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Supplementary appendix

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Supplementary Appendix

Manuscript Title

Long-term clinical outcomes of Covid-19 patients treated with imatinib

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Methods

Clinical data was obtained from the electronic medical records, and patients were called by a team of physician scientists at a minimum of 90 days after randomisation. All 385 patients included in the CounterCOVID study consented to pseudonymized data collection for the 90-day follow up. The general physician or next of kin was contacted in case any of the above information was missing. In case of a transfer or readmission elsewhere, the concerning hospital or health care facility was requested to provide additional information. The trial was conducted in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol of this follow-up study was approved by the ethics committee and institutional review board of the coordinating hospital.

The number of ventilator-free days was defined as the total number of days free from invasive ventilation, patients who died had zero ventilator free days. The number of additional organ support free days was defined as the total number of days free from cardiovascular support, renal replacement therapy (RRT), and extracorporeal mechanical oxygenation (ECMO). Patients that died before day 90 were assigned -1 additional organ support free days.

A modified version of the WHO ordinal scale was used to categorise the clinical status of a patient at baseline (day 0), day 9, day 28 and day 90. This ordinal scale ranges from 'discharged without oxygen supplementation' to 'death'. Category 1 indicates that the patient was not hospitalised, and received no oxygen supplementation; 2. was not hospitalised, but received supplemental oxygen; 3. was hospitalised, without the use of supplemental oxygen; 4. was hospitalised and received supplemental oxygen using a nasal cannula or mask ; 5. was hospitalised and received oxygen through non-invasive ventilation or high-flow devices; 6. was hospitalised and received invasive ventilation with no extra organ support ; 7. was hospitalised and received invasive ventilation plus additional organ support: vasopressors, renal replacement therapy (RRT), or extra corporal membrane oxygenation (ECMO); and 8. died.

During invasive ventilation, the courses of oxygenation parameters, ventilatory conditions, and the sequential organ failure assessment (SOFA) were assessed daily for the first 14 days. This was done in a subgroup of patients that received invasive ventilation and consisted of 30 (15%) patients who received imatinib and 26 (14%) who received placebo. These parameters were assessed at the time point with the lowest $P_aO2/FiO2$, in which P_aO2 was measured in arterial blood. Assessment of the total SOFA score was adapted from the method used by Ferreira et al., and was calculated as the sum of the SOFA scores of the 6 organ domains: respiratory, coagulation, hepatic, cardiovascular, neurological, and renal (1).

Data management and statistical analysis

Data for this study were collected retrospectively and recorded in an electronic database in the Castor Electronic Data Capture System (Castor EDC; Amsterdam, Netherlands). Statistical analyses were performed using RStudio version 2021.09.0 (https://cran.r-project.org/). The investigators that performed the statistical analyses were aware of treatment allocation.

Categorical variables were analysed using a chi-square test or Fisher's exact test. Continuous variables were analysed using an unpaired T-test or a Mann-Whitney U test depending on the distribution. Time to mortality was analysed using Cox regression analyses. Linear mixed models were used to assess the effect of imatinib on the eight-point ordinal scale. Recovery was treated as a dichotomous outcome and was defined as either being hospitalised and not requiring supplemental oxygen (category 3), not

being hospitalised, but received supplemental oxygen at home (category 2) or not being hospitalised, and received no oxygen supplementation (category 1). Death or respiratory failure was also treated as a dichotomous outcome and was defined as death (category 8), received mechanical ventilation with or without organ support (category 6 or 7), non-invasive ventilation (category 5) or high-flow oxygen devices (category 5). For recovery and respiratory failure or death, the effect of the intervention was derived from logistic generalized estimating equation (GEE) analyses. For the analysis of mortality and the eight-point ordinal scale, baseline characteristics that were imbalanced at baseline ($P<0{\cdot}10$) were carried forward as a correction factor (sex, diabetes, obesity (BMI > 30kg/m^2), and cardiovascular disease).

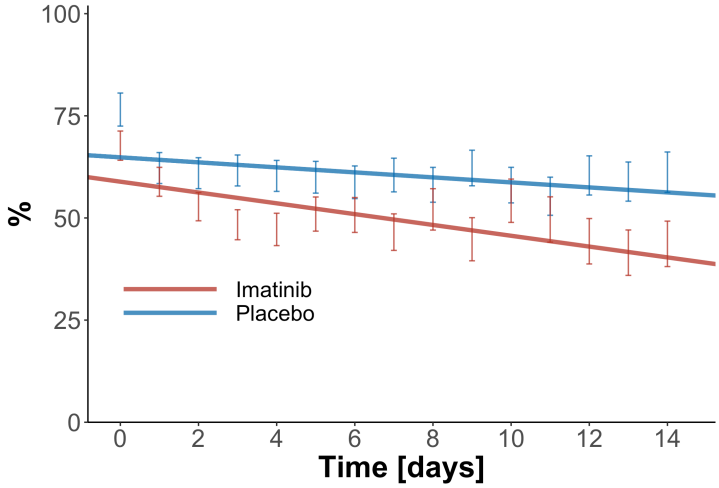
Linear mixed models were used to assess the effect of treatment with imatinib on the clinical parameters during invasive ventilation and to test whether treatment with imatinib is an effect modifier for time (interaction). In the linear mixed model, a random intercept on individual patient level was entered to adjust for the high correlation of these repeated measures. For all tests two-sided p-values are provided. P-values below 0·05 were considered significant.

References - supplementary appendix

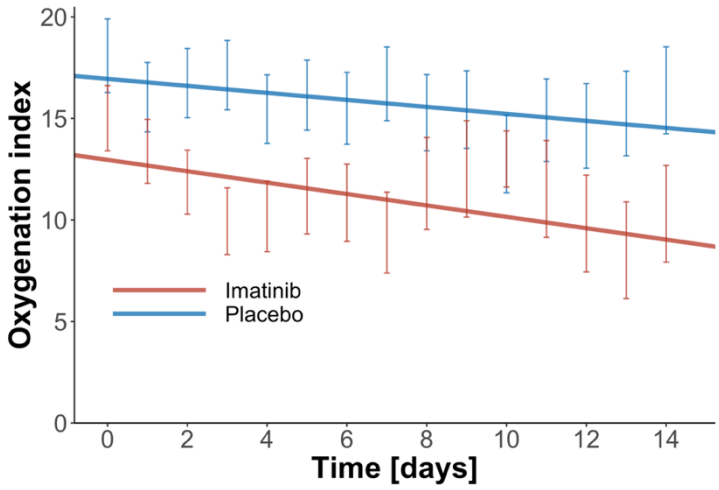
1. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA. 2001 Oct;286(14):1754–8.

Figure S1 Longitudinal course of ventilatory conditions and oxygenation parameters

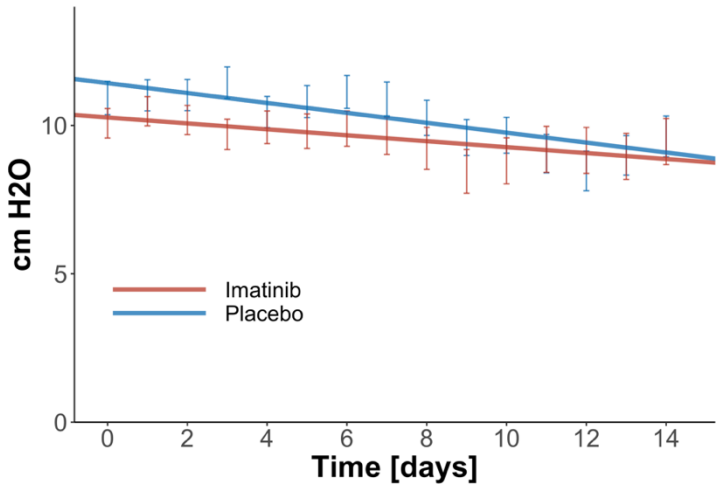
A. Fraction of inspired oxygen (FiO2)



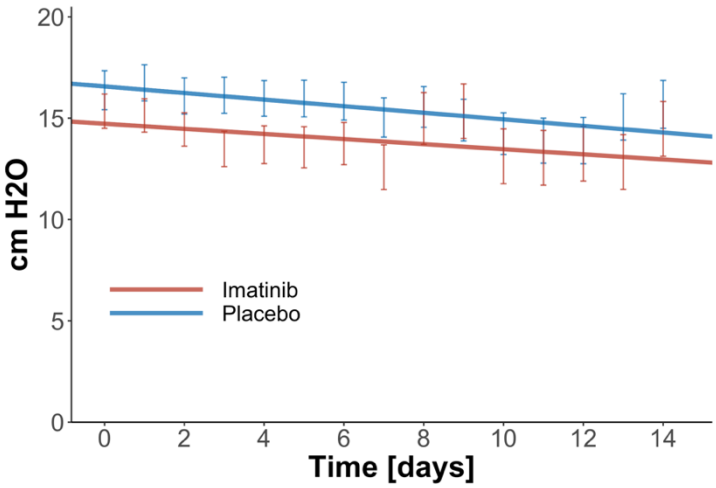
B. Oxygenation index (OI)



C. Positive end-expiratory pressure (PEEP)



D. Mean airway pressure (Pmaw)



The estimated longitudinal course of the oxygenation parameters and ventilatory conditions during the first 14 days of invasive ventilation (n=56) calculated using a linear mixed model. Treatment with imatinib, time, and time*treatment were entered as fixed effects. The error bars indicate the estimates, ± the standard error, in which baseline (day 0) was considered as the reference time point. A. Fraction of inspired oxygen (FiO2) B. Oxygenation index (OI) C. Positive end-expiratory pressure (PEEP) D. Mean airway pressure (Pmaw).

Table S1 – Demographic and clinical characteristics at baseline

	Total	Imatinib	Placebo
Number of patients	385	197	188
Age - median [IQR]	64 [56-73]	64 [57-73]	64 [55-74]
BMI - median [IQR]	28·5 [25·5-32·4]	27·5 [25·3-31·1]	29·7 [25·6-32·9]
Males – no. (%)	264 (69)	146 (74)	118 (63)
Comorbidities – no. (%)			
Current/former smoker	153 (40)	77 (39)	76 (40)
BMI>30	136 (38)	53 (29)	83 (47)
Diabetes Mellitus	95 (25)	41 (21)	54 (29)
Cardiovascular disease*	83 (22)	35 (18)	48 (26)
Hypertension	145 (38)	69 (35)	76 (40)
COPD/Asthma	71 (18)	38 (19)	33 (18)
Venous thromboembolism	10 (3)	5 (3)	5 (3)
Renal failure	14 (4)	7 (4)	7 (4)
Hepatic disease	2 (1)	1 (1)	1 (1)
Rheumatic disease	29 (8)	11 (6)	18 (10)
Heart failure	12 (3)	8 (4)	4 (2)
Modified WHO clinical score – Day 0 †			
3	9 (2)	5 (3)	4 (2)
4	355 (92)	181 (92)	174 (93)
5	18 (5)	9 (5)	9 (5)
6	1 (0)	1 (1)	0 (0)
7	1 (0)	0 (0)	1 (1)
8	1 (0)	1 (1)	0 (0)

* Cardiovascular disease includes arrhythmias (predominantly atrial fibrillation), valvular diseases, coronary artery diseases, and conduction disorders. † A score of 3. indicates that the patient was hospitalised, without the use of supplemental oxygen; 4. was hospitalised and received supplemental oxygen using a nasal cannula or mask; 5. was hospitalised and received oxygen through non-invasive ventilation or high-flow devices; 6. was hospitalised and received invasive ventilation with no extra organ support; 7. was hospitalised and received invasive ventilation plus additional organ support: vasopressors, renal replacement therapy (RRT) or extra corporal membrane oxygenation (ECMO); and 8. died.

BMI = body mass index, COPD = chronic obstructive pulmonary disease, IQR = interquartile range, n/no. = number, WHO = World Health Organization

Table S2 - Hazard ratios for mortality at 90 day follow up

Mortality (n=385)	Hazard Ratio (95% CI)	p-value
Unadjusted	0·53 (0·29, 0·94)	0·030
Adjusted for sex	0·50 (0·28, 0·90)	0·021
Adjusted for obesity (BMI > 30kg/m^2)	0·47 (0·25, 0·89)	0·020
Adjusted for diabetes	0·55 (0·31, 0·97)	0·045
Adjusted for cardiovascular disease	0·56 (0·31, 1·00)	0·048
Adjusted for all the above	0·52 (0·28, 0·99)	0·045

Hazard ratios and confidence intervals were calculated using Cox regression analysis

BMI = body mass index, CI = Confidence interval

Table S3 - Clinical outcome measures at 90 day follow up

Outcome	Imatinib N=197	Placebo N=188	Measure of Effect (95% CI)	p-value
Time to liberation of mechanical ventilation and oxygen supplementation >48h	167 (85)	152 (81)	0·94 (0·75, 1·17)	0·57*
Time to liberation of mechanical ventilation and receiving less than 3 liter/min of oxygen supplementation >48h	157 (84)	180 (91)	1·01 (0·81, 1·25)	0·96 *
Time to need for mechanical ventilation	30 (15)	26 (14)	1·07 (0·63, 1·80)	0·81*
Combined outcome: time to need for mechanical ventilation or death	40 (20)	46 (24)	0·78 (0·51, 1·19)	0·25*
Time to mortality	18 (9)	31 (16)	0·53 (0·29, 0·94)	0·030*
Duration of hospital admission (days)	7 [4-11]	6·5 [3-11]		0·66†
Number of readmissions	8 (4)	6 (3)		0·85‡
Duration of ICU admission (days) n=72	9 [5-15]	15 [7-21]		0·098†
Time between first treatment day and intubation (days) n=56	3 [1-10]	1 [1-2]		0·0018†
Duration of invasive ventilation (days) n=56	7 [3-15]	12 [7-22]		0·026†
Number of ventilator free days § n=72	84 [54-88]	64 [0-84]		0·036†
The number of additional organ support free days || n=72	24 [17-27]	20 [-1-26]		0·11†
Reintubations	0	2 (1)		0·62¶

The number of patients included in the analysis equals 385, unless stated otherwise.

* Hazard ratios were calculated using Cox regression. † Differences were calculated using a Mann-Whitney U test and are presented as median [Inter Quartile Range]. ‡ Differences in proportions were calculated using a Pearson Chi-squared test. § The number of ventilator-free days was defined as the total number of days free from invasive ventilation, patients who died had zero ventilator free days. || The number of additional organ support free days was defined as the total number of days free from cardiovascular support, renal replacement therapy (RRT), and extracorporeal mechanical oxygenation (ECMO). Patients that died before day 90 were assigned -1 additional organ support free days. ¶ Differences in proportions were calculated using Fisher's exact test.

CI = confidence interval, ICU = intensive care unit

Table S4 – Clinical outcome scores using an eight-point ordinal scale

Outcome	Imatinib N=197	Placebo N=188	Measure of Effect (95% CI)	p-value
Through day 90 - unadjusted			-0·53 (-0·94, -0·11)	0·014
Through day 90 - adjusted for baseline imbalances †			-0·56 (-0·99, -0·13)	0·012
Category at day 9			-0·54 (-0·99, -0·09)	0·018
1	118 (60)	108 (57)		
2	15 (8)	7 (4)		
3	5 (3)	6 (3)		
4	35 (18)	26 (14)		
5	7 (4)	3 (2)		
6	7 (4)	12 (6)		
7	1 (1)	7 (4)		
8	7 (4)	18 (10)		
Category at day 28			-0·52 (-0·97, -0·07)	0·023
1	161 (82)	140 (74)		
2	6 (3)	8 (4)		
3	2 (1)	2 (1)		
4	5 (3)	3 (2)		
5	1 (1)	1 (1)		
6	4 (2)	1 (1)		
7	1 (1)	5 (3)		
8	15 (8)	27 (14)		
Category at day 90			-0·51 (-0·96, -0·06)	0·025
1	174 (88)	153 (81)		
2	2 (1)	3 (2)		
3	0 (0)	0 (0)		
4	1 (1)	0 (0)		
5	0 (0)	0 (0)		
6	0 (0)	0 (0)		
7	0 (0)	0 (0)		
8	18 (9)	31 (16)		
Death or respiratory failure ‡				
Through day 90 - unadjusted			0·45 (0·26, 0·79)	0·005
Through day 90 - adjusted for baseline imbalances †			0·43 (0·23, 0·78)	0·006
At day 9	15 (8)	37 (20)	0·34 (0·18, 0·64)	0·001
At day 28	20 (10)	33 (18)	0·53 (0·29, 0·96)	0·037
At day 90	18 (9)	31 (16)	0·51 (0·27, 0·95)	0·033
Recovery §				
Through day 90 - unadjusted			1·49 (0·98, 2·27)	0·059
Through day 90 - adjusted for baseline imbalances †			1·57 (1·01, 2·44)	0·044
At day 9	140 (71)	120 (64)	1·32 (0·86, 2·04)	0·195
At day 28	171 (87)	151 (80)	1·61 (0·93, 2·79)	0·088
At day 90	179 (91)	157 (84)	1·85 (1·00, 3·41)	0·048

* The effect of the intervention is expressed as the coefficient with associated confidence interval derived from a linear mixed model. Category 1 indicates that the patient was not hospitalised, and received no oxygen supplementation; 2. was not hospitalised, but received supplemental oxygen; 3. was hospitalised, without the use of supplemental oxygen; 4. was hospitalised and received supplemental oxygen using a nasal cannula or mask ; 5. was hospitalised and received oxygen through non-invasive ventilation or high-flow devices; 6. was hospitalised and received invasive ventilation with no extra organ support ; 7. was hospitalised and received invasive ventilation plus additional organ support: vasopressors, renal replacement therapy (RRT), or extra corporal membrane oxygenation (ECMO); and 8. died.

† Adjusted for sex, diabetes, obesity (BMI > 30kg/m^2), and cardiovascular disease.

‡ The effect of the intervention is expressed as an odds ratio derived from logistic generalized estimating equation (GEE) analyses. Death or respiratory failure was defined as death (category 8), receiving mechanical ventilation with or without organ support (category 6 or 7), non-invasive ventilation (category 5) or high-flow oxygen devices (category 5).

§ The effect of the intervention is expressed as an odds ratio derived from logistic generalized estimating equation (GEE) analyses. Recovery was defined as either being hospitalised and not requiring supplemental oxygen (category 3), not being hospitalised, but received supplemental oxygen at home (category 2) or not being hospitalised, and received no oxygen supplementation (category 1).

CI = confidence interval

Table S5 - Clinical status during the first 14 days of invasive ventilation

	Time (treatment = imatinib)		Time (treatment = placebo)		Treatment (placebo = reference)		Time*treatment	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
P_aO2 (mmHg)	-0.55 (-0.88, -0.21)	0.001	-0.60 (-0.88, -0.31)	<0.001	1·05 (-2·70, 4·80)	0·59	0·05 (-0·39, 0·49)	0·82
P_aCO2 (mmHg)	0.26 (-0.10, 0.62)	0.16	0.84 (0.54, 1.14)	<0.001	1·29 (-4·00, 6·58)	0·64	-0·58 (-1·05, -0·11)	0·016
FiO2 (%)	-1.32 (-1.84, -0.80)	<0.001	-0.61 (-1.04, -0.18)	0.005	-5·98 (-14·2, 2·22)	0·16	-0·71 (-1·38, -0·04)	0·039
P_aO2/FiO2 (mmHg)	2.74 (1.48, 3.99)	<0.001	0.64 (-0.40, 1.68)	0.22	13·3 (7·79, 34·4)	0·22	2·10 (0·48, 3·71)	0·011
Oxygenation index	-0.28 (-0.49, -0.07)	0.010	-0.17 (-0.35, 0.01)	0.058	-3·99 (-7·75, -0·23)	0·042	-0·11 (-0·38, 0·17)	0·44
PEEP (cm H2O)	-0.10 (-0.17, -0.03)	0.006	-0.17 (-0.23, -0.11)	<0.001	-1·16 (-2·28, -0·04)	0·047	0·07 (-0·02, 0·16)	0·15
Pmaw (cm H2O)	-0.13 (-0.25, 0.00)	0.051	-0.16 (-0.27, -0.06)	0.003	-1·84 (-3·65, -0·04)	0·050	0·037 (-0·13, 0·20)	0·66
Ppeak (cm H2O)	-0.23 (-0.42, -0.04)	0.018	-0.05 (-0.21, 0.11)	0.564	-1·71 (-0·21, 0·11)	0·28	-0·18 (-0·43, 0·07)	0·15
SOFA score	-0.31 (-0.36, -0.27)	<0.001	-0.25 (-0.30, -0.20)	<0.001	-0·91 (-2·18, 0·36)	0·17	-0·07 (-0·13, 0·00)	0·062
Cdyn	1.38 (0.10, 2.67)	0.034	0.44 (-0.67, 1.54)	0.44	-3·61 (-19·7, 12·5)	0·66	0·96 (-0·74, 2·63)	0·27

Results of a linear mixed-effects model on the course of oxygenation parameters, ventilatory conditions, and the sequential organ failure assessment (SOFA) during the first 14 days of invasive ventilation (n=56). Treatment with imatinib, time, and time*treatment were entered as fixed effects.

Cdyn = dynamic compliance, FiO2 = fraction of inspired oxygen, mmHg = millimetres of mercury, P_aCO2 = partial pressure of carbon dioxide, P_aO2 = Partial pressure of oxygen, PEEP = positive end expiratory pressure, Pmaw = mean airway pressure, Ppeak = peak pressure, SOFA = Sequential Organ Failure Assessment

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Statements

Contributions

AV, ED, JS, MR, PS acquired the data and take responsibility for the integrity of the data. ED and JT performed the statistical analyses. AVN, ED, FM, HJB, JA, and JS were involved in data interpretation and drafting of the manuscript. All authors provided critical feedback for the manuscript and approved the final version. All authors had full access to the study data and take responsibility for the decision to submit for publication.

Declaration of interests

J. Aman and A. Vonk Noordegraaf are inventors on a patent (WO2012150857A1, 2011) covering protection against endothelial barrier dysfunction through inhibition of the tyrosine kinase abl-related gene (arg). All other authors have no competing interests. JA has served as a non-compensated scientific advisor for Exvastat^{TM}.

Data sharing

Qualified researchers can request access to anonymised patient-level data and related study documents after publication. Study documents include the study protocol, structure of the electronic case report form, statistical analysis plan, and dataset specifications.

Role of the funding source

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Clinical Trial Registration Information

This study is registered with the European Union Clinical Trials Register (EudraCT 2020–001236–10, https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001236-10/NL) and the Netherlands Trial Register (NL8491, https://www.trialregister.nl/trial/8491).