

**SURAT PERNYATAAN**

Yang bertanda tangan dibawah ini sebagai penulis utama,

Nama : dr. Fathur Nurkholis, SpPD, KP  
Jabatan : KPS Prodi Ilmu Penyakit Dalam FK UNDIP  
Unit Kerja : Prodi Ilmu Penyakit Dalam  
No. HP : 08156622291  
Judul Artikel : FACTORS INFLUENCING THE DELAY IN NEGATIVE CONVERSION OF PCR SWAB  
TEST RESULTS IN PATIENTS WITH COVID-19

Menyatakan bahwa manuskrip ini

1. Belum pernah diterbitkan dan / atau dikirim untuk diterbitkan pada jurnal lain
2. Bersedia diperbaiki apabila ada revisi
3. Bersedia diterbitkan dalam Medica Hospitalia : Journal of Clinical Medicine

Semarang, 14 Juni 2022

Yang Menyatakan



dr. Fathur Nurkholis, SpPD, K-P

**LEMBAR PERNYATAAN**

Manuskrip ini telah diperiksa dan disetujui untuk dikirimkan kepada Redaksi  
"Medica Hospitalia : Journal of Clinical Medicine"

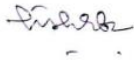
**Judul manuskrip :**

FACTORS INFLUENCING THE DELAY IN NEGATIVE CONVERSION OF PCR SWAB TEST RESULTS IN  
PATIENTS WITH COVID-19

**PENULIS UTAMA :**

Nama

Tanda Tangan



dr. Fathur Nurkholis, SpPD, K-P

**PENULIS PEMBANTU**

Banteng Hanang Wibisono

Agus Suryanto

Thomas Handoyo

Farida

Jimmy Tanamas



KOMITE ETIK PENELITIAN KESEHATAN  
HEALTH RESEARCH ETHICS COMMITTEE  
RSUP DR. KARIADI SEMARANG  
RSUP DR. KARIADI SEMARANG



**KETERANGAN LAYAK ETIK**  
*DESCRIPTION OF ETHICAL APPROVAL*  
**"ETHICAL APPROVAL"**

No.574/EC/KEPK-RSDK/2020

Protokol penelitian yang diusulkan oleh :  
*The research protocol proposed by*

Peneliti utama : dr. Fathur Nur Kholis, SpPD-KP  
*Principal In Investigator*

Nama Institusi : Fakultas Kedokteran Universitas Diponegoro  
*Name of the Institution*

Dengan judul:  
*Title*

**" Faktor yang Mempengaruhi Penundaan Konversi Negatif pada Swab PCR Pasien Covid-19 "**

*" Faktor yang Mempengaruhi Penundaan Konversi Negatif pada Swab PCR Pasien Covid-19 "*

Dinyatakan layak etik sesuai 7 (tujuh) Standar WHO 2011, yaitu 1) Nilai Sosial, 2) Nilai Ilmiah, 3) Pemerataan Beban dan Manfaat, 4) Risiko, 5) Bujukan/Eksploitasi, 6) Kerahasiaan dan Privacy, dan 7) Persetujuan Setelah Penjelasan, yang merujuk pada Pedoman CIOMS 2016. Hal ini seperti yang ditunjukkan oleh terpenuhinya indikator setiap standar.

*Declared to be ethically appropriate in accordance to 7 (seven) WHO 2011 Standards, 1) Social Values, 2) Scientific Values, 3) Equitable Assessment and Benefits, 4) Risks, 5) Persuasion/Exploitation, 6) Confidentiality and Privacy, and 7) Informed Consent, referring to the 2016 CIOMS Guidelines. This is as indicated by the fulfillment of the indicators of each standard.*

Pernyataan Laik Etik ini berlaku selama kurun waktu tanggal 13 Juli 2020 sampai dengan tanggal 13 Juli 2021.

*This declaration of ethics applies during the period July 13, 2020 until July 13, 2021.*

July 13, 2020  
Professor and Chairperson,

Dr. dr. M. Solyan Harahap, SpAn.,KNA

REKAM MEDIS RAWAT

Nama : ARI SUSANTI  
No RM : C833206  
Tgl Lahir : 25/01/1981 Umur : 39 Th, 9 Bin, 4  
No. Register : 11050531  
Tgl Masuk : 28/10/2020  
No Nama DPJP : FARIDA dr.Sp.PD  
Tgl Nama PPIJA : Nita Dewi Puspitastari  
No. :  
Nama : Ruang Rawat PRAJAWALI 5B  
*(Transfer file rekam medis pasien jika tersedia)*

**PERSETUJUAN / PENOLAKAN  
MENJADI SUBYEK PENELITIAN**

**JUDUL PENELITIAN:** Analisis karakteristik klinis, laboratorium, radiologis, biomarker, sistem skoring, keterlibatan multi organ, dan polimerisme genetik dengan derajat berat covid-19

**PEMBERIAN INFORMASI**

Nama Peneliti : TIM COVID-19 IPD  
Pemberi Informasi : dr. SP Ceno Anindito Sp.PD  
Penerima Informasi : Ny. Nurwati  
Diberikan pada tanggal / jam : 28/10/2020 - 14.15

No	JENIS INFORMASI	ISI INFORMASI	Tanda (✓)paraf Penerima informasi
1	Judul Penelitian	Analisis karakteristik klinis, laboratorium, radiologis, biomarker, sistem skoring, keterlibatan multi organ, dan polimerisme genetik dengan derajat berat covid-19	✓
2	Perkenalan Peneliti		✓
3	Tujuan Penelitian	1. Mengetahui karakteristik demografi, klinis, laboratorium, radiologi, biomarker pasien COVID-19. 2. Menganalisis keterlibatan organ paru, jantung, gastrointestinal, ginjal, sistem koagulasi dengan derajat beratnya COVID-19. 3. Menganalisis pola genetik polimerisme dengan ketersediaan dan derajat berat COVID-19	✓
4	Manfaat Penelitian	Dengan mengetahui karakteristik demografi dan klinis pasien serta keterlibatan organ terhadap beratnya COVID-19 dapat memberikan gambaran tentang pengelolaan pasien lebih awal dan berupaya menemukan masalah dan mortalitas bahkan pendekatan terapi.	✓
5	Prosedur Penelitian	1. Pasien dilakukan wawancara dan pemeriksaan jasmani 2. Diambil 24 cc darah EDTA dan 26 cc darah serum 3. Pemeriksaan foto rontgen dan EKG	✓
6	Lama Waktu Partisipasi Subyek	21-28 hari	✓
7	Risiko Penelitian	Nyeri pada tempat tusukan	✓
8	Alternatif Lain	Pengambilan darah EDTA 10 cc dari CVC jika pasien terpasang CVC	✓
9	Tanggung Jawab Bila Terjadi Efek Samping	Diolsakan salep analgetik, kompres dengan NaCl 0,9%	✓
10	Kerahasiaan Subyek Penelitian	RSUP Dr. Kariadi Semarang akan bertanggungjawab terhadap pasien yang menjadi subyek penelitian apabila terjadi efek samping akibat aktivitas penelitian ini	✓
11	Kerahasiaan Subyek Penelitian	Kerahasiaan subyek penelitian akan dijaga oleh peneliti	✓
12	Kebebasan Menyetujui / Menolak	Bila pada saat pelaksanaan penelitian, subyek penelitian memutuskan untuk berhenti, maka tidak akan mempengaruhi sikap maupun pelayanan yang diberikan terhadap yang bersangkutan sebagai pasien di RSUP Dr.Kariadi Semarang	✓
12	Informasi Tambahan	Penelitian ini sudah mendapatkan persetujuan etik dari komisi etik penelitian RSUP Dr.Kariadi dan persetujuan pelaksanaan penelitian dari Bagian Diklit RSUP Dr.Kariadi. Jika ada hal yang masih ingin ditanyakan atau diperjelas, anda dapat langsung menanyakan kepada saya, dr. Nur Farhanah, Sp.PD, K-PTI, Msi (08122524318) atau Bagian Diklit RSUP Dr. Kariadi di nomor (024) 8413476 ext. 4033	✓
Dengan ini menyatakan bahwa saya telah menerangkan hal-hal di atas secara benar dan jelas dan membenarkan kesempatan untuk bertanya dan/atau berdiskusi			Tanda tangan Penerima Informasi
Dengan ini menyatakan bahwa saya telah menerima informasi sebagaimana di atas yang saya beri tanda/paraf di kolom kanannya, dan telah memahaminya			Tanda tangan Pemberi Informasi


**Keterangan :**  
1. Bila pasien tidak kompeten/tidak mau menerima informasi, maka penerima informasi adalah keluarga terdekat atau wali  
2. Isi informasi tidak boleh diilangkat

Lanjut ke halaman 2



PERSETUJUAN MENJADI SUBYEK PENELITIAN	
Yang bertanda tangan di bawah ini saya,	
Nama	: <u>Nyayu Purno</u>
Umur	: <u>40 thn</u> tahun, laki-laki / perempuan*
Alamat	: <u>Pengung Boyolali RT.06 / RW.09</u>
dengan ini menyatakan <b>SETUJU</b> untuk menjadi responden penelitian terhadap saya / Ayah / Ibu / Anak / Keluarga saya,*	
Nama	: <u>Ari Susanti</u>
Umur	: <u>39 thn</u> tahun, laki-laki / perempuan*
Alamat	: <u>Pengung Boyolali RT.06 / RW.09</u>
Saya memahami tujuan dan manfaat penelitian tersebut sebagaimana telah dijelaskan seperti di atas kepada saya, termasuk risiko dan komplikasi yang mungkin timbul.	
Saya juga menyadari bahwa oleh karena ilmu kedokteran bukanlah ilmu pasti, maka keberhasilan tindakan kedokteran bukanlah keniscayaan, melainkan sangat bergantung kepada Tuhan Yang Maha Esa, oleh sebab itu saya membebaskan <b>RSUP Dr. Kariadi / dokter/Petugas lainnya</b> dari tanggung jawab hukum apabila risiko dan komplikasi yang tidak diharapkan benar-benar terjadi di kemudian hari.	
Semarang, tanggal <u>29/10/2020</u> Jam. <u>14.15</u>	
Yang menyatakan,	Saksi I, Saksi II
 (..... <u>Nyayu Purno</u> .....)	 (..... <u>Ari Susanti</u> .....)
PENOLAKAN MENJADI SUBYEK PENELITIAN	
Yang bertanda tangan di bawah ini saya,	
Nama	: .....
Umur	: ..... tahun, laki-laki / perempuan*
Alamat	: .....
dengan ini menyatakan <b>TIDAK SETUJU</b> untuk menjadi responden penelitian terhadap saya / Ayah / Ibu / Anak / Keluarga saya,*	
Nama	: .....
Umur	: ..... tahun, laki-laki / perempuan*
Alamat	: .....
Saya memahami tujuan dan manfaat penelitian tersebut sebagaimana telah dijelaskan seperti di atas kepada saya, termasuk risiko dan komplikasi yang mungkin timbul.	
Saya juga menyadari bahwa oleh karena ilmu kedokteran bukanlah ilmu pasti, maka keberhasilan tindakan kedokteran bukanlah keniscayaan, melainkan sangat bergantung kepada Tuhan Yang Maha Esa, oleh sebab itu saya membebaskan <b>RSUP Dr. Kariadi / dokter/Petugas lainnya</b> dari tanggung jawab hukum apabila akibat tindakan yang tidak saya setuju terdapat risiko dan komplikasi yang tidak diharapkan benar-benar terjadi di kemudian hari.	
Semarang, tanggal..... Jam.....	
Yang menyatakan	Saksi I, Saksi II
(.....)	(.....)

Keterangan : \*) Pilih salah satu

PERSETUJUAN / PENOLAKAN MENJADI SUBYEK PENELITIAN		S Nama : RONDIAH S No RM : C835362 T Tgl Lahir : 06/10/1960 Umur : 60 Th, 1 Bln, 6 H J No. Register : 11099784 N Tgl Masuk : 11/11/2020 Tj Nama DPJP : AVISSENA DUTHA PRATAMA, dr Sp P N Nama PPJA : Nita Devi Puspitasari Ni	
<p><b>JUDUL PENELITIAN:</b> Analisis karakteristik klinis, laboratorium, radiologi, biomarker, sistem skoring, keterlibatan multi organ, dan polimorfisme genetik dengan derajat berat covid-19</p>			
<p align="center"><b>PEMBERIAN INFORMASI</b></p>			
<p>Nama Peneliti : TIM COVID-19 IPD                  Pemberi Informasi : <i>dr. Murya Sp PD</i>                  Penerima Informasi :                  Diberikan pada tanggal / jam :</p>			
No	JENIS INFORMASI	ISI INFORMASI	Tanda (✓) Paraf Penerima Informasi
1	Judul Penelitian	Analisis karakteristik klinis, laboratorium, radiologi, biomarker, sistem skoring, keterlibatan multi organ, dan polimorfisme genetik dengan derajat berat covid-19	✓
2	Perkenalan Peneliti		✓
3	Tujuan Penelitian	1. Mengetahui karakteristik demografi, klinis, laboratorium, radiologi, biomarker pasien COVID-19. 2. Menganalisis keterlibatan organ paru, jantung, gastrointestinal, ginjal, sistem koagulasi dengan derajat beratnya COVID-19. 3. Menganalisis peran genetik polimorfisme dengan kerentanan dan derajat berat COVID-19	✓
4	Manfaat Penelitian	Dengan mengetahui karakteristik demografi dan klinis pasien serta keterlibatan organ terhadap beratnya COVID-19 dapat memberikan gambaran tentang pengelolaan pasien lebih awal dan berupaya menurunkan morbiditas dan mortalitas bahkan pendekatan terapi	✓
5	Prosedur Penelitian	1. Pasien dilakukan wawancara dan pemeriksaan jasmani 2. Diambil 24 cc darah EDTA dan 26 cc darah serum 3. Pemeriksaan foto rontgen dan EKG	✓
6	Lama Waktu Partisipasi Subyek	21-28 hari	✓
7	Risiko Penelitian	Nyeri pada tempat tusukan	✓
8	Alternatif Lala	Pengambilan darah EDTA 10 cc dan CVC jika pasien terpasang CVC	✓
9	Tanggung Jawab Bila Terjadi Efek Samping	Dioleskan salep analgetik, kompres dengan NaCl 0,9% RSUP Dr. Kariadi Semarang akan bertanggungjawab terhadap pasien yang menjadi subyek penelitian apabila terjadi efek samping akibat aktivitas penelitian ini	✓
10	Kerahasiaan Subyek Penelitian	Kerahasiaan subyek penelitian akan dijaga oleh peneliti	✓
11	Kebebasan Menyetujui / Menolak	Bila pada saat pelaksanaan penelitian, subyek penelitian memutuskan untuk berhenti, maka tidak akan mempengaruhi sikap maupun pelayanan yang diberikan terhadap yang bersangkutan sebagai pasien di RSUP Dr. Kariadi Semarang	✓
12	Informasi Tambahan	Penelitian ini sudah mendapatkan persetujuan etik dari komisi etik penelitian RSUP Dr. Kariadi dan persetujuan pelaksanaan penelitian dari Bagian Diklati RSUP Dr. Kariadi. Jika ada hal yang masih ingin ditanyakan atau diperjelas, anda dapat langsung menyanyikan kepada saya, dr. Nur Fatmahan, SpPD, K-FIT, Mui (08122524318) atau Bagian Diklati RSUP Dr. Kariadi di nomor (024) 841.3476 ext. 8032	✓
Dengan ini menyatakan bahwa saya telah memeringkan hal-hal di atas secara benar dan jelas dan memberikan kesempatan untuk bertanya dan/atau berdiskusi			Tanda tangan Pemberi Informasi 
Dengan ini menyatakan bahwa saya telah menerima informasi sebagaimana di atas yang saya beri tanda/paraf di kolom kerasanya, dan telah memahaminya			Tanda tangan Penerima Informasi 

**Keterangan :**

1. Bila pasien tidak kompeten/tidak mau menerima informasi, maka penerima informasi adalah keluarga terdekat/atau wali
2. Isi informasi tidak boleh disingkat

Lanjut ke halaman 2

PERSETUJUAN MENJADI SUBYEK PENELITIAN	
Yang bertanda tangan di bawah ini saya,	
Nama	MAS KOKAH
Umur	36 Tahun tahun, laki-laki / perempuan*
Alamat	TAMBAKROTA RT 04 RW 01
dengan ini menyatakan SETUJU untuk menjadi responden penelitian terhadap saya / Ayah / Ibu / Anak / Keluarga saya,*	
Nama	Rendiyah
Umur	60 Tahun tahun, laki-laki / perempuan*
Alamat	TAMBAKROTA RT 03 RW 01
Saya memahami tujuan dan manfaat penelitian tersebut sebagaimana telah dijelaskan seperti di atas kepada saya, termasuk risiko dan komplikasi yang mungkin timbul.	
Saya juga menyadari bahwa oleh karena ilmu kedokteran bukanlah ilmu pasti, maka keberhasilan tindakan kedokteran bukanlah keniscayaan, melainkan sangat bergantung kepada Tuhan Yang Maha Esa, oleh sebab itu saya membebaskan RSUP Dr. Kariadi / dokter/Petugas lainnya dari tanggung jawab hukum apabila risiko dan komplikasi yang tidak diharapkan benar-benar terjadi di kemudian hari.	
Yang menyatakan,	Semarang, tanggal ..... Jam .....
	Saksi I, Saksi II
(.....)	(.....) (.....)
PENOLAKAN MENJADI SUBYEK PENELITIAN	
Yang bertanda tangan di bawah ini saya,	
Nama	.....
Umur	..... tahun, laki-laki / perempuan*
Alamat	.....
dengan ini menyatakan TIDAK SETUJU untuk menjadi responden penelitian terhadap saya / Ayah / Ibu / Anak / Keluarga saya,*.	
Nama	.....
Umur	..... tahun, laki-laki / perempuan*
Alamat	.....
Saya memahami tujuan dan manfaat penelitian tersebut sebagaimana telah dijelaskan seperti di atas kepada saya, termasuk risiko dan komplikasi yang mungkin timbul.	
Saya juga menyadari bahwa oleh karena ilmu kedokteran bukanlah ilmu pasti, maka keberhasilan tindakan kedokteran bukanlah keniscayaan, melainkan sangat bergantung kepada Tuhan Yang Maha Esa, oleh sebab itu saya membebaskan RSUP Dr. Kariadi / dokter/Petugas lainnya dari tanggung jawab hukum apabila akibat tindakan yang tidak saya setuju terdapat risiko dan komplikasi yang tidak diharapkan benar-benar terjadi di kemudian hari.	
Yang menyatakan	Semarang, tanggal ..... Jam .....
Saksi I, Saksi II	
(.....)	(.....) (.....)

Keterangan : \*) Pilih salah satu

Medica Hospitalia - Journal of Clinical Medicine

Back to Submissions

755 / Nurkholis

Workflow

Submission

Subm

Swab

Pre-Review Discussions

Participants [Edit](#)

Dr. dr. Sp. G2 (K) Erwinanto Erwinanto (erwinantospog)  
Fathur Nurkholis (fathur)

Messages

Note From

TERLAMPIR fathur 2022-06-16 07:27 AM

Surat Pernyataan.pdf IC dr. Fathur.pdf IC ari susanti.pdf

IC Rendiyah.pdf

Mohon surat pernyataan dapat di tanda tangani oleh semua penulis. erwinantospog 2022-06-21 10:11 AM

Terima kasih

Add Message

Pre-Review Discussions

Add discussion

Name	From	Last Reply	Replies	Closed
<a href="#">PERSYARATAN</a>	fathur	erwinantospog 2022-06-16 07:27 AM	1 2022-06-21 10:11 AM	<input type="checkbox"/>
<a href="#">SIMILARITY</a>	erwinantospog	-	0	<input type="checkbox"/>

755 / Nurkholis et al. / Factors Influencing the Delay in Negative Conversion of PCR Swab Test Results in Patients with COVID-19 [Library](#)

Workflow **Publication**

Submission **Review** Copyediting Production

Submission Files [Search](#)

4046	Medica Hospitalia - Factors Influencing the Delay in Negative Conversion of PCR Swab Test Results in Patients with COVID-19.docx	June 16, 2022	Article Text
4101	Fat. Medica Kirim Reviewer.docx	June 23, 2022	Article Text

[Download All Files](#)

Pre-Review Discussions [Add discussion](#)

Name	From	Last Reply	Replies	Closed
<a href="#">PERSYARATAN</a>	fathur	erwinantospog 2022-06-16 07:27 AM	1 2022-06-21 10:11 AM	<input type="checkbox"/>
<a href="#">SIMILARITY</a>	erwinantospog	-	0	<input type="checkbox"/>



Submission

Review

Copyediting

Production

Round 1

**Round 1 Status**



Submission accepted.

**Notifications**

<a href="#">[MH]CMJ Editor Decision</a>	2022-06-30 09:40 AM
<a href="#">[MH]CMJ Editor Decision</a>	2022-07-21 02:56 AM
<a href="#">[MH]CMJ Editor Decision</a>	2022-07-21 05:37 AM

**Reviewer's Attachments**

Q Search

 4180 dr Indra Negative Conversion of PCR .pdf	June 30, 2022
 4179 Review Jurnal dr.Shinta (1).docx	June 30, 2022

**Revisions**

Q Search

Upload File

 4237 Medica Hospitalia - Revised.docx	July 5, 2022	Article Text
---	--------------	--------------

**Review Discussions**

Add discussion

Name	From	Last Reply	Replies	Closed
<a href="#">MASUKAN EDITOR KE 1</a>	santosa 2022-07-13 07:07 AM	fathur 2022-07-18 04:40 AM	1	<input type="checkbox"/>



# Medica Hospitalia

Journal of Clinical Medicine

#### Advisory Board :

Direktur Utama RSUP Dr. Kariadi  
Direktur SDM, Pendidikan, dan Penelitian

#### Journal Manager :

Dr.dr.Omega Meliyana, Sp.A(K)

#### Editor-in-chief :

Dr. dr. Erwinanto, Sp. OG(K)

#### Editors :

Dr.dr.Mexitalia Setiawati E, Sp.A (K)  
Dr.dr.Antonius Gurawan Santoso, Sp.Rad(K)  
Dr. dr.Eriawan Agung Nugroho, Sp.UJ,MI  
Dr.dr.Santosa, Sp.PD-KHOM  
Dr. dr.M. Sofyan Harshap, Sp.An.KNA  
Dr.dr. Muiyassaroh, SpTHT-KL, Msi.Med  
Dr.dr. Niken Puruhita, Sp.GK(K)  
dr.Aditya Kurnianto, Sp.N(K)  
Elyana Sri Sulistyowati, S.Kep.Ns, MARS  
Arief Basuki Rahmat, S.Kep, Ns, MANP

#### Alamat Redaksi & Sirkulasi

Bagian Diklit  
RSUP Dr. Kariadi  
Jl. Dr. Sutomo No. 16 Semarang

#### Website

[www.medicahospitalia.rskariadi.co.id](http://www.medicahospitalia.rskariadi.co.id)

#### Email

[medicahospitalia@rskariadi.co.id](mailto:medicahospitalia@rskariadi.co.id)

## SURAT KETERANGAN

DL.00.0110/MH.9.2/07/2022

Dewan Redaksi Jurnal Medica Hospitalia: *Journal of Clinical Medicine* RSUP Dr. Kariadi Semarang menerangkan bahwa:

Judul : **Factors Influencing the Delay in Negative Conversion of PCR Swab Test Results in Patients with COVID-19**

Penulis : Fathur Nur Kholis, Banteng Hanang Wibisono, Agus Suryanto,  
Thomas Handoyo, Farida, Jimmy Tanamas

Adalah benar judul artikel tersebut diatas **DITERIMA** untuk dipublikasikan dan diterbitkan pada Jurnal Medica Hospitalia: *Journal of Clinical Medicine* Volume 9 Nomor 2 Juli 2022 p-ISSN: 2301-4369 e-ISSN: 2685-7898.

Keterangan: Artikel masih dalam proses *layout* dan pengunggahan dilaman:

<http://medicahospitalia.rskariadi.co.id/medicahospitalia/index.php/mh/index>

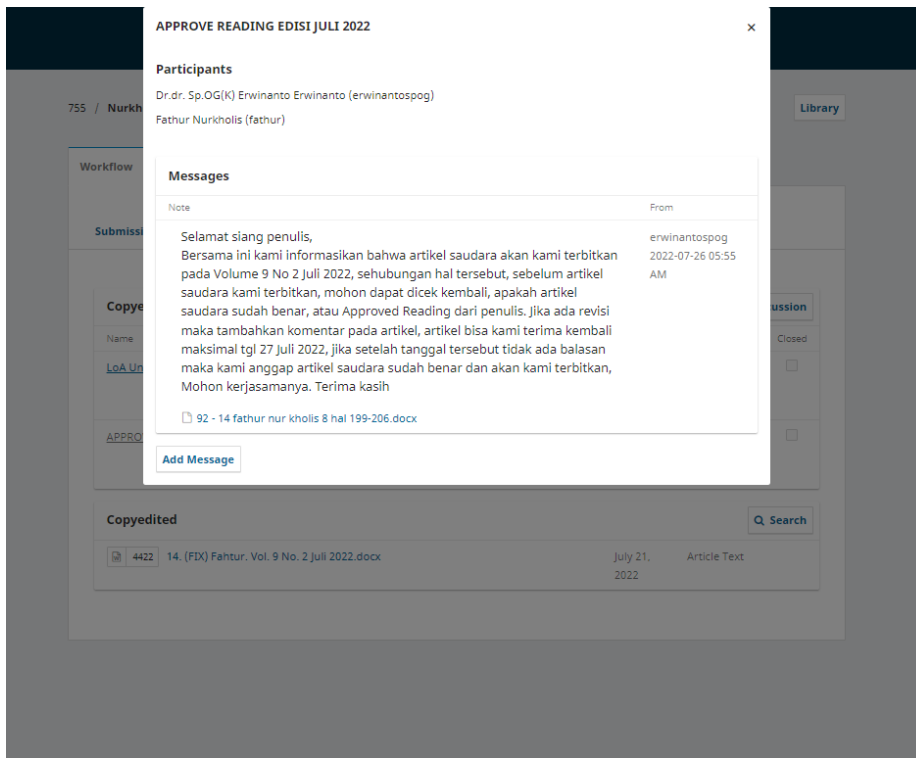
Dewan redaksi berharap kesediaan dan Kerjasama saudara untuk tidak mempublikasikan naskah tersebut di jurnal lain.

Demikian surat keterangan ini dibuat dengan sebenarnya agar dapat dipergunakan sebagaimana mestinya.

Semarang, 21 Juli 2022

Hormat kami,  
Editor in-chief

Dr.dr.Erwinanto, Sp. OG(K)



## Factors Influencing the Delay in Negative Conversion of PCR Swab Test Results in Patients with COVID-19

### 1. Introduction

Coronavirus disease 2019 (COVID-19) was an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus.<sup>1</sup> Among all patients infected with SARS-CoV-2, 80% presented with mild or no symptoms, while 15% presented with severe symptoms requiring oxygen treatment, and the rest were in critical condition requiring mechanical ventilation with severe lung injury and multiorgan dysfunction.<sup>2-4</sup>

The preferred method to detect virus was nucleic acid amplification test such as real-time reverse transcription polymerase chain reaction (rRT-PCR) and sequencing. Samples were confirmed (positive) as SARS-CoV-2 when rRT-PCR showed positive results in a minimum of two target genomes specific for SARS-CoV-2 or positive rRT-PCR for betacoronavirus supported by the result of whole or partial viral genome sequencing compatible with SARS-CoV-2.<sup>5,6</sup>

Hu et al. reported that SARS-CoV-2 RNA showed negative conversion on day 14 after the first positive RT-PCR result. Meanwhile, Zhou et al. reported that RNA viral load could

still be found for a mean duration of 20 days in patients that had recovered from COVID-19, and Ling et al. found that viral shedding lasted for a mean duration of 9.5 days. Different results from these previous studies may be influenced by the severity of disease and sampling method. Older age and comorbidity were also reportedly correlated with PCR negative conversion time. Factors influencing the delay in negative conversion of PCR results could provide early warning signal for poor prognosis.<sup>7-9</sup>

Many studies regarding COVID-19 cases were more focused on the epidemiological, clinical, laboratory, and radiologic characteristics to support the development of diagnostic and treatment strategy for patients. On the other hand, studies regarding the predictive factors associated with negative conversion time in patient with COVID-19 were very limited.<sup>7</sup> For this reason, the current study aims to identify the factors influencing the delay in negative conversion of PCR swab test results in patients with COVID-19

## 2. Methods

A retrospective cross-sectional study involving 68 diagnosed with COVID-19 that was treated in Dr. Kariadi General Hospital Medical Center Semarang from June 1st to December 30th 2020. Negative conversion was evaluated based on the RT-PCR swab test result on day 7, 14 and 21.

Inclusion criteria for the current study were patients with positive COVID-19 diagnosis based on the result of RT-PCR and rapid molecular test using specimens collected from nasal or throat mucosal swab or bronchial wash. Sixty-eight patients with confirmed diagnosis of COVID-19 were selected as study subjects.

Negative conversion of viral RNA was the outcome measure in the current study. Univariate Kaplan-Meier analysis and multivariate Cox proportional hazards model analysis analyses were performed to detect the independent factors influencing the duration of RNA negative conversion. The multivariate regression model was performed with the significant factors selected by univariate analysis. The association between independent factors and negative conversion was quantified by hazard ratio (HR), reported with the 95% confidence interval (CI).

Ethical approval was obtained from the The Medical Research Ethics Committee at The Faculty of Medicine Diponegoro University/Dr. Kariadi Hospital Medical Center Semarang.

## 3. Results

Sixty-eight patients that was treated in Dr. Kariadi General Hospital Medical Center Semarang for COVID-19 were included in the current study. Mean negative conversion time for all patients were  $11.63 \pm 5.08$  days. The majority of subjects were male (57.4%), and the overall average age was 48 (range 20-85).

Twenty-seven subjects (39.7%) had normal body mass index, while 33 (48.5%) were overweight, 6 (8.8%) were obese, and 1 (2.9%) was underweight. Forty-two (61.8%) subjects had fever (body temperature  $>38^{\circ}\text{C}$ ). Dry cough, shortness of breath, cold, sore throat, diarrhea, nausea, and vomiting were reported in 29 (57.4%), 34 (50%), 13 (19.1%), 21 (30.9%), 13 (19.1%), and 23 (33.8%) subjects, respectively. Diabetes mellitus, hypertension, cardiovascular disease, malignancy, chronic pulmonary disease, dyslipidemia, kidney failure and liver disease were reported in 17 (25%), 30 (44.1%), 5 (7.4%), 4 (5.9%), 9 (13.2%), 8 (11.8%), 2 (2.9%), and 3 (4.4%) subjects, respectively. Four (5.9%) subjects were reported to have smoking habit.

Mean leukocytes, platelets, lymphocytes, neutrophils, NLR, ALC, PLR, albumin, CRP and CAR values for all subjects were  $10.47 \pm 7.79 \times 10^3/\text{dL}$ ,  $278.66 \pm 157.98 \times 10^3/\text{dL}$ ,  $14.73 \pm 9.28\%$ ,

75.66±15.82%, 7.38±6.67%, 1674.02±2450.39, 254.15±183.07, 3.33±0.74, 12.84±12.23, and 3.73 ±3.77, respectively.

Forty subjects (58.8%) had received antiviral treatments, while antibiotic and steroids were each given to 50 (73.5%) subjects (Table 1). Negative conversion status on day 7, 14 dan 21 for all study subjects was presented on Table 1.

**Table 1.** Univariate analysis in 68 subjects with negative conversion.

Factors	Patient numbers (%)	Patient with negative conversion (%)			P value
		7 days	14 days	21 days	
<b>Total</b>	68 (100)	33 (48.5)	25 (36.8)	10 (14.7)	
<b>Gender</b>					0.166
<b>Male</b>	39 (57.4)	16 (48.5)	16 (64)	7 (70)	
<b>Female</b>	29 (42.6)	17 (51.5)	9 (36)	3 (30)	
<b>Age</b>					0.004*
<b>&lt;59 years</b>	39 (57.4)	27 (81.8)	18 (72)	3 (30)	
<b>≥59 years</b>	29 (42.6)	6 (18.2)	7 (28)	7 (70)	
<b>BMI</b>					0.001*
<b>&lt;18.5 kg/m<sup>2</sup></b>	1 (2.9)	1 (3)	1 (4)	-	
<b>18.5-24.9 kg/m<sup>2</sup></b>	27 (39.7)	21 (63.6)	5 (20)	1 (10)	
<b>25-29.9 kg/m<sup>2</sup></b>	33 (48.5)	7 (21.2)	18 (72)	8 (80)	
<b>≥30 kg/m<sup>2</sup></b>	6 (8.8)	4 (12.1)	1 (4)	1 (10)	
<b>Temperature</b>					0.014*
<b>&lt;38°C</b>	26 (38.2)	18 (54.5)	6 (24)	2 (20)	
<b>≥38°C</b>	42 (61.8)	15 (45.5)	19 (76)	8 (80)	
<b>Dry cough</b>					0.331
<b>Yes</b>	39 (57.4)	16 (48.5)	17 (68)	6 (60)	
<b>No</b>	29 (42.6)	17 (51.5)	8 (32)	4 (40)	
<b>Shortness of breath</b>					0.000*
<b>Yes</b>	34 (50)	8 (24.2)	17 (68)	9 (90)	
<b>No</b>	34 (50)	25 (75.8)	8 (32)	1 (10)	
<b>Cold</b>					0.309
<b>Yes</b>	13 (19.1)	5 (15.2)	5 (20)	3 (30)	
<b>No</b>	55 (80.9)	28 (84.8)	20 (80)	7 (70)	
<b>Sore throat</b>					0.558
<b>Yes</b>	21 (30.9)	11 (33.3)	5 (20)	5 (50)	
<b>No</b>	47 (69.1)	22 (66.7)	20 (80)	5 (50)	
<b>Diarrhea</b>					0.758
<b>Yes</b>	13 (19.1)	7 (21.2)	3 (12)	3 (30)	
<b>No</b>	55 (80.9)	26 (78.8)	22 (88)	7 (70)	
<b>Nausea, vomiting</b>					0.946
<b>Yes</b>	23 (33.8)	9 (27.3)	12 (48)	2 (20)	
<b>No</b>	45 (66.2)	24 (72.7)	13 (52)	8 (80)	
<b>Diabetes Mellitus</b>					0.000*
<b>Yes</b>	17 (25)	2 (6.1)	8 (32)	7 (70)	
<b>No</b>	51 (75)	31 (93.9)	17 (68)	3 (30)	
<b>Hypertension</b>					0.768

<b>Yes</b>	30 (44.1)	15 (45.5)	11 (44)	4 (40)	
<b>No</b>	38 (55.9)	18 (54.5)	14 (56)	6 (60)	
<b>Cardiovascular disease</b>					0.745
<b>Yes</b>	5 (7.4)	2 (6.1)	3 (12)	-	
<b>No</b>	63 (92.6)	31 (93.9)	22 (88)	10 (100)	
<b>Malignancy</b>					0.540
<b>Yes</b>	4 (5.9)	-	4 (16)	-	
<b>No</b>	64 (94.1)	33 (100)	21 (84)	10 (100)	
<b>Lung disease</b>					0.639
<b>Yes</b>	9 (13.2)	5 (15.2)	3 (12)	1 (10)	
<b>No</b>	59 (86.8)	28 (84.8)	22 (88)	9 (90)	
<b>Dyslipidemia</b>					0.526
<b>Yes</b>	8 (11.8)	5 (15.2)	2 (8)	1 (10)	
<b>No</b>	60 (88.2)	28 (84.8)	23 (92)	9 (90)	
<b>Renal failure</b>					0.672
<b>Yes</b>	2 (2.9)	-	2 (8)	-	
<b>No</b>	66 (97.1)	33 (100)	23 (92)	10 (100)	
<b>Liver disease</b>					0.860
<b>Yes</b>	3 (4.4)	2 (6.1)	-	1 (10)	
<b>No</b>	65 (95.6)	31 (93.9)	25 (100)	9 (90)	
<b>Smoking habit</b>					0.540
<b>Yes</b>	4 (5.9)	-	4 (16)	-	
<b>No</b>	64 (94.1)	33 (100)	21 (84)	10 (100)	
<b>Leukocytes</b>					0.525
<b>&lt; 4000</b>	10 (14.7)	4 (12.1)	4 (16)	2 (20)	
<b>≥ 4000</b>	58 (85.3)	29 (87.9)	21 (84)	8 (20)	
<b>Platelets</b>					0.414
<b>&lt; 150000</b>	15 (22.1)	6 (18.2)	6 (24)	3 (30)	
<b>≥ 150000</b>	53 (77.9)	27 (81.8)	19 (76)	7 (70)	
<b>Lymphocytes</b>					0.607
<b>&lt; 20%</b>	55 (80.9)	28 (84.8)	19 (76)	8 (80)	
<b>≥ 20%</b>	13 (19.1)	5 (15.2)	6 (24)	2 (20)	
<b>Neutrophils</b>					0.016*
<b>&lt; 70%</b>	15 (22.1)	4 (12.1)	6 (24)	5 (50)	
<b>≥ 70%</b>	53 (77.9)	29 (87.9)	19 (76)	5 (50)	
<b>NLR</b>					0.838
<b>&lt; 3.13</b>	11 (16.2)	5 (15.2)	5 (20)	1 (10)	
<b>≥ 3.13</b>	57 (83.8)	28 (84.8)	20 (80)	9 (90)	
<b>ALC</b>					0.344
<b>&lt; 1500</b>	49 (72.1)	22 (66.7)	19 (76)	8 (80)	
<b>≥ 1500</b>	19 (27.9)	11 (33.3)	6 (24)	2 (20)	
<b>PLR</b>					0.922
<b>&lt; 200</b>	31 (45.6)	16 (48.5)	10 (40)	5 (50)	
<b>≥ 200</b>	37 (54.4)	17 (51.5)	15 (60)	5 (50)	
<b>Albumin</b>					0.004*
<b>&lt; 3.0</b>	26 (38.2)	6 (18.2)	14 (56)	6 (60)	
<b>≥ 3.0</b>	42 (61.8)	27 (81.8)	11 (40)	4 (40)	
<b>CRP</b>					0.050*
<b>&lt; 10</b>	33 (48.5)	20 (60.6)	10 (40)	3 (30)	

$\geq 10$	35 (51.5)	13 (39.4)	15 (60)	7 (70)	
<b>CAR</b>					0.084
< 0.25	12 (17.6)	9 (27.3)	2 (8)	1 (10)	
$\geq 0.25$	56 (82.4)	24 (72.7)	23 (92)	9 (90)	
<b>Antiviral</b>					0.000*
Yes	40 (58.8)	28 (84.8)	10 (40)	2 (20)	
No	28 (41.2)	5 (15.2)	15 (60)	8 (80)	
<b>Antibiotic</b>					0.100
Yes	50 (73.5)	23 (69.7)	17 (68)	10 (100)	
No	18 (26.5)	10 (30.3)	8 (32)	-	
<b>Steroid</b>					0.706
Yes	50 (73.5)	10 (30.3)	6 (24)	4 (40)	
No	18 (26.5)	23 (69.7)	19 (76)	6 (60)	

\* $P < 0.05$ ; significant. *P* value from Kaplan-Meier analysis.

Abbreviation; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; ACL, absolute neutrophil count; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; CAR, C-reactive protein/albumin ratio.

Thirty-one factors were evaluated in the initial univariate Cox and Kaplan-Meier analysis (Table 1 and 2). Older age (>59 years), overweight (>25 kg/m<sup>2</sup>), fever (>38°C), shortness of breath, diabetes mellitus, neutrophilia, hypoalbuminemia, CRP and antiviral treatment showed significant association with negative conversion time. These factors were then included in a multivariate regression analysis. Hypoalbuminemia or albumin level of <3.0 g/dL was found as an independent factor associated with negative conversion time of viral RNA (HR:1.986; 95%CI:1.098-3.594), and hypoalbuminemia was presumed to cause prolonged viral clearance time in patients with COVID-19 (Table 2).

**Table 2.** Univariate and multivariate analysis in 68 subjects with negative conversion.

Factors	Univariate analysis			Multivariate analysis		
	HR	95%CI	<i>P</i> value	HR	95%CI	<i>P</i> value
<b>Gender</b>	0.901	0.708-1.148	0.400	-	-	-
<b>Age</b>	0.620	0.360-1.068	0.085*	0.905	0.487-1.681	0.752
<b>BMI</b>	0.718	0.492-1.050	0.087*	0.692	0.428-1.118	0.133
<b>Temperature</b>	0.680	0.413-1.119	0.129*	0.791	0.427-1.467	0.457
<b>Dry cough</b>	1.155	0.713-1.871	0.558	-	-	-
<b>Cold</b>	1.201	0.655-2.204	0.553	-	-	-
<b>Shortness of breath</b>	1.994	1.199-3.315	0.008*	1.385	0.791-1.425	0.254
<b>Sore throat</b>	1.097	0.652-1.846	0.727	-	-	-
<b>Diarrhea</b>	1.058	0.576-1.943	0.856	-	-	-
<b>Nausea, vomiting</b>	1.011	0.609-1.679	0.967	-	-	-
<b>Diabetes Mellitus</b>	1.986	1.115-3.537	0.020*	1.926	0.995-3.729	0.520

<b>Hypertension</b>	0.957	0.593-1.546	0.859	-	-	-
<b>Cardiovascular disease</b>	0.906	0.362-2.268	0.834	-	-	-
<b>Malignancy</b>	1.220	0.440-3.382	0.703	-	-	-
<b>Lung disease</b>	0.902	0.447-1.820	0.773	-	-	-
<b>Dyslipidemia</b>	0.864	0.413-1.808	0.698	-	-	-
<b>Kidney failure</b>	1.209	0.294-4.969	0.792	-	-	-
<b>Liver disease</b>	1.060	0.331-3.396	0.922	-	-	-
<b>Smoking habit</b>	1.220	0.440-3.382	0.703	-	-	-
<b>Leukocytes</b>	1.137	0.580-2.225	0.709	-	-	-
<b>Platelets</b>	1.152	0.648-2.045	0.630	-	-	-
<b>Lymphocytes</b>	0.910	0.497-1.666	0.759	-	-	-
<b>Neutrophils</b>	1.512	0.843-2.713	0.166*	1.306	0.683-2.498	0.419
<b>NLR</b>	0.959	0.502-1.832	0.900	-	-	-
<b>ALC</b>	1.170	0.688-1.990	0.562	-	-	-
<b>PLR</b>	0.986	0.611-1.589	0.953	-	-	-
<b>Albumin</b>	1.540	0.935-2.534	0.090*	1.986	1.098-3.594	0.023**
<b>CRP</b>	0.751	0.465-1.215	0.244*	0.953	0.561-1.619	0.860
<b>CAR</b>	0.704	0.375-1.322	0.275	-	-	-
<b>Antiviral</b>	0.519	0.312-0.862	0.011*	0.704	0.383-1.294	0.258
<b>Antibiotic</b>	1.357	0.778-2.368	0.283	-	-	-
<b>Steroid</b>	1.062	0.629-1.792	0.823	-	-	-

\* $P < 0.25$ ; significant, P value from univariate cox regression analysis.

\*\* $P < 0.25$ ; significant, P value from multivariate cox regression analysis.

Abbreviation; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; ALC, absolute neutrophil count; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; CAR, C-reactive protein/albumin ratio; HR, hazard ratio; 95%CI, confidence interval.

#### 4. Discussion

This was a retrospective study aimed to analyze the factors that may influence the delay in negative conversion of viral RNA in 68 patients with COVID-19 that was treated in Dr. Kariadi General Hospital Medical Center Semarang from June to December 2020. Factors such as clinical symptoms, comorbidities, laboratory test results and treatment were analyzed. Variables in the univariate analysis that showed significant value as influencing factors for prolonged negative conversion time of viral RNA ( $p < 0.05$ ) were age, body mass index, fever, shortness of breath, diabetes mellitus, neutrophilia, hypoalbuminemia and antiviral treatment.

The finding where older age (>59 years) was associated with delay in negative conversion time of SARS-CoV-2 RNA was consistent with the results from previous studies. Study by Hu et al. in 59 patients that were admitted with a diagnosis of COVID-19 reported that older age (>45 years) was an independent factor associated with delay in negative conversion time of viral RNA.<sup>7</sup> Another study by Zhang et al. in 70 patients that were diagnosed with COVID-19 also reported that older age (>50 years) significantly cause a delay in negative conversion time of viral RNA.<sup>10</sup> Elderly patients with COVID-19 reportedly had worse clinical outcome in comparison with younger patients.<sup>9</sup> Older age may also affected the number and function of T cells, resulting in uncontrolled viral replication and excessive host inflammatory response. This age-related disorder may also impair the ability of host cells to eradicate invasive pathogens, thus prolonging viral shedding in the elderly.<sup>7</sup> Comorbidities that came with older age also played a role in causing prolonged negative conversion time. Whilst the severity of disease and comorbidities has no direct influence to PCR conversion time, these may indirectly



influence the clearance of viral nucleic acid.<sup>11</sup> Older age was also reportedly associated with the numbers of viral RNA copies in patients with SARS-CoV infection, where increasing age was independently associated with higher viral load.<sup>12</sup>

Obesity was widely associated with a more severe clinical presentation of COVID-19 and a higher increase in inflammatory markers. This was possibly related to an increase in oxygen demand, thus prolonging the need of supplemental oxygen therapy during hospitalization, delaying viral clearance, and ultimately leading to prolonged hospitalization.<sup>13</sup> Univariate analysis found a significant association between body weight and prolonged negative conversion time of patients with COVID-19, where the negative conversion time will increase with increasing body weight. This result was supported by a previous study by Moriconi et al. that reported a longer negative conversion time in obese patients with COVID-19 (body mass index  $\geq 30$  kg/m<sup>2</sup>) in comparison with non-obese patients (19 $\pm$ 8 days vs. 13 $\pm$ 7 days,  $p=0.002$ ).<sup>13</sup> Obesity was known to cause disorders on both innate and adaptive immune systems, such as abnormal T cell activity, abnormal natural killer cell activity, disorders of phagocytic function, inhibition of neutrophil chemotaxis, and failure of the complement system.<sup>14</sup> Obesity may also cause hyper-activation of mammalian target of rapamycin (mTOR) signaling, thus prolonging the duration of viral shedding.<sup>15</sup>

The current study found that body temperature above 38°C may prolong negative conversion time, where patients with fever has a significantly longer negative conversion time in comparison to patients with normal body temperature. This was consistent with previous study by Li et al. where body temperature was reportedly found as an independent factor associated with the duration of viral shedding, in which patients with higher body temperature showed longer period of viral shedding (<37.3°C (9 days, IQR 7-11); 37.3-38.5°C (11 days, IQR 7-13);  $\geq 38.5^\circ\text{C}$  (12.5 days, IQR 9-17);  $p=0.046$ ). The study believed that the higher the body temperature of COVID-19 patients, the longer the patient will show persistent positive nucleic acid test results.<sup>16</sup> A retrospective study in children with COVID-19 also reported the same result, where longer duration of viral shedding was associated with higher body temperature. Fever was a manifestation of inflammatory response elicited by immune response. However, this study did not evaluate the cytokine levels in their subjects, thus the cause-and-effect relationship between longer viral clearance time and fever had not been clearly demonstrated.<sup>17</sup>

Patients with shortness of breath in the current study showed statistically longer negative conversion time in comparison with patients without this symptom. A similarly significant association between these two variables was also reported by Hu et al., wherein shortness of breath was proven to be an independent predictive factor for prolonged negative conversion time of viral RNA in patients with COVID-19 (HR: 0.290; 95%CI: 0.091-0.919).<sup>7</sup>

Diabetes mellitus (DM) was considered a comorbidity that may increase mortality and morbidity rate in patients with SARS CoV-2 infection. The current study found a significantly longer negative conversion time of SARS-CoV-2 RNA in patients with DM in comparison with those without this comorbidity. A retrospective cohort study in 70 patients diagnosed with COVID-19 reported that DM was an independent predictive factor for prolonged negative conversion time.<sup>10</sup> Another recent study also reported that DM comorbidity in patients with COVID-19 was associated with prolonged viral clearance.<sup>18</sup> Immune system dysregulation caused by diabetes mellitus may play a role in the pathogenesis COVID-19, particularly in prolonging the detection time of SAR-CoV-2 RNA. The mechanism underlying such dysregulation of the immune system in patients with DM were hyperglycemia, inhibition of neutrophil chemotaxis, cytokine dysregulation, and phagocytic cell dysfunction. Diabetic patients also presented with higher risk to develop severe disease, higher mortality rate, and was found to be a risk factor for disease progression.<sup>10</sup>

The current study found that increased neutrophil count (>70%) was significantly associated with prolonged negative conversion time of viral RNA. Similar result was also reported by Mo et al., where patients with prolonged negative conversion time (>18 days) had a significantly higher neutrophil count ( $3.94 [2.31-7.75] \times 10^9/L$ ), and that neutrophil count was proven to be an independent predictive factor for prolonged negative conversion time (OR, 0.097; 95%CI:0.015-0.631];  $p=0.015$ ).<sup>19</sup> Neutrophil was a widely known marker of systemic inflammation that was found to be a risk factor for the development of ARDS and progression from ARDS to mortality in patients with COVID-19.<sup>20</sup> Neutrophil, a main source of cytokines, would release cytokines and chemokines in a large number to help regulate the immune responses such as antiviral defense, hemopoietic action, angiogenesis or fibrogenesis.<sup>20</sup> Overproduction of neutrophil may contribute to acute lung injury and cytokine storm in COVID-19, thus prolonging the viral clearance time.<sup>19</sup> High neutrophil production was also associated with increased CD4<sup>+</sup> lymphocyte ratio. In a previous study, increased CD4<sup>+</sup> lymphocyte ratio was associated with a delay in negative conversion up to 24 days, most likely due to dysregulated immune system and prolonged viral clearance time.<sup>21</sup>

Patients with increased C-reactive protein (CRP) level (>10) in the current study showed significantly longer negative conversion time of viral RNA in comparison to patients with lower CRP level (<10). A previous study by Moriconi et al. also reported the same result, where higher CRP level in obese patients with COVID-19 was associated with longer time for negative result from oropharyngeal or nasal swab test.<sup>13</sup> Study by Gao et al. also reported an association between increased CRP level and prolonged viral RNA shedding up to 28 days in patients with COVID-19.<sup>22</sup> Two to ten-fold increase in serum CRP levels above normal value reportedly caused a significantly prolonged duration of viral shedding, and also showed a significant negative correlation with CD4<sup>+</sup> T lymphocyte counts, a factor that was known to influence immune response and viral shedding.<sup>23</sup> Analysis conducted with multiple linear regression model by Fu et al. found that CD4<sup>+</sup> T lymphocyte counts could help predict the duration of viral RNA shedding in stool specimen and lower absolute CD4<sup>+</sup> T lymphocyte counts before treatment may prolong the viral clearance time.<sup>8</sup>

Antiviral treatment was found to significantly shorten the negative conversion time in patient with COVID-19. Result from the univariate analysis in the current study indicated that patients receiving antiviral therapy had significantly shorter negative conversion time in comparison with patients that did not receive this therapy. Previous study by Fu et al. also reported that the time when antiviral therapy was first initiated was an independent factor associated with SARS-CoV-2 RNA shedding (HR=1.467, 95%CI: 1.187-1.815,  $p<0.001$ ).<sup>24</sup> The study reported shorter negative conversion time in patients who received antiviral therapy

## 5. Conclusion

Factors that were found to influence the delay in negative conversion of viral RNA in patients with COVID-19 based on univariate analysis were older age, overweight, fever, shortness of breath, diabetes mellitus, neutrophilia, hypoalbuminemia, CRP and antiviral treatment. Hypoalbuminemia was an independent predictor for prolonged negative conversion of viral RNA in patients with COVID-19.

## 6. Acknowledgements

All authors conceived this research. FNK, BHW, and AS collected and analyzed data. FNK designed and supervised the entire project scientifically. BHW and AS are major contributors in writing the manuscript, TH participated in the manuscript writing and submission, F and JT reviewed and edited the paper. FNK had final responsibility for the decision to submit for publication. Our thanks go to the Internal Medicine Department of the

Faculty of Medicine University Diponegoro and Dr Kariadi Hospital and who supported the research. All authors have read and approved the final manuscript. This research was not funded by any party.

## References

1. Chen D, Xu W, Lei Z, Huang Z, Liu J. Recurrence of positive SARS-CoV-2 RNA in COVID-19: A case report. *Int J Infect Dis.* 2020; 93:297–9.
2. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection—a review of immune changes in patients with viral pneumonia. *Emerg Microbes Infect.* 2020 Dec;9(1):727-732.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395 (10223):497-506.
4. Rokni M, Ghasemi V, Tavakoli Z. Immune responses and pathogenesis of SARS-CoV-2 during an outbreak in Iran: Comparison with SARS and MERS. *Rev Med Virol.* 2020 Apr 8.
5. World Health Organization. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases. Geneva: World Health Organization; 2020.
6. Direktorat Jenderal Pencegahan dan Pengendalian Penyakit. Pedoman Kesiapsiagaan Menghadapi Coronavirus Disease (COVID-19) Maret 2020. Jakarta: Kementerian Kesehatan Republik Indonesia; 2020.
7. Hu X, Xing Y, Jia J, Ni W, Liang J, Zhao D, et al. Factors associated with negative conversion of viral RNA in patients hospitalized with COVID-19. *Sci Total Environ* [Internet]. 2020;728(175):138812. Available from: <https://doi.org/10.1016/j.scitotenv.2020.138812>
8. Ling Y, Xu S, Lin Y, Tian D, Zhu Z, Dai F, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chin Med J.* 2020;133(9):1–5.
9. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054–62.
10. Zhang F, Hu H, Wang X, Li X, Yang Y, Li L, et al. Prediction for the Negative Conversion Probability of Nucleic Acid Testing in Patients with Nonsevere COVID-19 Pneumonia: A Model Based on Retrospective Cohort Study. 2020;1–17.
11. Liu K, Chen, Y., Lin, R., Han, K., 2020. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. *J. Infect.* <https://doi.org/10.1016/j.jinf.2020.03.005> (Epub ahead of print).
12. To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, et al. 2020. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis.* 2020 May;20(5):565-574.
13. Moriconi D, Masi S, Rebelos E, Viridis A, Manca ML, De Marco S, Taddei S, Nannipieri M. Obesity prolongs the hospital stay in patients affected by COVID-19, and may impact on SARS-COV-2 shedding. *Obes Res Clin Pract.* 2020 May-Jun;14(3):205-209.
14. Holly JMP, Biernacka K, Maskell N, Perks CM. Obesity, Diabetes and COVID-19: An Infectious Disease Spreading from the East Collides with the Consequences of an Unhealthy Western Lifestyle. *Front Endocrinol (Lausanne).* 2020; 11: 1–13.
15. Caci G, Albini A, Malerba M, Noonan DM, Pochetti P, Polosa R. COVID-19 and Obesity: Dangerous Liaisons. *J Clin Med.* 2020;9(8):2511.
16. Li TZ, Cao ZH, Chen Y, Cai MT, Zhang LY, Xu H, et al. Duration of SARS-CoV-2 RNA shedding and factors associated with prolonged viral shedding in patients with COVID-19. *J Med Virol.* 2020;(May):1–7.

17. Lu Y, Li Y, Deng W, Liu M, He Y, Huang L, et al. Symptomatic Infection is Associated with Prolonged Duration of Viral Shedding in Mild Coronavirus Disease 2019: A Retrospective Study of 110 Children in Wuhan. *Pediatr Infect Dis J.* 2020;39(7): E95–9.
18. Chen X, Hu W, Ling J, Mo P, Zhang Y, Jiang Q, et al. Hypertension and Diabetes Delay the Viral Clearance in COVID-19 Patients. *medRxiv [preprint].* 2020;
19. Mo P, Deng L, Liu X, Gao S, Liang K, Luo M, et al. Risk factors for delayed negative conversion of SARS-CoV-2 in patients with COVID-19 pneumonia: a retrospective cohort study. *Epidemiol Infect.* 2020;1–23.
20. Tecchio C, Micheletti A, Cassatella MA. Neutrophil-derived cytokines: Facts beyond expression. *Front Immunol.* 2014;5(OCT):1–7.
21. Wang H, Zhang Y, Mo P, Liu J, Wang H. Neutrophil to CD4+ lymphocyte ratio as a potential biomarker in predicting virus negative conversion time in COVID-19. *Int Immunopharmacol.* 2020;(January).
22. Tian D, Wang L, Wang X, Ge Z, Cui S, Xu Y, et al. Clinical research and factors associated with prolonged duration of viral shedding in patients with COVID-19. 2020;1–16.
23. Gao C, Zhu L, Jin CC, Tong YX, Xiao AT, Zhang S. Proinflammatory cytokines are associated with prolonged viral RNA shedding in COVID-19 patients. *Clin Immunol.* 2020;221(1095).
24. Fu Y, Han P, Zhu R, Bai T, Yi J, Zhao X, et al. Risk factors for viral RNA shedding in COVID-19 patients. *Eur Respir J.* 2020 Jul 2;56(1):2001190.

## Factors Influencing the Delay in Negative Conversion of PCR Swab Test Results in Patients with COVID-19

Fathur Nur Kholis<sup>1\*</sup>, Banteng Hanang Wibisono<sup>1</sup>, Agus Suryanto<sup>1</sup>, Thomas Handoyo<sup>1</sup>, Farida<sup>4</sup>, Jimmy Tanamas<sup>1</sup>

<sup>1</sup>Division of Pulmonology, Department of Internal Medicine, Faculty of Medicine, Diponegoro University/Dr. Kariadi General Hospital, Semarang, Indonesia

pISSN: 2301-4369 eISSN: 2685-7898

<https://doi.org/10.36408/mhjcm.2496>  
Med Hosp. 2019; Vol: 6 (1): 35-45

**Diajukan:**  
**Diterima:**

### Afiliasi Penulis:

Division of Pulmonology,  
Department of Internal Medicine,  
Faculty of Medicine, Diponegoro  
University/Dr. Kariadi General  
Hospital, Semarang, Indonesia

### Korespondensi Penulis:

Fathur Nur Kholis, MD, Division of  
Pulmonology, Department of Internal  
Medicine, Faculty of  
Medicine, Diponegoro  
University/Dr. Kariadi General  
Hospital, Semarang, Indonesia, email  
address: drfnkholis@gmail.com,  
contact person: 08156622291

### E-mail:

drfnkholis@gmail.com

### ABSTRACT

**BACKGROUND:** The negative conversion time of SARS-CoV-2 RNA was related to disease progression, and a prolonged negative conversion could provide early warning signal for poor prognosis in patients with COVID-19.

**OBJECTIVE:** To identify the factors influencing the delay in negative conversion of PCR swab test results in patients with COVID-19 to better evaluate the severity of disease, prognosis, and treatment strategy.

**METHODS:** A retrospective cross-sectional study involving 68 patients diagnosed with COVID-19 that was treated in Dr. Kariadi General Hospital Medical Center Semarang from June 1st to December 30th 2020. Negative conversion was evaluated based on the RT-PCR swab test result on day 7, 14 and 21.

**RESULTS:** Mean negative conversion time for all patients was 11.63±5.08 days. Thirty-one factors were evaluated in the initial univariate Cox and Kaplan-Meier analysis. Older age (>59 years), overweight (>25 kg/m<sup>2</sup>), fever (>38°C), shortness of breath, diabetes mellitus, neutrophilia, hypoalbuminemia, CRP and antiviral treatment showed significant association with negative conversion time. These factors were then included in a multivariate regression analysis. Hypoalbuminemia or albumin level of <3.0 g/dL was found as an independent factor associated with negative conversion time of viral RNA (HR:1.986; 95% CI:1.098-3.594), and hypoalbuminemia was presumed to cause prolonged viral clearance time in patients with COVID-19.

**CONCLUSION:** Factors influencing the delay in negative conversion of viral RNA in patients with COVID-19 were older age, overweight, fever, shortness of breath, diabetes mellitus, neutrophilia, hypoalbuminemia, CRP and antiviral treatment. Hypoalbuminemia was an independent predictor for prolonged negative conversion of viral RNA in patients with COVID-19.

**Keywords:** COVID-19, SARS-CoV-2, negative conversion time, RT-PCR.

Commented [MOU1]: Can change time with duration??

Commented [MOU2]: Use to (double)

Commented [MOU3]: Result of the RT-PCR swab test

Commented [MOU4]: The factors  
Delay =prolong?

## 1. Introduction

Coronavirus disease 2019 (COVID-19) was an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus.<sup>1</sup> Hu et al. reported that SARS-CoV-2 RNA showed negative conversion on day 14 after the first positive RT-PCR result. Meanwhile, Zhou et al. reported that RNA viral load could still be found for a mean duration of 20 days in patients that had recovered from COVID-19, and Ling et al. found that viral shedding lasted for a mean duration of 9.5 days. Different results from these previous studies may be influenced by the severity of disease and sampling method. Older age and comorbidity were also reportedly correlated with PCR negative conversion time. Factors influencing the delay in negative conversion of PCR results could provide early warning signal for poor prognosis.<sup>2-4</sup>

Many studies regarding COVID-19 cases were more focused on the epidemiological, clinical, laboratory, and radiologic characteristics to support the development of diagnostic and treatment strategy for patients. On the other hand, studies regarding the predictive factors associated with negative conversion time in patient with COVID-19 were very limited.<sup>7</sup> For this reason, the current study aims to identify the factors influencing the delay in negative conversion of PCR swab test results in patients with COVID-19

## 2. Methods

A retrospective cross-sectional study involving 68 patients diagnosed with COVID-19 that was treated in Dr. Kariadi General Hospital Medical Center Semarang from June 1st to December 30th 2020. Negative conversion was evaluated based on the RT-PCR swab test result on day 7, 14 and 21. Perdhana's described that the minimum number of samples for research is 30 respondents.<sup>5</sup> Data were collected from patient's medical record in Dr. Kariadi General Hospital, Semarang.

Inclusion criteria for the current study were patients with positive COVID-19 diagnosis based on the result of RT-PCR using specimens collected from nasal or throat mucosal swab or bronchial wash. Sixty-eight patients with confirmed diagnosis of COVID-19 were selected as study subjects. The preferred method to detect virus was nucleic acid amplification test such as real-time reverse transcription polymerase chain reaction (rRT-PCR) and sequencing. Samples were confirmed (positive) as SARS-CoV-2 when rRT-PCR showed positive results in a minimum of two target genomes specific for SARS-CoV-2 or positive rRT-PCR for betacoronavirus supported by the result of whole or partial viral genome sequencing compatible with SARS-CoV-2.<sup>6,7</sup> Patients who did not agree to be included in this study were excluded from the study.

Negative conversion of viral RNA was the outcome measure in the current study. Univariate Kaplan-Meier analysis and multivariate Cox proportional hazards model analysis analyses were performed to detect the independent factors influencing the duration of RNA negative conversion. The multivariate regression model was performed with the significant factors selected by univariate analysis. The association between independent factors and negative conversion was quantified by hazard ratio (HR), reported with the 95% confidence interval (CI).

Ethical approval was obtained from the The Medical Research Ethics Committee at The Faculty of Medicine Diponegoro University/ Dr. Kariadi General Hospital, Semarang.

## 3. Results

Sixty-eight patients that was treated in Dr. Kariadi General Hospital Medical Center Semarang for COVID-19 were included in the current study. All of the respondents were agreed to join in

Commented [MOU5]: Must be deleted

Commented [MOU6]: The different results of these.....

Commented [MOU7]: Wiht duration of PCR negative conversion

Commented [MOU8]: The factors...

Commented [MOU9]: ???????

Commented [MOU10]: This studyto indentify the factors.....bla bla bla

Commented [MOU11]: Result of....

Commented [MOU12]: The inclusion criteria wese....

Commented [MOU13]: Deleted please

Commented [MOU14]: Deleted please...

this study, so no respondents were excluded. Mean negative conversion time for all patients were 11.63±5.08 days. The majority of subjects were male (57.4%), and the overall average age was 48 (range 20-85).

Twenty-seven subjects (39.7%) had normal body mass index, while 33 (48.5%) were overweight, 6 (8.8%) were obese, and 1 (2.9%) was underweight. Forty-two (61.8%) subjects had fever (body temperature >38°C). Dry cough, shortness of breath, cold, sore throat, diarrhea, nausea, and vomiting were reported in 29 (57.4%), 34 (50%), 13 (19.1%), 21 (30.9%), 13 (19.1%), and 23 (33.8%) subjects, respectively. Diabetes mellitus, hypertension, cardiovascular disease, malignancy, chronic pulmonary disease, dyslipidemia, kidney failure and liver disease were reported in 17 (25%), 30 (44.1%), 5 (7.4%), 4 (5.9%), 9 (13.2%), 8 (11.8%), 2 (2.9%), and 3 (4.4%) subjects, respectively. Four (5.9%) subjects were reported to have smoking habit.

Mean leukocytes, platelets, lymphocytes, neutrophils, NLR, ALC, PLR, albumin, CRP and CAR values for all subjects were 10.47±7.79 x10<sup>3</sup>/dL, 278.66±157.98 x10<sup>3</sup>/dL, 14.73±9.28%, 75.66±15.82%, 7.38±6.67%, 1674.02±2450.39, 254.15±183.07, 3.33±0.74, 12.84±12.23, and 3.73 ±3.77, respectively.

Forty subjects (58.8%) had received antiviral treatments, while antibiotic and steroids were each given to 50 (73.5%) subjects (Table 1). Negative conversion status on day 7, 14 dan 21 for all study subjects was presented on Table 1.

Commented [MOU15]: Deleted please

Commented [MOU16]: The mean of duration to negative conversion for all subjects were....

Commented [MOU17]: The mean of Leukocyte change with white blood cell

Commented [MOU18]: Deleted please

**Table 1.** Univariate analysis in 68 subjects with negative conversion.

Factors	Patient numbers	Patient with negative conversion			P value
		7 days	14 days	21 days	
<b>Total</b>	68	33	25	10	
<b>Gender</b>					0.166
Male	39	16	16	7	
Female	29	17	9	3	
<b>Age</b>					0.004*
<59 years	39	27	18	3	
≥59 years	29	6	7	7	
<b>BMI</b>					0.001*
<18.5 kg/m <sup>2</sup>	1	1	1	-	
18.5-24.9 kg/m <sup>2</sup>	27	21	5	1	
25-29.9 kg/m <sup>2</sup>	33	7	18	8	
≥30 kg/m <sup>2</sup>	6	4	1	1	
<b>Temperature</b>					0.014*
<38°C	26	18	6	2	
≥38°C	42	15	19	8	
<b>Dry cough</b>					0.331
Yes	39	16	17	6	
No	29	17	8	4	
<b>Shortness of breath</b>					0.000*
Yes	34	8	17	1	
No	34	25	8		
<b>Cold</b>					0.309
Yes	13	5	5	3	
No	55	28	20	7	
<b>Sore throat</b>					0.558

Yes	21	11	5	5	
No	47	22	20	5	
<b>Diarrhea</b>					0.758
Yes	13	7	3	3	
No	55	26	22	7	
<b>Nausea, vomiting</b>					0.946
Yes	23	9	12	2	
No	45	24	13	8	
<b>Diabetes Mellitus</b>					0.000*
Yes	17	2	8	7	
No	51	31	17	3	
<b>Hypertension</b>					0.768
Yes	30	15	11	4	
No	38	18	14	6	
<b>Cardiovascular disease</b>					0.745
Yes	5	2	3	-	
No	63	31	22	10	
<b>Malignancy</b>					0.540
Yes	4	-	4	-	
No	64	33	21	10	
<b>Lung disease</b>					0.639
Yes	9	5	3	1	
No	59	28	22	9	
<b>Dyslipidemia</b>					0.526
Yes	8	5	2	1	
No	60	28	23	9	
<b>Renal failure</b>					0.672
Yes	2	-	2	-	
No	66	33	23	10	
<b>Liver disease</b>					0.860
Yes	3	2	-	1	
No	65	31	25	9	
<b>Smoking habit</b>					0.540
Yes	4	-	4	-	
No	64	33	21	10	
<b>Leukocytes</b>					0.525
< 4000	10	4	4	2	
≥ 4000	58	29	21	8	
<b>Platelets</b>					0.414
< 150000	15	6	6	3	
≥ 150000	53	27	19	7	
<b>Lymphocytes</b>					0.607
< 20%	55	28	19	8	
≥ 20%	13	5	6	2	
<b>Neutrophils</b>					0.016*
< 70%	15	4	6	5	
≥ 70%	53	29	19	5	
<b>NLR</b>					0.838
< 3.13	11	5	5	1	



$\geq 3.13$	57	28	20	9	
<b>ALC</b>					0.344
< 1500	49	22	19	8	
$\geq 1500$	19	11	6	2	
<b>PLR</b>					0.922
< 200	31	16	10	5	
$\geq 200$	37	17	15	5	
<b>Albumin</b>					0.004*
< 3.0	26	6	14	6	
$\geq 3.0$	42	27	11	4	
<b>CRP</b>					0.050*
< 10	33	20	10	3	
$\geq 10$	35	13	15	7	
<b>CAR</b>					0.084
< 0.25	12	9	2	1	
$\geq 0.25$	56	24	23	9	
<b>Antiviral</b>					0.000*
Yes	40	28	10	2	
No	28	5	15	8	
<b>Antibiotic</b>					0.100
Yes	50	23	17	10	
No	18	10	8	-	
<b>Steroid</b>					0.706
Yes	50	10	6	4	
No	18	23	19	6	

\* $P < 0.05$ ; significant. *P* value from Kaplan-Meier analysis.

Abbreviation; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; ALC, absolute neutrophil count; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; CAR, C-reactive protein/albumin ratio.

Thirty-one factors were evaluated in the initial univariate Cox and Kaplan-Meier analysis (Table 1 and 2). Older age (>59 years), overweight (>25 kg/m<sup>2</sup>), fever (>38°C), shortness of breath, diabetes mellitus, neutrophilia, hypoalbuminemia, CRP and antiviral treatment showed significant association with negative conversion time. These factors were then included in a multivariate regression analysis. Hypoalbuminemia or albumin level of <3.0 g/dL was found as an independent factor associated with negative conversion time of viral RNA (HR:1.986; 95%CI:1.098-3.594), and hypoalbuminemia was presumed to cause prolonged viral clearance time in patients with COVID-19 (Table 2).

Commented [MOU19]: duration

**Table 2.** Univariate and multivariate analysis in 68 subjects with negative conversion.

Factors	Univariate analysis			Multivariate analysis		
	HR	95%CI	<i>P</i> value	HR	95%CI	<i>P</i> value
<b>Gender</b>	0.901	0.708-1.148	0.400	-	-	-
<b>Age</b>	0.620	0.360-1.068	0.085*	0.905	0.487-1.681	0.752
<b>BMI</b>	0.718	0.492-1.050	0.087*	0.692	0.428-1.118	0.133
<b>Temperature</b>	0.680	0.413-1.119	0.129*	0.791	0.427-1.467	0.457
<b>Dry cough</b>	1.155	0.713-1.871	0.558	-	-	-
<b>Cold</b>	1.201	0.655-2.204	0.553	-	-	-

<b>Shortness of breath</b>	1.994	1.199-3.315	0.008*	1.385	0.791-1.425	0.254
<b>Sore throat</b>	1.097	0.652-1.846	0.727	-	-	-
<b>Diarrhea</b>	1.058	0.576-1.943	0.856	-	-	-
<b>Nausea, vomiting</b>	1.011	0.609-1.679	0.967	-	-	-
<b>Diabetes Mellitus</b>	1.986	1.115-3.537	0.020*	1.926	0.995-3.729	0.520
<b>Hypertension</b>	0.957	0.593-1.546	0.859	-	-	-
<b>Cardiovascular disease</b>	0.906	0.362-2.268	0.834	-	-	-
<b>Malignancy</b>	1.220	0.440-3.382	0.703	-	-	-
<b>Lung disease</b>	0.902	0.447-1.820	0.773	-	-	-
<b>Dyslipidemia</b>	0.864	0.413-1.808	0.698	-	-	-
<b>Kidney failure</b>	1.209	0.294-4.969	0.792	-	-	-
<b>Liver disease</b>	1.060	0.331-3.396	0.922	-	-	-
<b>Smoking habit</b>	1.220	0.440-3.382	0.703	-	-	-
<b>Leukocytes</b>	1.137	0.580-2.225	0.709	-	-	-
<b>Platelets</b>	1.152	0.648-2.045	0.630	-	-	-
<b>Lymphocytes</b>	0.910	0.497-1.666	0.759	-	-	-
<b>Neutrophils</b>	1.512	0.843-2.713	0.166*	1.306	0.683-2.498	0.419
<b>NLR</b>	0.959	0.502-1.832	0.900	-	-	-
<b>ALC</b>	1.170	0.688-1.990	0.562	-	-	-
<b>PLR</b>	0.986	0.611-1.589	0.953	-	-	-
<b>Albumin</b>	1.540	0.935-2.534	0.090*	1.986	1.098-3.594	0.023**
<b>CRP</b>	0.751	0.465-1.215	0.244*	0.953	0.561-1.619	0.860
<b>CAR</b>	0.704	0.375-1.322	0.275	-	-	-
<b>Antiviral</b>	0.519	0.312-0.862	0.011*	0.704	0.383-1.294	0.258
<b>Antibiotic</b>	1.357	0.778-2.368	0.283	-	-	-
<b>Steroid</b>	1.062	0.629-1.792	0.823	-	-	-

\*P<0.25; significant, P value from univariate cox regression analysis.

\*\*P<0.25; significant, P value from multivariate cox regression analysis.

Abbreviation; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; ALC, absolute neutrophil count; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; CAR, C-reactive protein/albumin ratio; HR, hazard ratio; 95%CI, confidence interval.

#### 4. Discussion

The finding where older age (>59 years) was associated with delay in negative conversion time of SARS-CoV-2 RNA was consistent with the results from previous studies. Study by Hu et al. in 59 patients that were admitted with a diagnosis of COVID-19 reported that older age (>45 years) was an independent factor associated with delay in negative conversion time of viral RNA.<sup>7</sup> Another study by Zhang et al. in 70 patients that were diagnosed with COVID-19 also reported that older age (>50 years) significantly cause a delay in negative conversion time of viral RNA.<sup>10</sup> Elderly patients with COVID-19 reportedly had worse clinical outcome in comparison with younger patients.<sup>9</sup> Older age may also affected the number and function of T cells, resulting in uncontrolled viral replication and excessive host inflammatory response. This age-related disorder may also impair the ability of host cells to eradicate invasive pathogens, thus prolonging viral shedding in the elderly.<sup>7</sup> Comorbidities that came with older age also played a role in causing prolonged negative conversion time. Whilst the severity of

Commented [MOU20]: This study found that older .....

disease and comorbidities has no direct influence on PCR conversion time, these may indirectly influence the clearance of viral nucleic acid.<sup>9</sup> Older age was also reportedly associated with the numbers of viral RNA copies in patients with SARS-CoV infection, where increasing age was independently associated with higher viral load.<sup>10</sup>

Obesity was widely associated with a more severe clinical presentation of COVID-19 and a higher increase in inflammatory markers. This was possibly related to an increase in oxygen demand, thus prolonging the need of supplemental oxygen therapy during hospitalization, delaying viral clearance, and ultimately leading to prolonged hospitalization.<sup>13</sup> Univariate analysis found a significant association between body weight and prolonged negative conversion time of patients with COVID-19, where the negative conversion time will increase with increasing body weight. This result was supported by a previous study by Moriconi et al. that reported a longer negative conversion time in obese patients with COVID-19 (body mass index  $\geq 30$  kg/m<sup>2</sup>) in comparison with non-obese patients (19 $\pm$ 8 days vs. 13 $\pm$ 7 days,  $p=0.002$ ).<sup>11</sup> Obesity was known to cause disorders on both innate and adaptive immune systems, such as abnormal T cell activity, abnormal natural killer cell activity, disorders of phagocytic function, inhibition of neutrophil chemotaxis, and failure of the complement system.<sup>12</sup> Obesity may also cause hyper-activation of mammalian target of rapamycin (mTOR) signaling, thus prolonging the duration of viral shedding.<sup>13</sup>

The current study found that body temperature above 38°C may prolong negative conversion time, where patients with fever has a significantly longer negative conversion time in comparison to patients with normal body temperature. This was consistent with previous study by Li et al. where body temperature was reportedly found as an independent factor associated with the duration of viral shedding, in which patients with higher body temperature showed longer period of viral shedding (<37.3°C (9 days, IQR 7-11); 37.3-38.5°C (11 days, IQR 7-13);  $\geq 38.5^\circ\text{C}$  (12.5 days, IQR 9-17);  $p=0.046$ ). The study believed that the higher the body temperature of COVID-19 patients, the longer the patient will show persistent positive nucleic acid test results.<sup>14</sup> A retrospective study in children with COVID-19 also reported the same result, where longer duration of viral shedding was associated with higher body temperature. Fever was a manifestation of inflammatory response elicited by immune response. However, this study did not evaluate the cytokine levels in their subjects, thus the cause-and-effect relationship between longer viral clearance time and fever had not been clearly demonstrated.<sup>15</sup>

Patients with shortness of breath in the current study showed statistically longer negative conversion time in comparison with patients without this symptom. A similarly significant association between these two variables was also reported by Hu et al., wherein shortness of breath was proven to be an independent predictive factor for prolonged negative conversion time of viral RNA in patients with COVID-19 (HR: 0.290; 95%CI: 0.091-0.919).<sup>7</sup>

Diabetes mellitus (DM) was considered a comorbidity that may increase mortality and morbidity rate in patients with SARS CoV-2 infection. The current study found a significantly longer negative conversion time of SARS-CoV-2 RNA in patients with DM in comparison with those without this comorbidity. A retrospective cohort study in 70 patients diagnosed with COVID-19 reported that DM was an independent predictive factor for prolonged negative conversion time.<sup>10</sup> Another recent study also reported that DM comorbidity in patients with COVID-19 was associated with prolonged viral clearance.<sup>16</sup> Immune system dysregulation caused by diabetes mellitus may play a role in the pathogenesis COVID-19, particularly in prolonging the detection time of SAR-CoV-2 RNA. The mechanism underlying such dysregulation of the immune system in patients with DM were hyperglycemia, inhibition of neutrophil chemotaxis, cytokine dysregulation, and phagocytic cell dysfunction. Diabetic patients also presented with higher risk to develop severe disease, higher mortality rate, and was found to be a risk factor for disease progression.<sup>10</sup>

Commented [MOU21]: Deleted please

Commented [MOU22]: Change with of..

Commented [MOU23]: duration

Commented [MOU24]: duration

Commented [MOU25]: delete please

Commented [MOU26]: delete please

The current study found that increased neutrophil count (>70%) was significantly associated with prolonged negative conversion time of viral RNA. Similar result was also reported by Mo et al., where patients with prolonged negative conversion time (>18 days) had a significantly higher neutrophil count ( $3.94 [2.31-7.75] \times 10^9/L$ ), and that neutrophil count was proven to be an independent predictive factor for prolonged negative conversion time (OR, 0.097; 95%CI:0.015-0.631];  $p=0.015$ ).<sup>17</sup> Neutrophil was a widely known marker of systemic inflammation that was found to be a risk factor for the development of ARDS and progression from ARDS to mortality in patients with COVID-19.<sup>20</sup> Neutrophil, a main source of cytokines, would release cytokines and chemokines in a large number to help regulate the immune responses such as antiviral defense, hemopoietic action, angiogenesis or fibrogenesis.<sup>18</sup> Overproduction of neutrophil may contribute to acute lung injury and cytokine storm in COVID-19, thus prolonging the viral clearance time.<sup>19</sup> High neutrophil production was also associated with increased CD4<sup>+</sup> lymphocyte ratio. In a previous study, increased CD4<sup>+</sup> lymphocyte ratio was associated with a delay in negative conversion up to 24 days, most likely due to dysregulated immune system and prolonged viral clearance time.<sup>19</sup>

Commented [MOU27]: the study found that.. ( delete current)

Patients with increased C-reactive protein (CRP) level (>10) in the current study showed significantly longer negative conversion time of viral RNA in comparison to patients with lower CRP level (<10). A previous study by Moriconi et al. also reported the same result, where higher CRP level in obese patients with COVID-19 was associated with longer time for negative result from oropharyngeal or nasal swab test.<sup>11</sup> Study by Gao et al. also reported an association between increased CRP level and prolonged viral RNA shedding up to 28 days in patients with COVID-19.<sup>20</sup> Two to ten-fold increase in serum CRP levels above normal value reportedly caused a significantly prolonged duration of viral shedding, and also showed a significant negative correlation with CD4<sup>+</sup> T lymphocyte counts, a factor that was known to influence immune response and viral shedding.<sup>21</sup> Analysis conducted with multiple linear regression model by Fu et al. found that CD4<sup>+</sup> T lymphocyte counts could help predict the duration of viral RNA shedding in stool specimen and lower absolute CD4<sup>+</sup> T lymphocyte counts before treatment may prolong the viral clearance time.<sup>8</sup>

Commented [MOU28]: change with this study

Antiviral treatment was found to significantly shorten the negative conversion time in patient with COVID-19. Result from the univariate analysis in the current study indicated that patients receiving antiviral therapy had significantly shorter negative conversion time in comparison with patients that did not receive this therapy. Previous study by Fu et al. also reported that the time when antiviral therapy was first initiated was an independent factor associated with SARS-CoV-2 RNA shedding (HR=1.467, 95%CI: 1.187-1.815,  $p<0.001$ ).<sup>22</sup> The study reported shorter negative conversion time in patients who received antiviral therapy. The limitation of this study are the small number of samples, and patients' data that is till diverse such as smoking habits, patients' comorbidities, and patient's severity of Covid-19.

Commented [MOU29]: please write again with better grammar

Hypoalbuminemia was an independent predictor for prolonged negative conversion of viral RNA in patients with COVID-19. Further study is needed to be done on more samples and a more homogenous population.

Commented [MOU30]: please deleted, change with " with"

## 6. Acknowledgements

All authors conceived this research. FNK, BHW, and AS collected and analyzed data. FNK designed and supervised the entire project scientifically. BHW and AS are major contributors in writing the manuscript, TH participated in the manuscript writing and submission, F and JT reviewed and edited the paper. FNK had final responsibility for the decision to submit for publication. We thank to the Internal Medicine Department of the Faculty of Medicine University Diponegoro and Dr Kariadi Hospital and who supported the research.

Commented [MOU31]: please write clearly.

Commented [MOU32]: clearly

Commented [MOU33]: ??????

Commented [MOU34]: ????

All authors have read and approved the final manuscript. This research was not funded by any party.

## References

Commented [MOU35]: References

25. Chen D, Xu W, Lei Z, Huang Z, Liu J. Recurrence of positive SARS-CoV-2 RNA in COVID-19: A case report. *Int J Infect Dis.* 2020; 93:297–9.
26. Hu X, Xing Y, Jia J, Ni W, Liang J, Zhao D, et al. Factors associated with negative conversion of viral RNA in patients hospitalized with COVID-19. *Sci Total Environ* [Internet]. 2020;728(175):138812. Available from: <https://doi.org/10.1016/j.scitotenv.2020.138812>
27. Ling Y, Xu S, Lin Y, Tian D, Zhu Z, Dai F, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chin Med J.* 2020;133(9):1–5.
28. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054–62.
29. Perdhana L, Shofa C, Yudo MM, Siti N. Peran Gejala Depresi sebagai Faktor Prediktor Kematian dalam Enam Bulan pada Lansia yang Menjalani Hemodialisis. *Jurnal Penyakit Dalam Indonesia*, 2021. 8(4), 179-186.
30. Zhang F, Hu H, Wang X, Li X, Yang Y, Li L, et al. Prediction for the Negative Conversion Probability of Nucleic Acid Testing in Patients with Nonsevere COVID-19 Pneumonia: A Model Based on Retrospective Cohort Study. 2020;1–17.
31. Liu K, Chen, Y., Lin, R., Han, K., 2020. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. *J. Infect.* <https://doi.org/10.1016/j.jinf.2020.03.005> (Epub ahead of print).
32. World Health Organization. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases. Geneva: World Health Organization; 2020.
33. Direktorat Jenderal Pencegahan dan Pengendalian Penyakit. Pedoman Kesiapsiagaan Menghadapi Coronavirus Disease (COVID-19) Maret 2020. Jakarta: Kementerian Kesehatan Republik Indonesia; 2020.
34. To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis.* 2020 May;20(5):565-574.
35. Moriconi D, Masi S, Rebelos E, Virdis A, Manca ML, De Marco S, Taddei S, Nannipieri M. Obesity prolongs the hospital stay in patients affected by COVID-19, and may impact on SARS-COV-2 shedding. *Obes Res Clin Pract.* 2020 May-Jun;14(3):205-209.
36. Holly JMP, Biernacka K, Maskell N, Perks CM. Obesity, Diabetes and COVID-19: An Infectious Disease Spreading from the East Collides with the Consequences of an Unhealthy Western Lifestyle. *Front Endocrinol (Lausanne).* 2020; 11: 1–13.
37. Caci G, Albini A, Malerba M, Noonan DM, Pochetti P, Polosa R. COVID-19 and Obesity: Dangerous Liaisons. *J Clin Med.* 2020;9(8):2511.
38. Li TZ, Cao ZH, Chen Y, Cai MT, Zhang LY, Xu H. Duration of SARS-CoV-2 RNA shedding and factors associated with prolonged viral shedding in patients with COVID-19. *J Med Virol.* 2020;(May):1–7.
39. Lu Y, Li Y, Deng W, Liu M, He Y, Huang L, et al. Symptomatic Infection is Associated with Prolonged Duration of Viral Shedding in Mild Coronavirus Disease 2019: A Retrospective Study of 110 Children in Wuhan. *Pediatr Infect Dis J.* 2020;39(7): E95–9.
40. Chen X, Hu W, Ling J, Mo P, Zhang Y, Jiang Q, et al. Hypertension and Diabetes Delay the Viral Clearance in COVID-19 Patients. *medRxiv* [preprint]. 2020;
41. Mo P, Deng L, Liu X, Gao S, Liang K, Luo M, et al. Risk factors for delayed negative conversion of SARS-CoV-2 in patients with COVID-19 pneumonia: a retrospective cohort study. *Epidemiol Infect.* 2020;1–23.

42. Tecchio C, Micheletti A, Cassatella MA. Neutrophil-derived cytokines: Facts beyond expression. *Front Immunol.* 2014;5(OCT):1–7.
43. Wang H, Zhang Y, Mo P, Liu J, Wang H. Neutrophil to CD4+ lymphocyte ratio as a potential biomarker in predicting virus negative conversion time in COVID-19. *Int Immunopharmacol.* 2020;(January).
44. Tian D, Wang L, Wang X, Ge Z, Cui S, Xu Y, et al. Clinical research and factors associated with prolonged duration of viral shedding in patients with COVID-19. 2020;1–16.
45. Gao C, Zhu L, Jin CC, Tong YX, Xiao AT, Zhang S. Proinflammatory cytokines are associated with prolonged viral RNA shedding in COVID-19 patients. *Clin Immunol.* 2020;221(1095).
46. Fu Y, Han P, Zhu R, Bai T, Yi J, Zhao X. Risk factors for viral RNA shedding in COVID-19 patients. *Eur Respir J.* 2020 Jul 2;56(1):2001190.

*CHECK LIST MANUSCRIPT CROSS SECTIONAL  
MEDICA HOSPITALIA : JOURNAL OF CLINICAL MEDICINE*

Judul : Factors Influencing the Delay in Negative Conversion of PCR Swab Test Results in Patients with Covid-19

Penulis :

SUBSTANSI	DESKRIPSI	BERI TANDA ✓☒
<b>JUDUL</b>	Tidak terlalu panjang / pendek, 12 – 14 kata	✓
	Tidak menggunakan singkatan kecuali baku	✓
	Menggambarkan isi makalah secara keseluruhan	✓
<b>ABSTRAK</b>	Terstruktur (latar belakang, tujuan, metode, hasil, kesimpulan)	✓
	Tidak menggunakan singkatan kecuali baku	✓
	Informatif	✓
	Kata kunci 3 – 5 kata	✓
<b>PENDAHULUAN</b>	Terdiri atas dua paragraf atau bagian	<ul style="list-style-type: none"> <li>• Latar Belakang terlalu Panjang (lebih dari 2 bagian. Keterangan pada</li> <li>• Alinea ke-2 sebaiknya dimasukkan dalam Metode, bukan di latar belakang</li> </ul>
	Paragraf / bagian pertama: Latar belakang penelitian (justifikasi mengapa penelitian perlu dilakukan): apa yang sudah diketahui, apa yang perlu ditambahkan	<ul style="list-style-type: none"> <li>• Paragraf ke 3 di latar belakang sebaiknya menjadi paragraph 1 di latar belakang setelah definisi Covid-19</li> </ul>
	Paragraf kedua: Hipotesis atau tujuan penelitian	✓
	Didukung oleh pustaka yang relevan dan kuat	✓
	Tidak lebih dari 1 halaman	Latar belakang terlalu Panjang meskipun tidak lebih dari 1 halaman
<b>METODE</b>	Menunjukkan kata kunci tentang desain penelitian pada awal tulisan	✓
	Menjelaskan keadaan, tempat, waktu penelitian termasuk lama pengumpulan data	✓
	Menyebutkan kriteria inklusi, sumber dan metode pengumpulan data / subyek	✓
	Menyebut variabel penelitian, keluaran, paparan dan hal-hal yang dapat mempengaruhi hasil penelitian	✓
	Menyebut metode pengukuran secara detail	✓
	Jelaskan semua hal untuk mencegah terjadinya bias	Tidak dijelaskan

	Jelaskan perhitungan jumlah sampel (rumus tidak perlu dicantumkan)	Tidak dijelaskan pada metode
	Outcome primer	✓
	Outcome sekunder	✓
	Definisi variabel yang penting	Tidak dijelaskan Definisi operasional Faktor yang mempengaruhi, misalnya definisi Diabetes Melitus, Dislipidemia, Smoking Habit
	Cara pengumpulan dan manajemen data	Tidak dijelaskan apakah data berasal dari data sekunder rekam medis terutama keterangan tentang faktor-faktor yang mempengaruhi
	Jelaskan semua metode statistik yang digunakan, termasuk yang untuk mengendalikan faktor perancu	Metode statistic di jelaskan tetapi pengendalian faktor perancu tidak dijelaskan
	Analisis dilakukan dengan uji yang sesuai dengan data, batas kemaknaan dan interval kepercayaan	✓
	Ethical clearance	✓
	Persetujuan setelah penjelasan ( <i>informed consent</i> )	Tidak dijelaskan
	Program komputer yang digunakan	
<b>HASIL</b>	Laporkan jumlah subyek penelitian pada setiap tahapan (misal jumlah subyek yang memenuhi syarat, jumlah subyek yang mengikuti penelitian, jumlah yang menyelesaikan <i>follow up</i> dan jumlah yang dianalisis.	Tidak dijelaskan secara detail, hanya menjelaskan jumlah subjek yang ikut dalam penelitian
	Sajikan dalam urutan yang logis	✓
	Karakteristik subyek penelitian (dalam bentuk tabel)	✓
	Penyajian bilangan numerik ditulis secara benar	✓
	Tidak menggunakan persentase bila jumlah subyek sedikit (< 40)	Masih menggunakan % meskipun jumlah subyek < 40
	Sertakan hasil dan uji hipotesis tanpa komentar	✓
	Batasi tabel 3-4 tiap artikel	✓
	Sebutkan tabel dan gambar dalam nas	✓
<b>DISKUSI</b>	Sebutkan hasil utama berdasarkan tujuan penelitian	<ul style="list-style-type: none"> <li>• Tidak dijelaskan secara eksplisit.</li> <li>• Alinea 1 discussion tidak perlu dicantumkan pada discussion karena sudah</li> </ul>



		dijelaskan pada metode (agar tidak terjadi pengulangan)
	Bahas keterbatasan penelitian, hal-hal yang dapat menjadi penyebab bias. Pembahasan secara menyeluruh dari segala aspek	Pada pembahasan penulis hanya membandingkan dengan hasil dari penelitian lain tapi tidak menjelaskan penyebab bias dan pembahasan menyeluruh dari segala aspek
	Sebutkan interpretasi menyeluruh dari hasil penelitian dihubungkan dengan tujuan, keterbatasan, analisis, hasil penelitian serupa dan bukti-bukti relevan lainnya	Keterbatasan penelitian tidak dijelaskan pada penelitian ini
	Dibahas kemungkinan hasil penelitian digeneralisasikan (validitas eksterna)	Sebenarnya penelitian ini memiliki hasil HR dan 95% CI tapi di pembahasan tidak tersampaikan apa makna hasil ini untuk generalisasi hasil
<b>KESIMPULAN</b>	Kesimpulan pada paragraf terakhir diskusi, tidak menjadi sub bab tersendiri	Kesimpulan dipisahkan dalam sub bab tersendiri
	Harus menjawab pertanyaan penelitian	✓
	Harus didasarkan pada data penelitian, bukan dari pustaka	Kesimpulan memasukkan hampir keseluruhan faktor yang mempengaruhi padahal hasil penelitian yang bermakna sebagai faktor yang mempengaruhi hanya albumin
	Dapat disertakan saran untuk penelitian selanjutnya	Tidak dicantumkan
<b>KEPUSTAKAAN</b>	Menurut Vancouver (lihat <i>Uniform Requirements for Manuscript Submitted to Biomedical Journals</i> ). www.icjme.	Pada literatur no 3 hanya menuliskan 3 penulis langsung et al, sebaiknya dituliskan 6 penulis dulu baru et al
<b>INFORMASI LAIN</b>	Ucapan terimakasih tidak secara berlebihan	Sedikit aneh pemilihan kata Our thanks go to untuk menyatakan terima kasih.
	Sumber pendanaan bila ada dan ingin disebutkan	✓
<b>REKOMENDASI ARTIKEL</b>	Diterima dengan perbaikan	✓
	Diterima tanpa perbaikan	
	Ditolak	

Tambahkan informasi lain yang ingin disampaikan :

Sebaiknya penulis melihat kembali Author Guideline dari jurnal ini dan memperbaiki manuskript sesuai author guideline. Pemilihan kata dalam bahasa Inggris mohon diperbaiki, jangan menggunakan Bahasa Inggris dari google translate.

Nama dan tanda tangan

A handwritten signature in black ink, appearing to read 'Shinta Oktya Wardhani'.

DR.dr.Shinta Oktya Wardhani,Sp.PD-KHOM

**CHECK LIST MANUSCRIPT CROSS SECTIONAL**  
**MEDICA HOSPITALIA : JOURNAL OF CLINICAL MEDICINE**

Judul : **Factors Influencing the Delay in Negative Conversion of PCR Swab Test Results in Patients with COVID-19**

Penulis : unknown

SUBSTANSI	DESKRIPSI	BERI TANDA ✓/✗
<b>JUDUL</b>	Tidak terlalu panjang / pendek, 12 – 14 kata	✓
	Tidak menggunakan singkatan kecuali baku	✓
	Menggambarkan isi makalah secara keseluruhan	✓
<b>ABSTRAK</b>	Terstruktur (latar belakang, tujuan, metode, hasil, kesimpulan)	✓
	Tidak menggunakan singkatan kecuali baku	✓
	Informatif	✓
	Kata kunci 3 – 5 kata	✓
<b>PENDAHULUAN</b>	Terdiri atas dua paragraf atau bagian	Tidak
	Paragraf / bagian pertama: Latar belakang penelitian (justifikasi mengapa penelitian perlu dilakukan): apa yang sudah diketahui, apa yang perlu ditambahkan	Tidak
	Paragraf kedua: Hipotesis atau tujuan penelitian	Tidak
	Didukung oleh pustaka yang relevan dan kuat	✓
	Tidak lebih dari 1 halaman	✓
<b>METODE</b>	Menunjukkan kata kunci tentang desain penelitian pada awal tulisan	✓
	Menjelaskan keadaan, tempat, waktu penelitian termasuk lama pengumpulan data	✓
	Menyebutkan kriteria inklusi, sumber dan metode pengumpulan data / subyek	✓
	Menyebut variabel penelitian, keluaran, paparan dan hal-hal yang dapat mempengaruhi hasil penelitian	✓
	Menyebut metode pengukuran secara detail	✓
	Jelaskan semua hal untuk mencegah terjadinya bias	Tidak *
	Jelaskan perhitungan jumlah sampel (rumus tidak perlu dicantumkan)	Tidak dijelaskan**
	Outcome primer	-
	Outcome sekunder	-
	Definisi variabel yang penting	
	Cara pengumpulan dan manajemen data	Seharusnya dijelaskan mengambil data dari medical record
	Jelaskan semua metode statistik yang digunakan, termasuk yang untuk mengendalikan faktor perancu	✓
	Analisis dilakukan dengan uji yang sesuai dengan data, batas kemaknaan dan interval kepercayaan	✓
	Ethical clearance	✓
	Persetujuan setelah penjelasan ( <i>informed consent</i> )	✓
Program komputer yang digunakan	-	

<b>HASIL</b>	Laporkan jumlah subyek penelitian pada setiap tahapan (misal jumlah subyek yang memenuhi syarat, jumlah subyek yang mengikuti penelitian, jumlah yang menyelesaikan follow up dan jumlah yang dianalisis.	Tidak ada
	Sajikan dalam urutan yang logis	✓
	Karakteristik subyek penelitian (dalam bentuk tabel)	✓
	Penyajian bilangan numerik ditulis secara benar	✓
	Tidak menggunakan persentase bila jumlah subyek sedikit (< 40)	✓
	Sertakan hasil dan uji hipotesis tanpa komentar	-
	Batasi tabel 3-4 tiap artikel	✓
	Sebutkan tabel dan gambar dalam naskah	✓
<b>DISKUSI</b>	Sebutkan hasil utama berdasarkan tujuan penelitian	✓
	Bahas keterbatasan penelitian, hal-hal yang dapat menjadi penyebab bias. Pembahasan secara menyeluruh dari segala aspek	Tidak
	Sebutkan interpretasi menyeluruh dari hasil penelitian dihubungkan dengan tujuan, keterbatasan, analisis, hasil penelitian serupa dan bukti-bukti relevan lainnya	✓
	Dibahas kemungkinan hasil penelitian digeneralisasikan (validitas eksternal)	Tidak
<b>KESIMPULAN</b>	Kesimpulan pada paragraf terakhir diskusi, tidak menjadi sub bab tersendiri	✓
	Harus menjawab pertanyaan penelitian	✓
	Harus didasarkan pada data penelitian, bukan dari pustaka	✓
	Dapat disertakan saran untuk penelitian selanjutnya	-
<b>KEPUSTAKAAN</b>	Menurut Vancouver (lihat <i>Uniform Requirements for Manuscript Submitted to Biomedical Journals</i> ). <a href="http://www.icjme">www.icjme</a> .	Perbaiki ref 12, 13, 16, 20, 21, 23, 24
<b>INFORMASI LAIN</b>	Ucapan terimakasih tidak secara berlebihan	✓
	Sumber pendanaan bila ada dan ingin disebutkan	✓
<b>REKOMENDASI ARTIKEL</b>	Diterima dengan perbaikan	YA
	Diterima tanpa perbaikan	-
	Ditolak	-

Tambahkan informasi lain yang ingin disampaikan :

Penelitian yang menarik dan bagus, selamat untuk penulis.

Ada beberapa yang ingin saya tanyakan dan butuh klarifikasi:

- \* Kriteria inklusi pada penelitian ini menilai COVID menggunakan PCR dan Rapid TES? Mengapa tidak semua dengan PCR? Ini dapat mengganggu hasil penelitian mengingat rapid test bukan standar diagnosis untuk COVID, sehingga bisa saja pasien yang konversi negatif dihari ke 7 adalah pasien yang sebenarnya adalah COVID negatif. Jadi baiknya ditampilkan berapa pasien yang diagnosis awal dengan rapid tes dan berapa yang dengan PCR.

- Lalu jika diagnosis awal menggunakan PCR, bagaimana dengan nilai CT (cycle threshold)-nya? Seharusnya juga menentukan tingkat konversi pCR penyembuhan.
- \*\* tidak dijelaskan jumlah 68 didapat dari mana? Apakah total sampling atau random atau bagaimana?
- Tidak dijelaskan 68 subjek yang masuk dalam penelitian ini apakah termasuk covid ringan? Sedang? Berat? Ini akan berpengaruh terhadap konversi PCR (Hu X, et al, referensi nomor 7) apakah semua pasien rawat inap atau ada yang rawat jalan.
- Pemeriksaan 7 14 dan 21 hari, mohon ditambahkan apakah terhitung dari hari sakit, bukan hari rawat?

Selamat ...good job

Nama dan tanda tangan



Indra Wijaya

[MHJCM] New notification from **Medica Hospitalia** : Journal of Clinical Medicine

Dr. dr. Sp. OG(K) Erwinanto Erwinanto erwinanto.spoq@gmail.com [lapang saad hit.id](#)

Sab, 30 Jul 2022, 10:59

Terjemahkan ke Indonesia

You have a new notification from **Medica Hospitalia** - Journal of Clinical Medicine

An issue has been published.

Link: <http://medicahospitalia.rskafid.co.id/medicahospitalia/index.php/mh/issue/current>

Dr. dr. Erwinanto, Sp. OG(K)

Best Regards,

**Medica Hospitalia**  
Journal of Clinical Medicine  
RSUP Dr. Karlandi Semarang

Father Nur Kholis fatherkholis@gmail.com

Sab, 30 Jul 2022, 11:56

thank you very much

xxx

Balas Teruskan