

1 **Corticosteroid therapy for patients with CoVID-19 pneumonia: a before-after study**

2 Firouzé BANI-SADR¹, Maxime HENTZIEN¹, Madeline PASCARD², Yohan N’GUYEN¹, Amélie
3 SERVETTAZ¹, Laurent ANDREOLETTI³, Lukshe KANAGARATNAM², Damien JOLLY²

4

5 1- Department of Internal Medicine, Clinical Immunology and Infectious Diseases, Reims
6 University Hospital, Reims, France

7 2- Department of Research and Public Health, Reims University Hospital, Reims, France

8 3- Department of Virology, Reims University Hospital, Reims, France

9

10

11 **Corresponding author:**

12 Prof. Firouzé BANI-SADR
13 Department of Internal Medicine, Infectious Diseases, and Clinical Immunology
14 CHU Robert Debré
15 rue du Général Koenig
16 51092 Reims, France
17 Telephone number: (+33) 3 26 78 71 89
18 Fax number: (+33) 3 26 78 40 90
19 E-mail address: fbanisadr@chu-reims.fr

20

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25 **Abstract**

26 **Background:** Anti-inflammatory drugs such as corticosteroids may beneficially modulate the
27 host inflammatory response to CoVID-19 pneumonia.

28 **Aims:** To evaluate the impact of addition of corticosteroids to the hospital protocol for
29 treatment of suspected or confirmed CoVID-19 pneumonia on rates of death or intensive
30 care unit (ICU) admission.

31 **Methods:** A before-after study was performed to evaluate the effect of addition of corticosteroids
32 to our institution's COVID-19 treatment protocol on hospital mortality.

33 **Results:** Between March 3rd and April 14th 2020, 257 patients with CoVID-19 diagnosis were
34 included. As corticosteroids were wide used since 27 March 2020, two periods were
35 considered for the purposes of our study: the before period from March 3rd to 20th (n= 85)
36 and the “after period” (n=172) from March 26th to April 14th 2020.

37 The “after” period was associated with a lower risk of death (HR 0.47; 95% CI, 0.23 - 0.97;
38 p=0.04), and a lower risk of intensive care admission or death before ICU admission (HR 0.37
39 95% CI 0.21 - 0.64; p=0.0005) by multivariate analysis adjusted for age, National Early
40 Warning score and institutionalization status.

41 **Conclusions:** In the “after period”, the addition of corticosteroids to our institution's CoVID-19
42 treatment protocol was associated with a significant reduction in hospital mortality.

43

44 **Introduction**

45 There is evidence that severe CoVID-19 patients present overwhelming inflammatory
46 reactions with high levels of cytokines and inflammatory biomarkers, leading to lung injury
47 [1,2]. Anti-inflammatory drugs such as corticosteroids may beneficially modulate the host
48 immune response to CoVID-19 pneumonia. With an average of 2-3 days between the
49 occurrence of dyspnea and intensive care unit (ICU) admission, we postulate that
50 corticosteroid treatment initiated as soon as the patient has shortness of breath or needs
51 oxygen therapy, might be effective in preventing acute respiratory distress syndrome and
52 death [3]. Therefore, since 27 March 2020, we have systematically included corticosteroids
53 in the treatment of patients with CoVID-19 pneumonia. Prednisone or methylprednisolone
54 at a dose of 1 mg/kg equivalent per day (0.5 mg/kg for patients also receiving antiviral
55 therapy with ritonavir as coadministration of corticosteroid and ritonavir lead to an increase
56 corticosteroid plasma concentrations and their half-life) for 3 to 4 weeks, according to the
57 severity of pneumonia, with dose tapering over the last week, was added to our initial
58 therapeutic protocol for hospitalized CoVID-19 patients [4]. This protocol included antiviral
59 therapy (lopinavir plus ritonavir or darunavir plus ritonavir) and/or hydroxychloroquine,
60 empiric broad-spectrum antibiotic treatment for 14 days and preventive anticoagulation for
61 14 to 21 days. The long duration of corticosteroid treatment was chosen by analogy with
62 that recommended for severe pneumocystis pneumonia in order to additionally prevent
63 pulmonary fibrosis [5]. As lopinavir-ritonavir treatment was not available after mid-March
64 due to a drug shortage in our hospital, most of our patients received another HIV protease
65 inhibitor (darunavir-ritonavir) after this date.

66 In order to evaluate the impact of addition of corticosteroids to the hospital protocol for
67 treatment of suspected or confirmed CoVID-19 pneumonia, we compared rates of death

68 (primary outcome) or intensive care unit (ICU) admission and/or death before ICU admission
69 (secondary outcome) in a before-and-after study, with the introduction of corticosteroids in
70 our therapeutic protocol as the event defining the start of the “after” period.

71

72 **Patients and Methods**

73 Between March 3rd and April 14th 2020, 319 patients with CoVID-19 diagnosis defined as a
74 positive result on an polymerase-chain reaction testing of a nasopharyngeal sample or
75 presence of characteristic findings on chest CT scan were followed in the University Hospital
76 of Reims, France [6]. Two periods were considered for the purposes of our study: the first,
77 from March 3rd to 20th, corresponded to the “before” period, and the admission of the first
78 cases to our center. During the “before” period, corticosteroid therapy was not
79 recommended. The second period comprised March 26th through April 14th 2020, (“after”),
80 with wide use of corticosteroid therapy in this period following our decision to introduce it
81 systematically due to the biological rationale of its use in the inflammatory phase. Patients
82 with initiation of corticosteroid therapy during the transition period (from March 21st to
83 March 25th 2020) were not included in the before-after analysis. Patients with fewer than 7
84 days between symptom onset and April 14th, 2020 - that was the end point date of follow up
85 - were not included.

86 Individual follow-up was defined as the time from first symptoms to death during
87 hospitalization for the primary outcome and to ICU admission or death before ICU admission
88 for the secondary outcome. ICU admission alone was not considered as an outcome, since
89 we did not exclude patients aged over 80 years and/or with comorbidities, who were less
90 likely to have access to ICU care. Data are expressed as mean \pm standard deviation, or
91 number (percentage), as appropriate. Quantitative variables were compared between the

92 two periods using the Student t test and qualitative variables using the Chi square test or
93 Fisher's exact test, as appropriate. For the impact of the period on death and on ICU
94 admission and/or death, we constructed Kaplan Meier curves and compared them using the
95 log rank test. For multivariate analysis, we used Cox proportional hazard models
96 systematically adjusted for age, National Early Warning score and institutionalization status
97 at hospital admission [7].

98

99 **Results**

100 At the time of data extraction, a total of 319 patients were included in the cohort, namely 85
101 patients in the "before" period (until March 20th, 2020), 62 patients in the transition period
102 (March 21st – 25th), and 172 patients in the "after" period (March 26th through April 14th).
103 Eleven patients (12.9%) received corticosteroid therapy in the "before period", 20 (32.3%) in
104 the transition period and 119 (69.2%) in the "after" period. The main characteristics of the
105 257 patients in the "before" and "after" periods are summarized in Table 1. Patients in the
106 "after" period were significantly more frequently nursing home residents, had higher
107 prevalence of dementia, a longer time from symptom onset to hospitalization, less
108 frequently received lopinavir and/or hydroxychloroquine, and more often required oxygen
109 therapy than in the "before" period. Patients in the "after" period also had higher serum
110 creatinine. The mean duration of follow-up was 16.0 ± 7.0 days, and was similar between
111 periods (16.0 ± 8.7 versus 16.1 ± 6.2 ; $p=0.92$). Of note, deceased patients hospitalized in
112 medical ward were older than those who were transferred to ICU (mean age $83.9 (\pm 11.3)$
113 versus $69.6 (\pm 7.2)$ years).

114 The "after period" was not associated with a lower risk of death (hazard ratio (HR) =0.86;
115 95% confidence interval (CI), 0.47-1.56; $p=0.62$) by bivariate analyses but was associated by

116 multivariate analysis adjusted for age, National Early Warning score and institutionalization
117 status (HR = 0.47; 95% CI 0.23 - 0.97; p=0.04).

118 The “after period” was associated with a lower risk of ICU admission and/or death before
119 ICU admission by bivariate analyses (HR=0.25; 95% CI = 0.11-0.55) and by multivariate
120 analysis adjusted for age, National Early Warning score and institutionalization status (HR
121 =0.37 95% CI 0.21 - 0.64; p=0.0005).

122

123 **Discussion**

124 In this before-and-after study of 319 hospitalized CoVID-19 patients, after adjustment for age,
125 National Early Warning score and institutionalization status, the "after" period (n=172) -during which
126 corticosteroids were routinely recommended for patients presenting with CoVID-19 pneumonia
127 at our institution- was associated with a lower risk of death (HR =0.47; 95% CI 0.23 - 0.97; p=0.04),
128 and a lower risk of ICU admission and/or death before ICU admission (HR =0.37 95% CI 0.21 - 0.64;
129 p=0.0005).

130 To this day, corticosteroids are not recommended by the World Health Organization for the
131 treatment of CoVID-19 pneumonia due to their potential adverse effects, such as secondary
132 infections and prolonged virus shedding [8]. However, with our improving knowledge of the
133 role played by overwhelming inflammation in severe CoVID-19 patients, immunomodulatory
134 drugs such as Interleukin-6 or -1 blockade or anti-tumor necrosis factor therapy are being
135 evaluated and all are in favor of a beneficial effect of immunomodulatory drugs during the
136 inflammatory phase of CoVid-19 infection [1,9]. Corticosteroids are old medicines that are
137 inexpensive and accessible to the whole world. In our study, they were associated with a
138 decrease of over 50% in mortality, and in the rate of death and/or ICU admission, even

139 though patients were more dependent and more often required oxygen in the “after” period
140 at the censoring date (although follow-up duration was similar between the two groups).

141 We acknowledge that a before-and-after study yields a low level of evidence, the difference
142 may be the result of overall better patient care with improvements in thrombosis
143 prophylaxis and some of these patients remained hospitalized at end of follow-up and were
144 thus censored for outcomes. Furthermore, the favorable outcome observed with
145 corticosteroids may be partly due to the use of concurrent antiviral drugs in our patients.
146 Another limitation of our study is that CoVID-19 pneumonia diagnosis was more often
147 performed by chest CT scan in patients who received corticosteroids group than in patients
148 who did not. Positive reverse transcriptase polymerase-chain reaction is the gold standard
149 for confirming diagnosis of COVID-19 but its performance presents variable sensitivities,
150 ranging from 37% to 71% [10]. Although chest CT scan is highly sensitive for detecting
151 COVID-19 pneumonia, overlapping CT image features with others viral pneumonia and other
152 respiratory diseases make an exclusion diagnosis difficult and could be therefore a source of
153 bias in our study [10]. Finally, the unavailability of safety data should be acknowledged as a
154 limitation.

155 Nevertheless, these preliminary data support the initiation of clinical trials testing
156 corticosteroids during the inflammatory phase of CoVID-19, and may potentially lead to a
157 change in treatment recommendations.

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160 **Reims COVID Study Group**

161 Ailsa ROBBINS, Kévin DIDIER, Pauline ORQUEVAUX, Violaine NOEL, Paola MARIANETTI,
162 Juliette ROMARU, Dorothée LAMBERT, Jean Luc BERGER, Sandra DURY, Maxime DEWOLF,
163 Jean Hugues SALMON, Jérôme COSTA, Julia SIMON, Natacha NOEL, Sara BARRAUD, Marion
164 BARROIS, Hédia BRIXI, Quentin LAURENT-BADR, Manuelle VIGUIER, Clélia VANHAECKE,
165 Laurence GUSDORF, Isabelle QUATRESOUS, Aline CARSIN-VU, Véronique BRODARD, Antoine
166 HUGUENIN, Morgane BONNET, Aurore THIERRY

167

168 **DECLARATIONS**

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170 **Competing Interests** : None

171 **Ethical Approval** : Not required

172

173 **Author contributions:**

174 All authors participated in the design of the study protocol and data collection. MH, LK, MP,
175 DJ performed the data management and statistical analyses. FBS, MH and DJ wrote the first
176 manuscript draft. All authors participated in interpretation of the data and writing of the
177 final manuscript and all authors approved the final manuscript. FBS was responsible for the
178 overall supervision of the study.

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182 **Table I: Main characteristics of patients in the periods before and after introduction of**
 183 **corticosteroids for CoVID-19 pneumonia in Reims University Hospital**

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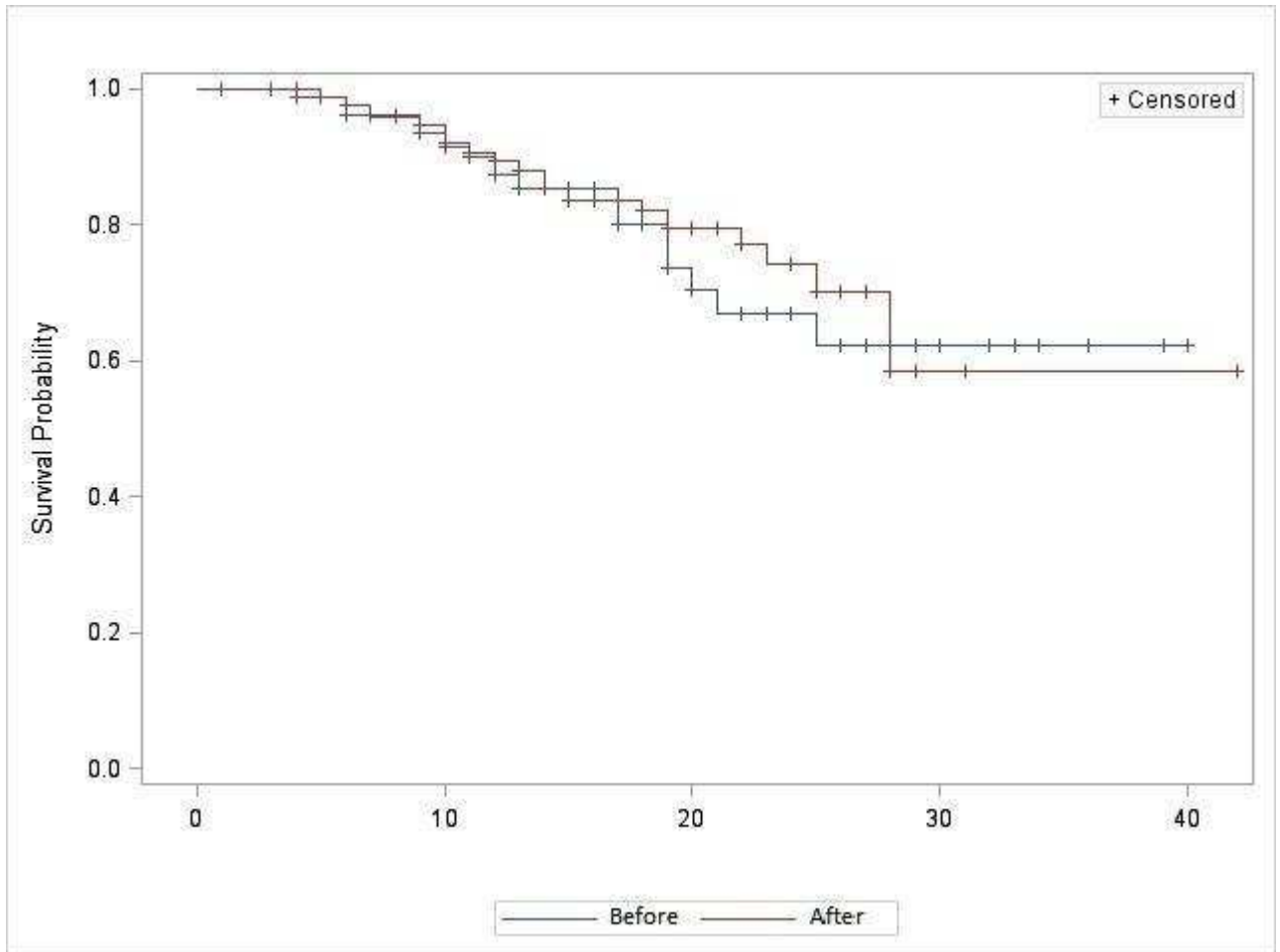
	Before (N=85) n (%) or mean \pm SD		After (N=172) n (%) or mean \pm SD		p
Received corticosteroids	11	12.9	119	69.2	<0.0001
Age	70.1	\pm 15.1	71.8	\pm 16.4	0.44
Male sex	46	54.1	51.7	41.7	0.72
Charlson comorbidity score	1.8	\pm 2.0	2.05	\pm 1.94	0.42
Dementia	8	9.4	33	19.2	0.04
Nursing home resident	8	9.4	47	27.3	0.001
Time from symptom onset to hospitalization (days)	5.8	\pm 4.2	7.5	\pm 4.9	0.009
Diagnosis by positive PCR	80	94.1	143	83.1	0.01
Diagnosis by chest CT scan	5	5.9	29	16.9	
Risk factor of severity	71	83.5	156	90.7	0.09
- Immunocompromised	11	12.9	22	12.8	0.97
- Cardiovascular disease	41	48.2	94	54.7	0.33
- Complicated diabetes	7	8.2	23	13.4	0.23
- Cirrhosis	1	1.2	3	1.7	0.99
- Chronic respiratory disease	22	25.9	32	18.6	0.18
- Chronic renal disease	4	4.7	16	9.3	0.20
- Cancer	7	8.2	10	5.8	0.46
- BMI>40	2	2.4	13	7.7	0.15
- National Early Warning Score	6.2	3.8	6.9	3.2	0.12
Biological characteristics					
- Lymphocyte count G/L	1.1	\pm 0.56	1.1	\pm 1.0	0.73
- Lymphopenia<1G/L	43	51.2	91	53.9	0.69
- Neutrophil count, G/L	5.0	\pm 3.6	5.6	\pm 4.0	0.26
- C-reactive protein, mg/L	98.0	\pm 90.2	89.9	\pm 77.1	0.46
- Serum creatinine, \square mol/L	103.5	\pm 106.2	137.7	\pm 174.3	0.05
Treatment use with expected antiviral activity	63	75.0	135	79.4	0.43
- Lopinavir	46	54.8	13	7.9	<0.0001
- Darunavir	27	32.5	133	78.2	<0.0001
- Hydroxychloroquine	11	13.3	10	6.0	0.049
Antibiotic therapy	80	95.2	162	95.9	0.99
Evolution					
- Required oxygen therapy	52	61.9	125	76.7	0.01
- Maximum oxygen flow in medical ward †	5.0	\pm 7.6	5.7	\pm 5.2	0.48
- Death	17	20.0	31	18.0	0.70
- ICU admission and/or Death	29	34.1	40	23.6	0.07

185 †Among those who received oxygen therapy.

186

187 **Fig 1: Kaplan Meier curves for death before ICU admission between patients “before” and “after”**
188 **implementation of corticosteroids for CoVID-19 pneumonia in Reims University Hospital**

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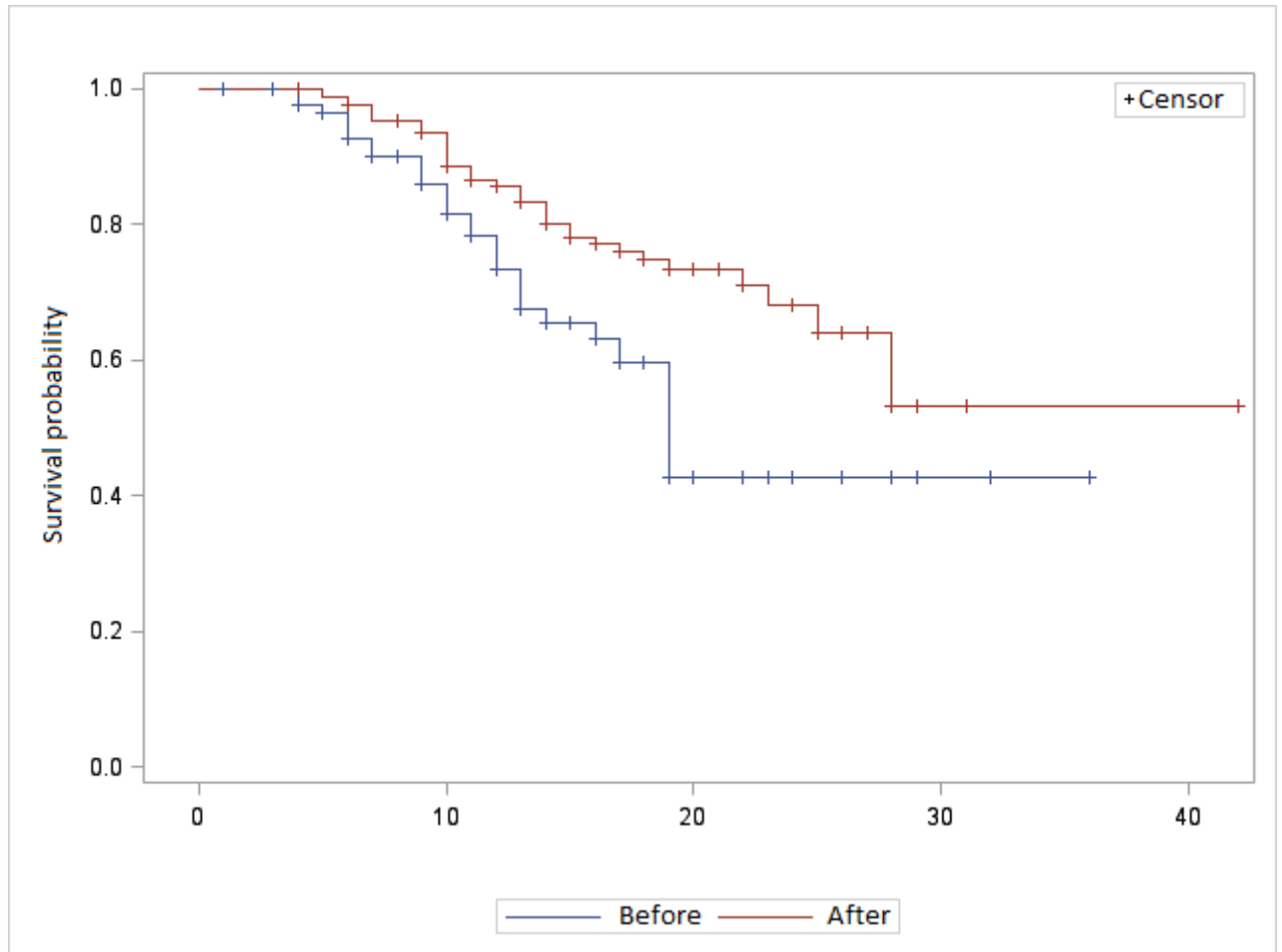
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203 Kaplan Meier curves for ICU admission and/or death before ICU admission between patients
204 “before” and “after” implementation of corticosteroids for CoVID-19 pneumonia in Reims
205 University Hospital

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209 The “before” period was until March 20th, 2020 and the “After” period began on March 26th, 2020.
210 Log -rank: (p=0.006)

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212

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