

# The Relationship Between the Effectiveness of Heparin Administration and Hypercoagulation Complications in Hospitalized Patients With Confirmed COVID-19

**Muhammad Fachri**

Universitas Muhammadiyah Jakarta

**Mochammad Hatta** (✉ [hattaram@yahoo.com](mailto:hattaram@yahoo.com))

Hasanuddin University

**Sefia Nabila Nur Azmi Tarigan**

Universitas Muhammadiyah Jakarta

**Risky Akapura**

Universitas Muhammadiyah Jakarta

**Ressy Dwiyanti**

Tadulako University

**Ahmad Syukri**

Hasanuddin University

**Ade Rifka Junita**

Hasanuddin University

**Andini Febrianty**

Hasanuddin University

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## Research Article

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# Abstract

**Background:** Thrombotic complications of COVID-19 are a worrisome aspect of the disease due to its high incidence in critically ill patients and poor clinical manifestations. The aim of this study was to determine the relationship between the effectiveness of heparin administration and complications of hypercoagulation in hospitalized patients with confirmed COVID-19.

**Method:** This research was analytically observational. The study design used was a retrospective cohort approach of pre- and post-tests. This study used secondary data taken from medical records of inpatients with confirmed COVID-19 at Islamic Hospital Jakarta Sukapura. The total sampling technique was used.

**Result:** There were 98 study subjects, with 35 patients receiving UFH and 63 patients receiving LMWH (fondaparinux). Most of the subjects were women (52%), with the most common age group being >60 years (30.6%). In the UFH group, the greatest decrease ( $0.01 \pm 0.5$  g FEU/mL) was observed in 12 patients (34.3%). In the LMWH group (fondaparinux), the greatest decrease ( $0.01 \pm 0.5$  g FEU/mL) was observed in 15 patients (23.8%). Additionally, there was no significant difference between UFH and fondaparinux ( $p$  0.193) in hospitalized patients with confirmed COVID-19 for the period of August 2020 – August 2021. Most inpatients with confirmed COVID-19 at RSIJ Sukapura were aged 50-59 years and were women.

**Conclusion:** There was a tendency toward increased D-dimer values, normal PT values, normal APTT values, and increased fibrinogen values in each COVID-19 patient, but there was no statistically significant relationship. There was also no significant relationship between the D-dimer and APTT parameters, whereas the PT parameter showed a significant relationship in confirmed COVID-19 inpatients.

## Background

Since being notified on December 31, 2019, of a new virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which attacks the respiratory system, coronavirus disease-19 (COVID-19) has been labelled a global pandemic. COVID-19 has had a disastrous effect on the global demography, causing more than 3.8 million deaths in various countries, later giving rise to the most important global health crisis after the influenza pandemic of 1918. On January 30, 2020, the WHO declared COVID-19 a “Public Health Emergency of International Concern” because of its rapid transmission and consequent casualties affecting the public as well as health services worldwide [1].

Indonesia announced its first COVID-19 case on March 2, 2020, which is 4 months after the first case in China, which amounted to 2 cases, and after that on March 6, 2020, 2 positive confirmed cases of COVID-19 were found. The addition of cases that initially only amounted to hundreds has subsequently reached far into the thousands. As of September 15, 2021, the Government of the Republic of Indonesia has reported that 4,178,164 people have been confirmed positive for COVID-19, with a death toll of 139,682 related to COVID-19 that has been reported and a cure rate of 3,953,519 having recovered from the disease [2].

Patients with confirmed COVID-19 usually present with fever, cough, and dyspnoea. Other less common symptoms include myalgia, rhinorrhea, sore throat, headache, and diarrhoea. On laboratory examination, we found lymphocytopenia and increased CRP, while abnormalities from other laboratory tests in cases complicated by coagulopathy included increased D-dimer, thrombocytopenia, a prolonged prothrombin

time, increased fibrinogen, increased lactate dehydrogenase, and increased ferritin. Typical imaging findings include bilateral ground-glass opacities, as well as bilateral multiple lobular and subsegmental areas of consolidation. In severe cases, complications include respiratory failure, septic shock, and multiple organ failure [3,4,5].

Thrombotic complications of COVID-19 are a worrisome aspect of the disease due to its high incidence in critically ill patients and its poor clinical manifestations. There are several reports that coagulopathy has been found in COVID-19 patients as either arterial or venous thrombosis. COVID-19 causes patients to develop a hypercoagulable state, but the pathophysiology behind the thrombotic complications seen in this disease is still not well understood. Several mechanisms have been proposed, and these possibly involve the host immune response, which contributes to vascular endothelial cell injury, inflammation, activation of the coagulation cascade through tissue factor expression, and cessation of fibrinolysis [3,4,5].

Management guidelines for thromboembolism in COVID-19 have been established by the WHO. The management of adolescents and adults hospitalized with confirmed COVID-19 involves using low molecular weight heparin (LMWH) to prevent venous thromboembolism (VTE). Apart from the anticoagulant effect of heparin, LMWH has also been shown to have anti-inflammatory properties, which may be beneficial in combating the proinflammatory state caused by the coronavirus. Heparin is also known to have a suppressive effect on the expression of IL-6 and IL-8 in lung epithelial cells, which may help reduce the thrombotic complications associated with the host immune response to COVID-19. LMWH (fondaparinux) is an indirect factor Xa inhibitor, but LMWH (fondaparinux) does not inhibit thrombin at all, which is why LMWH (fondaparinux) is better for preventing heparin-induced thrombocytopenia (HIT) [3,4,6]. The purpose of this study was to determine the effectiveness of the anticoagulant heparin in hospitalized COVID-19 patients with hypercoagulable complications and to compare this effectiveness with that of UFH or LMWH (fondaparinux).

## **Method**

### **Research Design**

This study was analytically observational. The research design used was a retrospective cohort approach of pre- and post-tests. This study used secondary data taken from medical records of inpatients who had a confirmed diagnosis of COVID-19 at Islamic Hospital Jakarta Sukapura. The study used the total sampling technique.

### **Statistical Analysis**

The collected data were edited, coded, and entered into a computer file, and the data were cleaned and then categorized into five groups that focused on the D-dimer reference value using the CLIA method, namely, 0.036–0.708 g FEU/mL. Next, the chi-square test was performed to compare the two variables in each group, and the independent samples T test was performed. To determine whether there was a significant difference between each group, the Kolmogorov–Smirnov normality test was carried out, which showed that the data obtained were normally distributed. The chi-square test and the Kolmogorov–Smirnov normality test were also performed on the

characteristic data from those collected. For all statistical tests, a p value < 0.05 was considered significant. All calculations used IBM SPSS Statistics version 26.

## Results

Of the 702 inpatients who were confirmed to test positive at Islamic Hospital Jakarta Sukapura, certain patients underwent PT and aPTT examinations before and after administration of the anticoagulants heparin and LMWH (fondaparinux): only 11 patients underwent PT and aPTT examinations before and after anticoagulation, with 9 of them given heparin and the other 2 given LMWH (fondaparinux). Therefore, research on the effectiveness of heparin administration could not be carried out based on the PT and aPTT values due to the unequal number of populations from each group. The patients who received the fibrinogen test before and after anticoagulation were not noted. Therefore, the study of the effectiveness of heparin administration could not be carried out based on the fibrinogen value.

Table 1 shows that from 98 samples of confirmed COVID-19 inpatients at Islamic Hospital Jakarta Sukapura for the period August 2020 - August 2021, distributed based on age, it was found that inpatients confirmed COVID-19 at Islamic Hospital Jakarta Sukapura during the period August 2020 - August 2021 showed that most patients were in the >60-year age group, as many as 30 patients (30.6%). The fewest number of patients found in the 21-30 years age group was 6 patients (6.1%).

**Table 1. Frequency and Percentage of Distribution by Age of Inpatients with Confirmed COVID-19 at Islamic Hospital Jakarta Sukapura Period August 2020 – August 2021**

Age	Number of Patients	
	N	%
21–30	6	6.1
31–40	18	18.4
41–50	19	19.4
51–60	25	25.5
>60	30	30.6
Amount	98	100.0

Table 2 shows that among 98 samples of confirmed COVID-19 inpatients at Islamic Hospital Jakarta Sukapura in the period August 2020 – August 2021, distributed by sex, there was a greater proportion of women, that is, a total of 51 women (52%) and 47 men (48%).

**Table 2. Frequency and Percentage of Distribution by Gender of Inpatients with Confirmed COVID-19 at Islamic Hospital Jakarta Sukapura in the Period of August 2020 – August 2021**

Gender	Number of Patients	
	N	%
Men	47	48
Women	51	52
Amount	98	100.0

Table 3 shows that of the 98 samples of confirmed COVID-19 inpatients at Islamic Hospital Jakarta Sukapura in the period of August 2020 – August 2021, the distribution was based on the D-dimer value of patients who first entered the hospital. The D-dimer value was the highest (1.01–5 g FEU/mL) in 44 patients (44.9%), and the lowest D-dimer values (<0.708 g FEU/mL) were found in 8 patients (8.2%).

**Table 3. Frequency and Percentage of Distribution Based on the D-Dimer Values of Patients Entering Hospital for Inpatient Confirmed COVID-19 at Islamic Hospital Jakarta Sukapura in the Period of August 2020 – August 2021**

Early D-Dimer	Number of Patients	
	N	%
<0.708 g FEU/mL	8	8.2
0.708-1 g FEU/mL	21	21.4
1.01-5 g FEU/mL	44	44.9
5.01-10 g FEU/mL	10	10.2
>10 g FEU/mL	15	15.3
Amount	98	100.0

Based on Table 4, the 98 samples were then divided into 5 age groups. In the 21-30-year age group, there were 6 samples (6.1%), consisting of 2 samples in the UFH group and 4 samples in the LMWH group (fondaparinux). In the 31-40-year age group, there were a total of 18 samples (18.4%), consisting of 4 samples in the UFH group and 14 samples in the LMWH group (fondaparinux). The 41-50-year age group totalled 19 samples (19.4%), consisting of 4 samples in the UFH group and 15 samples in the LMWH group (fondaparinux). The 51-60-year age group totalled 25 samples (25.5%), consisting of 10 samples in the UFH group and 15 samples in the LMWH group (fondaparinux). The group aged 60 years and over had a total of 30 samples (30.6%), consisting of 15 samples in the UFH group and 15 samples in the LMWH group (fondaparinux). In the gender group, there were a total of 47 (48%) male samples, namely, 16 samples from the UFH group and 31 samples from the LMWH group (fondaparinux). The total number of women was 51 (52%), consisting of 19 samples from the UFH group and 32

samples from the LMWH group (fondaparinux). Table 1 shows that there was no significant difference ( $p > 0.05$ ) in the age and gender variables between the UFH and LMWH (fondaparinux) groups.

**Table 4. Frequency Comparison of the Age and Gender of Inpatients with Confirmed COVID-19 at Islamic Hospital Jakarta Sukapura in the period of August 2020 – August 2021 between the UFH and LMWH (fondaparinux) groups**

Variable	UFH (n = 35)		LMWH (fondaparinux) (n = 63)		Total		P
	N	%	n	%	n	%	
	<b>Age</b>						
21–30	2	2%	4	4.1%	6	6.1%	p = 0.193
31–40	4	4.1%	14	14.3%	18	18.4%	
41–50	4	4.1%	15	15.3%	19	19.4%	
51–60	10	10.2%	15	15.3%	25	25.5%	
>60	15	15.3%	15	15.3%	30	30.6%	
<b>Gender</b>							
Man	16	16.3%	31	31.6%	47	48%	p = 0.740
Woman	19	19.4%	32	32.7%	51	52%	

Table 5 shows the following:

1. Two patients were hospitalized before being given UFH, with D-dimer values  $<0.708$  g FEU/mL. After being given UFH, 1 patient had an increase in the D-dimer value, and 1 patient experienced a decrease of  $0.01 \pm 0.5$  g FEU/mL in the D-dimer value.
2. Seven patients were hospitalized before being given UFH, with a D-dimer value of  $0.708 - 1$  g FEU/mL. After being given UFH, 3 patients exhibited an increase in D-dimer values and 4 patients exhibited a decrease of  $0.01 \pm 0.5$  g FEU/mL in the D-dimer value.
3. Sixteen patients were hospitalized before being given UFH, with a D-dimer value of  $1.01 - 5$  g FEU/mL. After being given UFH, 4 patients experienced an increase in the D-dimer value, 6 patients experienced a decrease of  $0.01 \pm 0.5$  g FEU/mL in the D-dimer value, and 3 patients experienced a decrease of  $0.501 \pm 1$  g FEU./mL in the D-dimer value, and 3 patients had a decrease of  $1 \pm 5$  g FEU/mL in the D-dimer value.

4. Four patients were hospitalized before being given UFH, with a D-dimer value of 5.01-10 g FEU/mL. After being given UFH, 1 patient experienced a decrease of  $0.01 \pm 0.5$  g FEU/mL in the D-dimer value, and 3 patients experienced a decrease of  $1 \pm 5$  g FEU/mL in the D-dimer value.
5. Six patients were hospitalized before being given UFH, with D-dimer values  $>10$  g FEU/mL, all of whom experienced a decrease of  $>5$  g FEU/mL in the D-dimer value after being given UFH.

**Table 5. Comparison of D-dimer values before and after UFH was administered to inpatients with confirmed COVID-19 at Islamic Hospital Jakarta Sukapura in the Period from August 2020 – August 2021**

		D-Dimer (post-UFH)					P Value	
		increase	0.01±0.5 g FEU/mL decrease	0.501±1 g FEU/mL decrease	1±5 g FEU/mL decrease	>5 g FEU/mL decrease		Total
<b>D-Dimer (pre-UFH)</b>	<0.708 g FEU/mL	1	1	0	0	0	2	<b>p = &lt;0.001</b>
	0.708-1 g FEU/mL	3	4	0	0	0	7	
	1.01-5 g FEU/mL	4	6	3	3	0	16	
	5.01-10 g FEU/mL	0	1	0	3	0	4	
	>10 g FEU/mL	0	0	0	0	6	6	
<b>Total</b>		8	12	3	6	6	35	
		22.9%	34.3%	8.6%	17.1%	17.1%	100%	

Table 6 shows the following:

1. Six patients were hospitalized before being given LMWH (fondaparinux), with D-dimer values  $<0.708$  g FEU/mL. After being given LMWH (fondaparinux), 4 patients experienced an increase in D-dimer values, and 2 patients experienced a  $0.01 \pm 0.5$  g FEU/mL decrease in the D-dimer value.
2. Fourteen patients were hospitalized before being given LMWH (fondaparinux), with a D-dimer value of 0.708–1 g FEU/mL. After being given LMWH (fondaparinux), 6 patients experienced an increase in D-dimer values, 6 patients experienced a  $0.01 \pm 0.5$  g FEU/mL decrease in the D-dimer value, and 2 patients experienced a  $0.501 \pm 1$  g FEU/mL decrease in the D-dimer value.
3. Twenty-eight patients were hospitalized before being given LMWH (fondaparinux), with a D-dimer value of 1.01-5 g FEU/mL. After being given LMWH (fondaparinux), 5 patients experienced an increase in the D-dimer value, 7 patients experienced a decrease of  $0.01 \pm 0.5$  g FEU/mL in the D-dimer value, 9 patients

experienced a decrease of  $0.501 \pm 1$  g FEU/mL in the D-dimer value, and 7 patients had a decrease of  $1 \pm 5$  g FEU/mL in the D-dimer values.

4. Six patients were hospitalized before being given LMWH (fondaparinux), with D-dimer interval values of 5.01-10 g FEU/mL. After being given LMWH (fondaparinux), 1 patient experienced an increase in the D-dimer value, 4 patients experienced a  $1 \pm 5$  g FEU/mL decrease in the D-dimer value, and 1 patient experienced a  $>5$  g FEU/mL decrease in the D-dimer value.
5. Nine patients were hospitalized before being given LMWH (fondaparinux), with D-dimer values  $>10$  g FEU/mL, all of whom experienced a  $>5$  g FEU/mL decrease in the D-dimer values.

**Table 6 Comparison of D-dimer values before and after the administration of LMWH (fondaparinux) to confirmed COVID-19 inpatients at Islamic Hospital Jakarta Sukapura in the period of August 2020 – August 2021**

		D-Dimer (post- LMWH (fondaparinux))					P Value	
		increase	0.01±0.5 g FEU/mL decrease	0.501±1 g FEU/mL decrease	1±5 g FEU/mL decrease	>5 g FEU/mL decrease		Total
<b>D-Dimer (pre- LMWH (fondaparinux))</b>	<0.708 g FEU/mL	4	2	0	0	0	6	<b>p = &lt;0.001</b>
	0.708-1 g FEU/mL	6	6	2	0	0	14	
	1.01-5 g FEU/mL	5	7	9	7	0	28	
	5.01-10 g FEU/mL	1	0	0	4	1	6	
	>10 g FEU/mL	0	0	0	0	9	9	
<b>Total</b>		16	15	11	11	10	63	
<b>%</b>		25.4%	23.8%	17.5%	17.5%	15.9%	100%	

Based on Table 7, the Kolmogorov–Smirnov normality test was carried out, and it was found that the data obtained were normally distributed. To compare the two groups, an independent sample t test was performed.

After conducting a different test using the independent sample T test, the D-dimer value after UFH administration and the D-dimer value after LMWH (fondaparinux) administration were compared. The results obtained revealed no significant difference between the two groups ( $p = 0.193$ ,  $p > 0.05$ .) This means that there was no significant relationship between the APTT value and patient status.

**Table 7. Comparison of the Effectiveness of UFH and LMWH (fondaparinux) in Confirmed COVID-19 Inpatients at Islamic Hospital Jakarta Sukapura in the Period of August 2020 – August 2021**

Variable	UFH (n = 35)		LMWH (fondaparinux) (n = 63)		P Value
	N	%	N	%	
	Post-D-Dimer Value				
increase	8	22.9%	16	25.4%	p = 0.193
decrease of 0.01-0.5 g FEU/mL	12	34.3%	15	23.8%	
0.501-1 g FEU/mL decrease	3	8.6%	11	17.5%	
1-5 g FEU/mL decrease	6	17.1%	11	17.5%	
> 5 g FEU/mL decrease	6	17.1%	10	15.9%	

## Discussion

Several studies have shown that coagulopathic complications are common in severe COVID-19 patients and are associated with increased mortality. COVID-19 can predispose patients to both venous and arterial thromboembolic disease, due to the activation of coagulation caused by excessive inflammation, activation of platelets, endothelial dysfunction, and stasis of blood flow due to immobility. Indications of disease severity and the establishment of coagulopathy may vary; these indications include increased D-dimer, thrombocytopenia, elevated D-dimer levels, prolongation (PT), and prolongation of aPTT in patients [7,8,9].

One of the hypercoagulable states can be enforced through the finding of an increased D-dimer value, where D-dimer is the end result of breaking down fibrin clots that have cross-links in the D-domain. Consequently, D-dimer can be used as one of the parameters for measuring thrombus formation. An increase in the D-dimer value indicates the presence of a fibrinolysis process in these patients, so that a negative value on the D-dimer examination can rule out the suspicion of a diagnosis of venous or arterial thrombosis; in contrast, an increase in the D-dimer value indicates a sign of thrombus formation [10,11].

In this study, it was found that outpatients who had confirmed COVID-19 with coagulopathy were mostly in the >60 year age group and comprised as many as 30 patients (30.6%) of the 98 patients studied. This result is in line with a study at Tongji Hospital that divided the sample into two groups of inpatients confirmed positive for COVID-19 and showed that there was a significant difference between the young and old age groups, with an increase in the D-dimer value of up to 1 g/mL, PT prolongation, and increased fibrinogen. It is also supported by research conducted at Union Hospital, Wuhan, China, which showed that of the 81 inpatients who were confirmed positive for COVID-19 and were evaluated for VTE, the age group of 60-69 years was the most common, comprising 28 patients (35%); 18 (22%) patients were in the 70-year age group [12,13].

In addition to the distribution by age, in this study, it was also found that the female gender had a slightly higher prevalence than men, namely, 51 patients (52%) of the 98 patients studied, although the difference shown was not very significant (47 male patients, 48%). The results of this study are in line with research conducted at Union

Hospital, Wuhan, China, which showed that of the 81 hospitalized patients who were confirmed to be positive for COVID-19 with VTE being studied, the number of female patients was 44 (54%), and the number of male patients was 37 (46%). In general, female sex is a risk factor associated with hypercoagulation disorders, but in COVID-19 patients with native arterial occlusion, this is more common in men. In addition, women taking combined oral contraceptives (COC) and oestrogen replacement therapy (ERT) may have an exacerbated risk of VTE occurrence in COVID-19. COC use is associated with a 2- to 6-fold increase in the risk of VTE. The risk of VTE in COVID-19 can also be exacerbated in pregnancy (the risk increases by 4 to 5 times) and in postmenopausal women [13,14,15].

The value of D-dimer in this study when the patient first entered the hospital was found to be in the interval of 1.01–5 g FEU/mL in as many as 44 patients (44.9%), and the lowest D-dimer value was found in the interval <0.708 g FEU/mL, namely, in 8 patients (8.2%). The results of this study are in accordance with research at Tongji Hospital, which showed that 449 patients studied had a D-dimer value of 1.47 (0.78–4.16) g FEU/mL (315 patients), and the rest had a D-dimer value of 4.70 (1.42-21.00) g FEU/mL [16,17].

In this study, it was also shown that 63 patients with hypercoagulation complications used LMWH (fondaparinux) as an anticoagulant, with the highest group showing an increase of 16 patients (25.4%). However, the number of patients who experienced an increase rather than a decrease was only 25.4% of the total 63 patients studied. The second highest order was found in the decreased group ( $0.01 \pm 0.5$  g FEU/mL), comprising 15 patients (23.8%). This is consistent with the study in which PVT disappeared completely and the target blood vessels were patent in 2 patients 7 days after drug administration, in 4 patients 14 days after drug administration, and in 1 patient 21 days after drug administration. The D-dimer value decreased significantly during treatment. Decreased D-dimer had a predictive value for portal vein recanalization ( $P = 0.018$ ). No side effects, such as bleeding, hypohepatia, or thrombocytopenia, occurred in any of the patients. These results indicate that the decrease in the D-dimer value is the result of fibrin formation and fibrinolysis caused by the administration of LMWH (fondaparinux) [18,19,20,21].

There are increasing data reporting a high incidence of coagulopathy and VTE among hospitalized patients with COVID-19. However, little is known about the potential association between antithrombotic therapy and COVID-19 or prognosis. Thromboprophylactic anticoagulants LMWH, low-dose UFH, or LMWH (fondaparinux) are recommended for acutely ill hospitalized medical patients with an increased risk of thrombosis. In this study, there was a slight difference between treatments in patients with hypercoagulable complications who were given UFH and LMWH (fondaparinux)  $p = 0.193$  ( $p > 0.05$ ). This is in line with research by Russo et al., who reported the main finding that the incidence of VTE and bleeding events, including MB and CRNMB, did not significantly differ between patients with COVID-19 who were taking LMWH (fondaparinux) and patients on UFH therapy. In addition, compared with the use of UFH, treatment with LMWH (fondaparinux) did not yield statistically significant differences in ARDS progression and in-hospital mortality, with numerically lower rates of both ARDS and event mortality [22].

## Conclusion

Hospitalized patients with confirmed COVID-19 are in the >60-year age group and are predominantly female. There is a significant decrease in D-dimer values in patients given both UFH and LMWH (fondaparinux) among hospitalized COVID-19 patients with hypercoagulable complications. UFH and LMWH (fondaparinux) have a similar effectiveness in the treatment of coagulopathy.

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## Declarations

### Ethical approval and consent to participate

This research was submitted to the ethics committee of the Faculty of Medicine and Health, Universitas Muhammadiyah Jakarta, Jakarta, Indonesia (No. 186/PE/KE/FKKUMJ/X/2021) for approval of the ethical study. Written informed consent was obtained from all participants.

### Data availability

All data generated or analysed during this study are included in this published article.

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## **Author contributions**

M.F, M.H and S.N.N.A.T designed the study. M.F, M.H, S.N.N.A.T and R.D carried out the laboratory analyses. M.F, R.A, A.S and A.R.J reviewed the data, conducted the statistical analyses and interpreted the results. M.F, M.H, S.N.N.A.T, R.A and A.F wrote the first draft of the paper, which all authors critically reviewed. All authors read and approved the final manuscript.

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## **Competing interests**

The authors declare no competing interests. Additional information Correspondence and requests for materials should be addressed to M.H

## **Additional information**

Correspondence and requests for materials should be addressed to M.H