning score: a multi-parameter screening tool to identify highly suspected patients. https://doi.org/10.1101/2020.03.05.20031906.

CONTOH Ny A,35 TAHUN

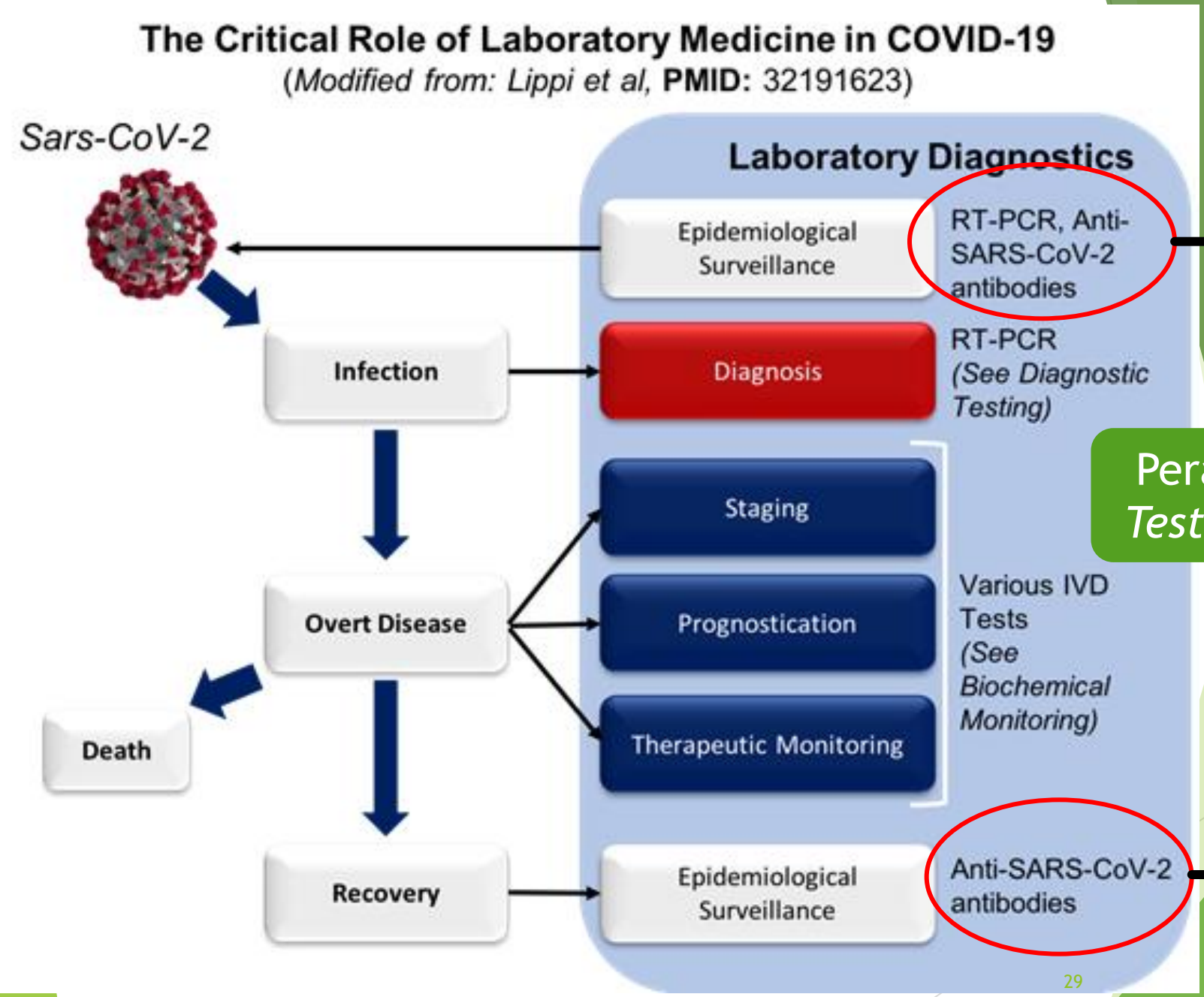
	30-Mar-20	02-Apr-20	05-Apr-20	08-Apr-20
HB	13,8	12,6	13,2	12,4
Eritrosit	4,82	4,43	4,71	4,41
Lekosit	9000	8000	6600	6300
LED	13	21	35	23
Hematokrit	41,1	37,6	40,2	37,7
Trombosit	238,000	264,000	358,000	463,000
Neutrofil	83,4	76,9	72,9	69,9
Limfosit (%)	12,1	12,3	19,3	26,7
MXD	4,50	10,80	7,80	3,70
ALC	1.089	984	1.274	1.682
NLR	6,975	6,255	3,78	2,61
CRP (mg/L)	44,57	54,48	45,48	7,79

4.4). Surveilan/*contact tracing*

a). Pemeriksaan laboratorium

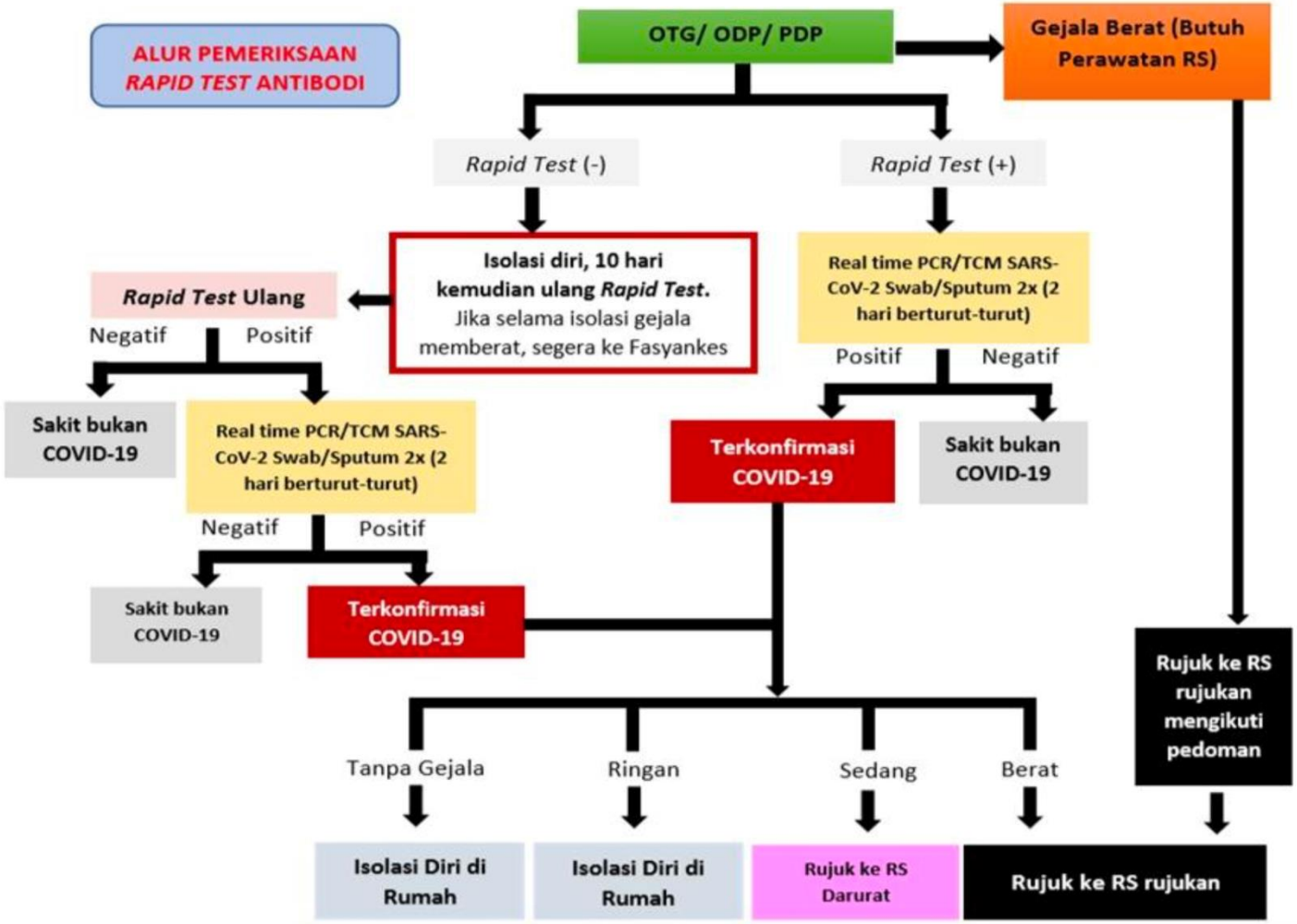
i). Kombinasi *rapid test antibody* dengan PCR (konvensional/TCM/*Real Time*)

Catatan: Pemeriksaan *rapid test Antibody* dan PCR: hasil dilaporkan ke Dinas Kesehatan setempat



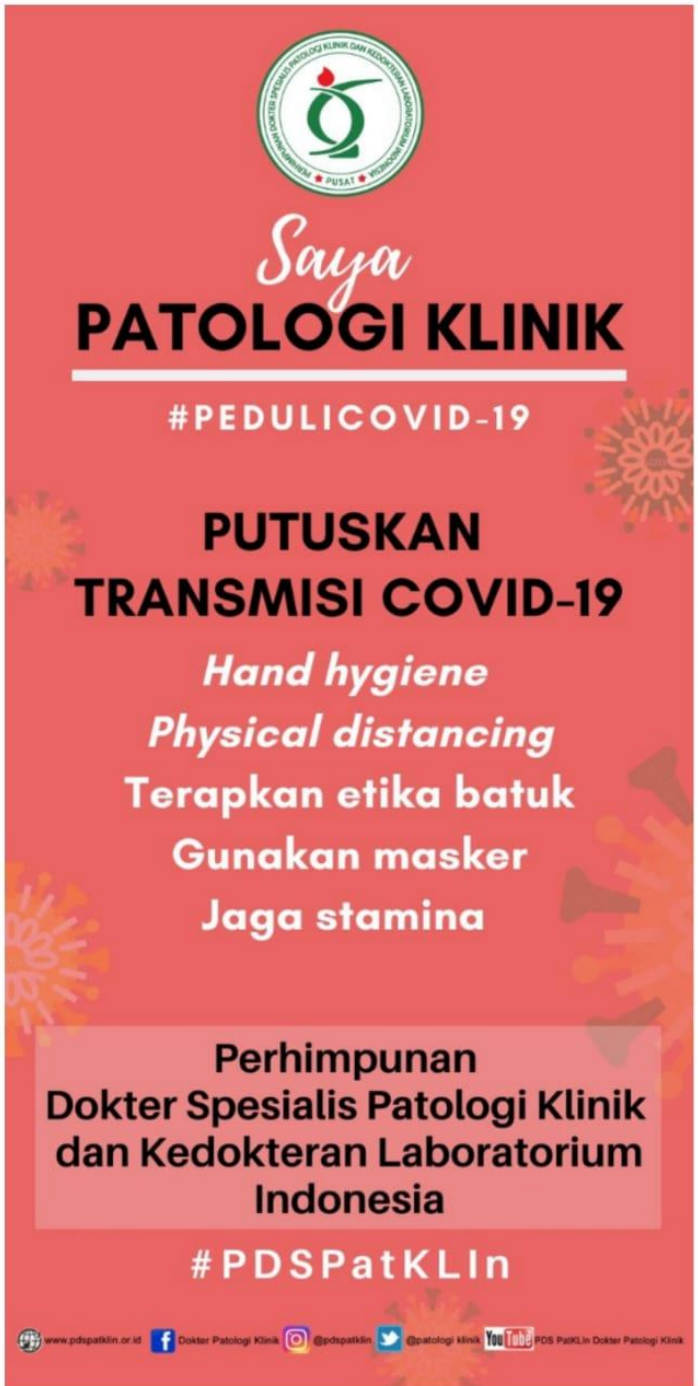
Peran *Rapid Test* Antibodi

https://www.ifcc.org/ifcc-news/2020-03-26-ifcc-information-guide-on-covid-19/



Gambar alur pemeriksaan *rapid test antibody*

Sumber: Pedoman Pencegahan dan Pengendalian Coronavirus Disease (COVID-19) Revisi 4, Direktorat Jenderal Pencegahan dan Pengendalian Penyakit, Kementerian Kesehatan, Maret 2020


Saya
PATOLOGI KLINIK
#PEDULICOVID-19
PUTUSKAN
TRANSMISI COVID-19
Hand hygiene
Physical distancing
Terapkan etika batuk
Gunakan masker
Jaga stamina
Perhimpunan
Dokter Spesialis Patologi Klinik
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TERIMA KASIH