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**Convalescent plasma improves overall survival in patients with B-cell lymphoid malignancies and COVID-19: a longitudinal cohort and propensity score analysis**

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## Abstract

Patients with hematological malignancies and COVID-19 display a high mortality rate. In such patients, immunosuppression due to underlying disease and previous specific treatment impair humoral response limiting viral clearance. COVID-19 convalescent plasma (CCP) therapy appears as a promising approach in such patients through the transfer of neutralizing antibodies specific of SARS-CoV2.

We report the effect of CCP in a cohort of patients with hematological malignancies and COVID-19 between May 1<sup>st</sup> 2020 and April 1<sup>st</sup> 2021. 121 hospitalized patients with severe COVID-19 (83 with B-cell neoplasm, 19 with plasma cell neoplasm and 10 with myeloid neoplasm) were included. The overall survival of whole cohort was 64.9 % [56-74.9] and 77.5 % [68.5-87.7] for patients with B-cell neoplasm. Prior anti-CD20 therapy was associated with a better overall survival whereas age, high blood pressure and COVID-19 severity were associated with a poor outcome after CCP transfusion

A nested retrospective analysis in a group of COVID-19 patients with B-cell neoplasm treated with CCP was compared to a similar group of patients treated with standard of care (without CCP). An inverse probability of treatment weighting (IPTW) approach was performed to limit confusion and immortality bias revealed a decreased mortality of 63% (95%CI=31%-80%) in CCP-treated group of patients with similar findings in in multivariate analysis.

Convalescent plasma may be beneficial in COVID-19 patients with B-cell neoplasm unable to mount a humoral immune response. Comparing CCP to other passive immunotherapy approaches such as anti-SARS-CoV-2 monoclonal antibodies is warranted.

## Introduction

Patients with hematological malignancies and SARS-CoV2 infection display a high rate mortality with an estimated risk of death of 34% that reach 39% in hospitalized patients <sup>1,2</sup>. In such patients, several studies highlighted that both underlying cellular or humoral immunosuppression may hamper virus clearance resulting in prolonged shedding and high risk of severe form of COVID-19<sup>3,4</sup>. Furthermore, vaccine response in patients with hematological malignancies is lower compared to general population especially in patients with B-lymphoid disease<sup>5,6</sup>. Thus, therapeutic approaches to inhibit viral replication and enhance viral clearance are mandatory in this specific population.

Passive immunotherapy by means of COVID-19 convalescent plasma (CCP) has emerged as a promising therapy to target SARS-CoV2 and achieve clinical recovery<sup>7,8</sup>. In France, CCP has been proposed in a national monitored access program, notably to hospitalized COVID-19 patients with underlying immunosuppression such as patients with hematological malignancy. While most randomized trials have not reported a benefit of CCP in a general population with COVID-19<sup>9</sup>, we observed that B-cell depleted patients with protracted COVID-19 and unable to mount a specific humoral response may benefit from CCP transfusion along with a decrease of all inflammatory parameters, oxygen weaning and viral clearance<sup>10</sup>. A retrospective propensity score matched analysis of 966 patients with a wide range of haematological malignancies among whom 143 received CPP found that CCP was associated a 40% lower mortality<sup>11</sup>, without however taking into consideration immortal time bias and specificity of each hematological malignancies<sup>12</sup>. Based on these preliminary and encouraging results, we report on the outcome after CPP transfusion in a cohort of COVID-19 patients with hematological malignancies as well as on the results of a nested comparison of the survival among patients with B-cell neoplasm transfused or not with CCP

## Methods

### Patients and inclusion criteria

We analyzed all patients with hematological malignancies and virologically-documented COVID-19 included from May 1st 2020 to April 1st 2021 in a CCP monitored access program implemented in France (CCP cohort). Underlying disease included B lymphoid neoplasm (such as diffuse B-cell lymphoma (DLBCL), chronic lymphoid leukemia (CLL) , follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL) or B-acute lymphoblastic leukemia (B-ALL)) plasma cell neoplasm requiring treatment and myeloid neoplasm (myelodysplastic syndrome or acute myeloid leukemia).

The subset of patients with B-lymphoid neoplasm was then compared to a cohort of patients with similar disease who were not treated with CCP in French hospitals during the successive COVID-19 outbreaks periods (Figure 1). Both cohorts were treated as per standard of care for COVID-19. Patients gave their written informed consent for the retrospective data collection, and ethical clearance was obtained from the French Infectious Diseases Society (IRB number: 00011642).

### Data collection

All patients included in the CCP monitored access program received 2 consecutive transfusions of 2 ABO compatible CPP units (200-220 mL each) at day 0 and day +1 (a total of 4 CCP, most often from 4 different donors). Convalescent donors were eligible for plasma donation 15 days after resolution of COVID-19. Collected apheresis plasma underwent pathogen reduction (Intercept blood system; Cerus, Concord, CA) and standard testing, as per current regulations in France. Additionally, anti-SARS-CoV-2 antibody content was assessed in each donation, with a requirement for a SARS-CoV-2 seroneutralization titer  $\geq 40$  ( $\geq 80$



after October 2020) and/or an immunoglobulin G (IgG) enzyme-linked immunosorbent assay (EUROIMMUN, Bussy-Saint-Martin, France) ratio > 5.6 ( $\geq 8$  after October 2020).

Clinical parameters (temperature and oxygen need) as well grading on the WHO scale for COVID-19 severity and biological parameters, including inflammatory markers (C-reactive protein [CRP], ferritin, fibrinogen, ddimers) were recorded at the time of CCP transfusion (day 0)<sup>13</sup>. SARS-CoV2 serological status as well circulating lymphocyte subpopulations at day 0 were assessed. PCR in nasopharyngeal swab (with cycle threshold when available) was performed at day 0 and day +7 after CCP. Adverse events were recorded.

## Outcomes

The primary outcome was 90 days-overall survival and factors associated with the risk of death in all patients with hematological malignancies and COVID-19 after CCP transfusion treated in the monitoring access program. Then, among patients with B-cell neoplasm, overall survival of patients who received CPP (CCP group) was compared to survival of those who did not (standard group) from the first day of hospitalization for COVID-19. Secondary outcomes included safety and kinetics of inflammatory parameters after CPP transfusion.

## Statistics

Continuous variables are described with their medians and interquartile ranges, whereas categorical variables are expressed as raw numbers and percentages. In the CCP cohort, a Wilcoxon paired test was performed to compare clinical and biological parameters at day 0 and day+7 after CCP transfusion. Overall survival (OS) was evaluated using Kaplan-Meier estimates from the time of CCP transfusion. Log-rank test was used to compare survival curves. Crude and adjusted hazards ratio (HR) of death were estimated by univariable and multivariable Cox proportional hazard model. The multivariable model was built after

stepwise selection of the variables from the variables with p-value below 0.05 in univariable regressions. Covariates considered in univariable analysis were gender, age ( $\geq 70$  years versus below), comorbidities (diabetes, high blood pressure and body mass index), type of hematological malignancies, previous B-cell depletion therapy such as anti-CD20 or CD19 monoclonal antibodies, time between symptoms onset and CCP transfusion and disease status (complete remission, partial remission/stable disease, progressive disease).

To study the effectiveness of convalescent plasma therapy in patients with B-cell neoplasms, we compared the 81 patients exposed to CCP with B-cell neoplasms of the CCP cohort with 120 patients non-exposed to CCP with B-cell neoplasms were selected from the cohort described in Dulery et al. (standard group)<sup>14</sup>. To estimate the effect of CCP on survival in non-randomized settings where patients' characteristics associated with CCP exposure could differ in the two groups, an inverse probability of treatment weighting (IPTW) approach was retained aiming to control for indication bias in several population analyses. Individual propensity score, ie the probability of treatment by CCP, was retrieved from logistic regression model including potential confounders both prognostic of survival and associated with CCP indication: age (" $<65$  years" vs. " $\geq 65$  years"), comorbidity (high blood pressure or diabetes or  $BMI \geq 25 \text{ kg/m}^2$  \_yes vs. no), corticosteroid therapy (yes vs. no). A pseudopopulation was built by weighting observations by propensity scores. In order to check if weighting improved the comparability of the two groups, absolute standardized differences were estimated in the unweighted and weighted samples. According to IPTW common practice, standardized differences  $< 0.20$  were considered negligible. For each analysis the distribution of probability of receiving CPP in the two groups was examined visually in order to see if overlap existed and positivity assumption was not violated.

Then, hazard ratios (HR) of death associated with CCP were derived from weighted Cox proportional hazards. Estimates of HR of death associated with CCP from univariable and

multivariable (adjusted for variables included in the propensity score and described above) unweighted Cox proportional hazards model were also provided for main and sensitivity analyses population. Of note, the number of variables included in both IPTW and multivariable models was limited by the relative low number of events; therefore, only variables strongly associated with indication of CCP and with sufficient numbers of patients for each modality were kept. Main analysis was restricted to patients previously treated with anti-CD20 therapy and alive 16 days after hospitalization for COVID-19 that corresponded to the median time of CPP transfusion after hospitalization. In order to limit the immortal time bias which can arise because patients treated with CCP had to survive long enough after hospitalization to receive CPP <sup>12</sup>, a landmark approach was chosen. Follow-up of patients who received CCP after more than 16 days following hospitalization was censored at time of CPP initiation. Since the use of CCP could differ in terms of area and period of recruitment, exposure to cancer therapies and to COVID-19 medications that were not accounted for in IPTW, several sensitivity analyses in which baseline was date of hospitalization were conducted to assess for the robustness of the main results: i) in the overall population of exposed and non-exposed patients to CCP, ii) in a population restricted to anti-CD20 therapy pre-treated patients, excluding patients over 85 years, and patients pre-exposed to tocilizumab, remdesivir or azithromycin/hydroxychloroquine, iv) in a population excluding the first epidemic wave from March, 2020 to June, 2020, v) in a population restricted to Paris-region (Ile-de-France area, see Figure 1 and Table S1). Another sensitivity landmark analysis with baseline at date of hospitalization plus 16 days has been carried out in patients alive 16 days after hospitalization. Of note, other sensitivity analyses on overall population were also adjusted for gender. All analyses were done using R software version 3.6.1 and SAS® Software version 9.4 (Cary, North Carolina, USA). P-value below 0.05 denoted statistical significance.

## Results

### COVID-19 convalescent plasma cohort analysis

One hundred and twelve patients (33 F/79 M) aged 62.5 (range) (20-88) years with hematological malignancies and COVID-19 received CCP. 83 (74%) patients were treated for B-lymphoid neoplasm, 10 (8%) for myeloid neoplasm and 19 (36.9%) for multiple myeloma. Eighty-one (72%) patients had received anti-CD20 or anti-CD19 targeted therapy at a median of 42 (137-14) days before first symptoms of COVID-19. Ninety eight patients (87.5%) patients had a negative serology at the time of CCP transfusion. Median circulating B-lymphocytes count was 0 (interquartile range) (0-0)/mm<sup>3</sup> in 58 evaluable patients with B-cell lymphoid disease, 9 (0-48)/mm<sup>3</sup> in 6 patient with myeloid neoplasm and 7 (1-17)/mm<sup>3</sup> in 9 patients with plasma cell neoplasm. Of note, 11/83 patients with B-lymphoid neoplasm (13%), 2/10 (20%) with myeloid neoplasm and 8/19 (42%) with plasma cell neoplasm were mechanically ventilated (WHO scale 7), at the time of CCP transfusion. Previous COVID-19 treatments included corticosteroids (n=72, 64%), tocilizumab (n=8, 7%) and remdesivir (n=13, 12%). No patients received anti-spike monoclonal antibodies or were vaccinated. The remaining characteristics are described in Table 1.

No transfusion-related adverse events were reported after CCP infusion. CCP transfusion was associated with decreased of (d+7 vs d0) temperature ( $p<0.0001$ ), CRP ( $p<0.0001$ ), ferritin ( $p=0.0004$ ) and fibrinogen ( $p=0.07$ ). Conversely, PCR cycle threshold values significantly increased ( $p=0.001$ ) (Figure 2). The overall survival was 64.9 % (95 % CI= 56.2-74.9), 77.5 % (95 % CI= 68.5-87.7) in patients with B-lymphoid neoplasm, 20 % (95 % CI= 5.8-69.1) with myeloid neoplasm and 36.8 % (95% CI= 20.4-66.4) with plasma-cell neoplasm. Deaths were all associated with COVID-19. In univariable analysis, age > 70 years ( $p=0.006$ ), high blood pressure ( $p=0.003$ ), the type of hematological disease ( $p< 0.0001$ ), a previous B-

depletion therapy ( $p < 0.0001$ ), COVID-19 severity ( $p = 0.0003$ ) and the time of CCP administration ( $p = 0.002$ ) were significantly associated with overall survival (Table 2 and Figure 3). In multivariable analysis only age  $> 70$  yrs (HR= 2.63, 95% CI= 1.31-5.27;  $p = 0.008$ ), high blood pressure (HR= 2.71, 95% CI= 1.215-6.06;  $p = 0.015$ ) and COVID-19 severity (WHO scale 6 & 7) (HR= 5.36, 95% CI= 1.12-25.64 and 6.31, 95% CI= 1.31-30.39;  $p = 0.038$  respectively) were associated with lower overall survival whereas previous B-cell depletion therapy was strongly associated with better overall survival (HR= 0.22, 95% CI= 0.09-0.51;  $p < 0.001$ ) (Figure 4).

#### Propensity score analysis in patients with B-lymphoid neoplasm

The numbers of patients included in each population analysis are provided in the flow chart Figure 1. The main population analysis included 147 patients pre-exposed to anti-CD20 therapy and alive at day 16 after hospitalization for COVID.

The characteristics of patients of each analyzed population are detailed in supplementary table S1. This table shows that patients treated with CPP differ from the untreated ones, including for variables that could not be included in the propensity score. To account for the latter variables, sensitivity analysis populations restricted to specific wave, to pre-exposure to anti-CD20 or to specific area of hospitalization were performed.

In the main IPTW analysis, the exposure to CCP was associated with a 63% (95% CI=31%-80%) decrease in risk of death in the 16 day-anti-CD20 pre-exposed population as shown in table 4. The HR estimated by IPTW varied across the different analysis populations from 40% in waves 2-4 population to 63% in main analysis population. Multivariable models provided similar results to IPTW (Table 4). Addition of gender to propensity score did not modify the estimation of the effect of the convalescent plasma exposure. Hazard ratios of death

associated with each variable included in the propensity score are provided in supplementary table S2.

## **Discussion**

Our study reports the effect of CCP in a large and representative cohort of patients with hematological malignancies and hospitalized for severe COVID-19. Overall 90-days survival was 64.9% for all cohort and 77.9 % in B-cell neoplasm. This appears to be lower than previous studies in particularly in the Thompson *et al* study with a crude rate mortality of 13.3% 28 days after CCP in patients with hematological malignancies and COVID-19 <sup>11,15</sup>. This difference could be explained by a longer follow up (90 days) and a lower representation of B-cell neoplasm in our cohort.

We report also a significant decrease of all inflammatory parameters as well as negativation of PCR in nasopharyngeal swab at d+7 was also observed, consistent with our previous report <sup>10</sup>. Furthermore, CPP infusion was well tolerated <sup>16</sup>. As previously described, age and comorbidities such as high blood pressure and COVID-19 severity emerged as the most important risk factors of death due to COVID-19 <sup>17</sup>. Interestingly, although an increased risk of death was associated with B-depletion therapy such as anti-CD20 or CD19 mAbs in a recently published retrospective lymphoma cohort <sup>14</sup>, previous B-cell therapy depletion was strongly associated with better overall survival in patients receiving convalescent plasma even after adjustment for confounding factors. Since in our study most patients (87%) transfused with CCP had a negative serology for COVID-19, we assume that such patients were unable to produce neutralizing SARS-CoV-2 antibodies due to the underlying hematological disease or the previous administered drugs targeting B-cells <sup>18</sup>. Subsequent transfer of neutralizing antibodies in such patients by mean of CCP transfusion resulted in the control of viral

replication and allowed for clinical recovery. The poor benefit of CCP transfusion in patients with plasma cell or myeloid neoplasm, who did not commonly receive previous anti-CD20 or CD19 monoclonal antibodies, supports our hypothesis.

To further investigate the effect of CCP, we compared the subset of CCP-treated patients with B-cell lymphoid malignancies and COVID-19 to a similar cohort of patients who were treated with standard of care only. The methodology used aimed at controlling for biases inherent to observational design of this retrospective comparison, included indication and immortal time biases. We showed that patients with B-cell neoplasm and previously pre-exposed to anti-CD20 therapy treated with CCP exhibited a significantly better survival probability than those who did not receive CCP. This important result supports the results reported in a US-retrospective cohort <sup>11</sup> and confirms the essential role of convalescent plasma in the COVID-19 therapeutics landscape of patients with B-cell malignancies.

However, those results present several limitations and raise several questions. In our longitudinal cohort, the risk of death reaches 80% and 64 % for myeloid neoplasm and plasma cell neoplasm respectively that is twofold higher than reported in previous studies <sup>1</sup>. We have to note a higher COVID-19 severity with 34% of patients with myeloid and plasma-cell neoplasm requiring for mechanical ventilation whereas only 13% for B-cell neoplasm at the time of CCP. In the same way, previous studies reported a better outcome after early CCP transfusion in non-hospitalized patients <sup>19</sup>. Of note, we observed a lower overall survival in patients transfused within the first 10 days after symptoms onset in univariable analysis, an association that disappeared in the multivariable analysis. A similar observation was made in the Recovery trial (in the CCP arm as well as the control arm) and may reflect more severe disease in patients hospitalized early in the course of the disease (Recovery, lancet 2021). Furthermore, 62% of patients transfused earlier (within the first 10 days) presented with myeloid or plasma-cell neoplasm who did not benefit from CCP transfusion in our cohort.

In our retrospective nested analysis, data were collected prospectively from two data sources: one for patients exposed to CPP and another one for patients not exposed to CPP. Such comparison could not identify causal effect of treatment exposure with the level of proof provided by randomized clinical trials. We have tried to limit bias by using statistical methods controlling indication bias (propensity score) and the immortal bias (time-lead analysis). The benefit of CPP appears to be robustly identified in all our sensitivity analysis. In addition, the main analysis which controls more strictly indication and immortal bias (use of 16 day landmark and IPW) identifies the strongest effect. We also have no data on the type of viral strain that infected the patients who received CPP, and thus could not analyze the impact of virological parameters in the response to CPP. However, during the inclusion period, SARS-CoV2 strains circulating in France were mainly the Wuhan original strain and its alpha variant. We cannot therefore extend our results to the variant of concern Delta that is currently getting dominant world-wide. CCP from convalescent and vaccinated donors exhibit high titer crossvariant antibodies that may provide a higher efficacy than CPP used in our study <sup>20,21,22</sup>. We presently favor the issuing of such CCP for treatment of immunosuppressed patients with B-cell malignancies.

Although our study brings some strong arguments in favor of the use of CCP in B-cell depleted COVID-19 patients several recent issues need to be considered. Indeed, initiation of the anti-SARS-CoV-2 vaccination <sup>23</sup>, the availability and use of anti-spike monoclonal antibodies in patients at risk of developing severe form of COVID-19 <sup>24</sup> and the emergence of SARS-CoV-2 variants have changed the course of COVID-19 outbreak. Firstly, none of the patients in both cohorts (CCP-treated and non CCP-treated) were vaccinated against SARS-CoV-2. Although prospective randomized trial strongly supports the efficacy of vaccination in general population, results are less favorable in immunosuppressed patients especially patients with CLL or MM who exhibit a lower serological response despite two



administrations of BNT162b2 mRNA COVID-19 vaccine<sup>5,25,26</sup>. Further investigations are needed to evaluate the efficacy of vaccination on mortality linked to COVID-19 in such patients. Secondly, use of anti-spike mAb opened a new perspective especially in frail patients with a reduction of related hospitalization or death in mild to moderate COVID-19 patients<sup>27</sup>. Besides the cost of such an approach (over 2000 euros per administration compared to 120 euros/CPP) and possibly limited availability, immune escape mutations have been described especially in patients with B-cell lymphoid disease justifying a successful treatment rescue with CCP<sup>28,29</sup>. In the light of this, emergence of variants due to protracted shedding or therapy-related selection<sup>30,31,32</sup> remains the most important challenge to face. In our series, although we did not assess the SARS-CoV-2 lineages we did not observe a difference of overall survival between the three epidemic outbreaks.

In conclusion, among patients with hematological malignancies and COVID-19, CPP represents an interesting approach especially in patients with in B-cell lymphoid malignancies. Importantly, such patients have poor response to vaccination and may present escape variant due to prolonged shedding or anti-spike mAbs administration. The place of CCP in the treatment of COVID-19 patients unable to mount a humoral response could be strengthened if confirmed in a randomized prospective trial, and should also be discussed in light of the increasing availability of anti-spike monoclonal antibodies.

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Table 1. Convalescent Plasma therapy (CPP cohort) characteristics

<b>Patients characteristics</b>	<b>Patients n = 112</b>
<b>Age, mean (range)</b>	62.5 (20-88)
<b>B-lymphoid neoplasm, n (%)</b>	
Diffuse large B-cell lymphoma	28 (25)
Follicular lymphoma	23 (20)
Mantle cell lymphoma	11 (10)
Marginal zone lymphoma	4 (3)
Chronic lymphoid leukemia	13 (12)
Waldenström Macroglobulinemia	2 (2)
B-acute lymphoblastic leukemia	2 (2)
<b>Myeloid neoplasm, n (%)</b>	
Myelodysplastic syndrome	2 (2)
Acute myeloid leukemia	8 (7)
<b>Plasma cell neoplasm, n (%)</b>	19 (17)
<b>Previous anti-CD19 or CD20 mAbs, n (%)</b>	81 (72)
<b>Previous anti-CD38 mAbs, n (%)</b>	10 (9)
<b>Median time between last anti-CD19 or CD20 mAbs and COVID-19, days (range)</b>	42 (137-14)
<b>Previous stem cell transplantation, n (%)</b>	
Autologous	27 (25)
Allogeneic	5 (4)
<b>Disease status at the time of COVID-19, n (%)</b>	
Complete remission	48 (43)
Partial remission/stable disease	29 (25)
Progressive disease	22 (20)
Missing data	13 (12)
<b>B-Lymphocyte count at the time of CCP transfusion, median (IQR)</b>	
B-lymphoid neoplasm	0 (0-0)
Myeloid neoplasm	9 (0-48)
Plasma cell neoplasm	7 (1-17)
<b>Serological status for COVID-19, n (%)</b>	
Positive	2 (2)
Negative	98 (87)
Unknown	12 (11)
<b>Previous COVID-19 specific treatment, n (%)*</b>	
Steroid	72 (64)
Tocilizumab	8 (7)
Remdesivir	13 (12)
Others	8 (7)
Nothing	32 (29)

\* Some patients may have simultaneous treatment

Table 2. Univariable analysis

Patients characteristics	Patients		90 days overall survival			P
	n = 112	%	95% CI	HR	95% CI	
<b>Overall</b>	112	64.9	56.2-74.9			
<b>Gender</b>						<b>0.02</b>
Female	33	79.7	66.1-96.0	0.38	0.16-0.90	
Male	79	58.9	48.7-71.3	1		
<b>Age</b>						<b>0.006</b>
< 70 yrs	77	70.9	60.6-83.0	1		
≥ 70 yrs	35	50.2	36-70.2	2.41	1.26-4.60	
<b>High blood pressure</b>						<b>0.003</b>
Yes	20	42.9	25.5-72	2.77	1.37-5.62	
No	92	69.5	60.2-80.3	1		
<b>Diabete</b>						0.216
Yes	7	42.9	18.2-100	1.93	0.68-5.44	
No	105	66.7	57.9-76.9	1		
<b>Body mass index</b>						0.05
< 25	51	59.7	47.4-75.2	1		
25-30	32	77.6	64.2-93.7	0.48	0.2-1.13	
≥ 30	11	23.3	5.1-100	1.68	0.71-3.99	
Missing data	16	80.4	62.7-100	0.44	0.13-1.49	
<b>Hematological disease</b>						<b>&lt; 0.0001</b>
B-lymphoid neoplasm	83	77.5	68.5-87.7	1		
Myeloid neoplasm	10	20.0	5.8-69.1	7.79	3.26-18.61	
Plasma cell neoplasm	19	36.8	20.4-66.4	4.6	2.17-9.78	
<b>Previous B-depletion therapy</b>						<b>&lt; 0.0001</b>
Yes	81	76.9	67.7-87.4	0.21	0.11-0.42	
No	31	35.5	22.1-57	1		
<b>Disease status</b>						0.8
Complete remission	48	66.5	53.8-82.2	1		
Partial remission/stable disease	29	68.1	52.9-87.7	1	0.44-2.30	
Progressive disease	22	56.4	38.5-82.7	1.45	0.63-3.38	
Missing data	13	69.2	48.2-99.5	1	0.33-3.04	
<b>WHO scale (COVID-19 severity)</b>						<b>0.0004</b>
WHO 4	22	90	77.8-100	1		
WHO 5	47	71.7	59.8-86	3.35	0.76-14.85	
WHO 6	22	50	30.4-82.2	4.86	1.05-22.55	
WHO 7	21	38.1	22.1-65.7	10.9	2.45-48.48	
<b>Steroid administration</b>						0.8
Yes	72	63.7	53.2-76.3	1.12	0.56-2.23	
No	40	67.5	53.6-84.9	1		
<b>Time from COVID-19 onset to CCP</b>						<b>0.002</b>
< 10 days	29	43.4	28.3-66.8	1		
> 10 days	83	72.8	63.3-83.6	0.37	0.20-0.72	

Table 3. Characteristics of patients with B-lymphoid neoplasm according to analyzed population (main analysis, overall population analyses).

	Analyzed population			
	16d anti-CD20 population		Overall population	
	Group CP+ N (%)	Group CP- N (%)	Group CP+ N (%)	Group CP- N (%)
<b>All</b>	<b>32 (100%)</b>	<b>115 (100%)</b>	<b>81 (100%)</b>	<b>120 (100%)</b>
<b>Epidemic wave</b>				
1st 2020,mar-jun	2 (6%)	81 (71%)	19 (23%)	94 (77%)
2nd 2020,jul-oct	8 (25%)	20 (17%)	26 (32%)	10 (8%)
3rd 2020,nov-dec	18 (56%)	13 (11%)	32 (40%)	11 (9%)
4th 2021,jan-apr	4 (13%)	1 (1%)	4 (5%)	5 (4%)
<b>Area</b>				
Paris region	13 (41%)	69 (60%)	33 (41%)	85 (71%)
Grand-Est	1 (3%)	26 (23%)	9 (11%)	30 (25%)
Other	18 (56%)	20 (17%)	39 (48%)	5 (4%)
<b>Gender</b>				
male	19 (59%)	76 (66%)	56 (69%)	72 (60%)
female	13 (41%)	39 (34%)	25 (31%)	48 (40%)
<b>Age (years)</b>				
<55	9 (28%)	17 (15%)	18 (22%)	11 (9%)
55-64	11 (35%)	41 (36%)	27 (33%)	35 (29%)
65-74	9 (28%)	37 (32%)	24 (30%)	36 (30%)
>=75	3 (9%)	20 (17%)	12 (15%)	38 (32%)
<b>BMI (kg/m<sup>2</sup>)</b>				
<18.5	2 (6%)	5 (4%)	3 (4%)	6 (5%)
[18.5;25[	14 (44%)	56 (49%)	34 (41%)	61 (51%)
[25;30[	10 (31%)	29 (25%)	24 (30%)	29 (24%)
>=30	4 (13%)	15 (13%)	8 (10%)	17 (14%)
missing	2 (6%)	10 (9%)	12 (15%)	7 (6%)
<b>Arterial hypertension</b>				
no	27 (84%)	80 (70%)	69 (85%)	70 (58%)
yes	5 (16%)	35 (30%)	12 (15%)	50 (42%)
<b>Diabetes</b>				
no	30 (94%)	98 (85%)	76 (94%)	93 (77%)
yes	2 (6%)	17 (15%)	5 (6%)	27 (23%)
<b>AH or diabetes or BMI&gt;25kg/m<sup>2</sup> - PS*</b>				
no	14 (44%)	52 (45%)	41 (51%)	45 (38%)
yes	18 (56%)	63 (55%)	40 (49%)	75 (63%)
<b>WHO at hospitalization</b>				
missing	0 (0%)	2 (2%)	0 (0%)	6 (5%)
4	8 (25%)	41 (36%)	29 (36%)	33 (28%)
5	22 (69%)	58 (50%)	44 (55%)	69 (57%)

<b>6</b>	2 (6%)	7 (6%)	6 (7%)	6 (5%)
<b>7</b>	0 (0%)	7 (6%)	2 (2%)	6 (5%)
<b>Anti-cd20 therapy</b>				
<b>no</b>	0 (0%)	0 (0%)	3 (4%)	26 (22%)
<b>yes</b>	32 (100%)	115 (100%)	78 (96%)	94 (78%)
<b>Corticotherapy - PS*</b>				
<b>no</b>	11 (34%)	67 (58%)	29 (36%)	83 (69%)
<b>yes</b>	21 (66%)	48 (42%)	52 (64%)	37 (31%)
<b>Tocilizumab</b>				
<b>no</b>	31 (97%)	106 (92%)	75 (93%)	115 (96%)
<b>yes</b>	1 (3%)	9 (8%)	6 (7%)	5 (4%)
<b>Azithromycin-hydroxychloroquine</b>				
<b>no</b>	32 (100%)	107 (93%)	79 (98%)	109 (91%)
<b>yes</b>	0 (0%)	8 (7%)	2 (2%)	11 (9%)
<b>Remdesivir</b>				
<b>no</b>	29 (91%)	107 (93%)	72 (89%)	117 (98%)
<b>yes</b>	3 (9%)	8 (7%)	9 (11%)	3 (3%)
<b>B-lymphoid neoplasm</b>				
<b>CLL</b>	6 (19%)	11 (10%)	13 (16%)	18 (15%)
<b>NHL/DLBCL</b>	12 (37%)	48 (41%)	28 (35%)	49 (42%)
<b>NHL/FL</b>	6 (19%)	32 (28%)	23 (28%)	22 (18%)
<b>NHL/LZM</b>	1 (3%)	10 (9%)	4 (5%)	16 (13%)
<b>NHL/MCL</b>	5 (16%)	13 (11%)	11 (14%)	11 (9%)
<b>WM</b>	2 (6%)	1 (1%)	2 (2%)	4 (3%)

The proportion of treated patients differed greatly among the strata of variables included in the propensity score such as age: 54% of treated in <65 years vs. 36% in  $\geq 65$  years in RCT-like population, 48% of treated in absence of comorbidity vs. 35% in presence of comorbidity in overall population, 14% of treated in patients not receiving corticotherapy vs. 30% in patients receiving corticotherapy. Moreover, this table shows that the proportion of treated patients differed also for variables which could not be included in the propensity score but defined sensitivity analysis populations such as wave, pre-exposure to antiCD20, area of hospitalization. AH : arterial hypertension, BMI: body mass index, PS\*: included in the propensity score, N: number of patients, WHO: world health organization

Table 4: Estimation of hazard ratio (HR) of death associated with Covid-19 plasma therapy and its 95% confidence interval (CI)

Analysed population	N at risk/n deaths	Crude association		Adjusted association*		IPW**	
		HR [95%CI]	p-value	HR [95%CI]	p-value	HR [95%CI]	p-value
16 day- anti-CD20 population (Main analysis)	147/28	0.47 [0.16;1.3]	0.157	0.33 [0.11;0.99]	0.049	<b>0.37 [0.20;0.69]</b>	<b>0.002</b>
Overall population	201/64	0.45 [0.26;0.79]	0.005	0.46 [0.26;0.84]	0.012	0.50 [0.34;0.72]	<0.001
RCT-like population	137/42	0.54 [0.29;1.0]	0.064	0.58 [0.29;1.2]	0.117	0.57 [0.37;0.89]	0.014
Wave 2-4 population	88/26	0.44 [0.20;0.97]	0.042	0.50 [0.23;1.1]	0.083	0.60 [0.35;1.0]	0.069
Paris region population	118/37	0.40 [0.17;0.95]	0.039	0.39 [0.16;0.96]	0.040	0.40 [0.24;0.67]	<0.001
16 day- population	172/29	0.55 [0.19;1.6]	0.263	0.46 [0.15;1.4]	0.165	0.43 [0.23;0.78]	<0.001
Anti-CD20 population	172/59	0.37 [0.21;0.65]	<0.001	0.32 [0.17;0.60]	<0.001	0.39 [0.26;0.58]	<0.001

IPW: inverse probability of convalescent plasma exposure weighting, RCT: randomized controlled trial. Confounding factors - age (<65 years vs. ≥65 years), arterial hypertension or diabetes or body mass index >25kg/m<sup>2</sup> (yes vs. not) and corticotherapy (yes vs. not) - were included in multivariable Cox proportional models for estimating \*Adjusted associations and in weight computation for \*\*IPW models.



## Figures

Figure 1. Flow chart

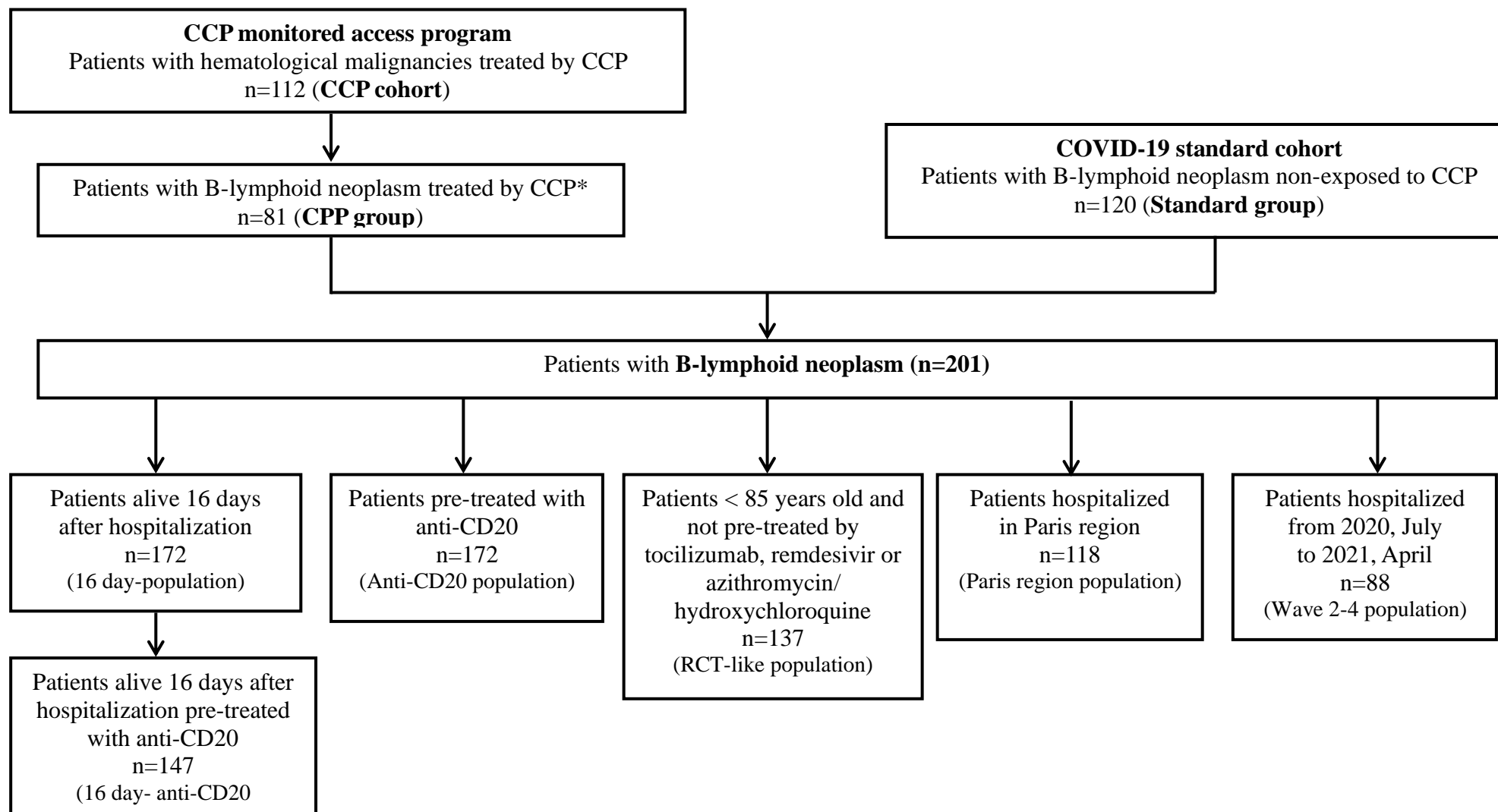
Figure 2: Kinetic of inflammatory parameters. All parameters were assessed the day of convalescent plasma transfusion (day 0) and 7 days after (d+7). A cycle threshold value over 40 was considered negative. A Wilcoxon-paired test was assessed. The median and interquartile range is represented.

Figure 3: Overall survival after COVID-19 convalescent plasma transfusion represented using the Kaplan-Meier method.

Figure 4: Forest Plot representing hazard ratio of death obtained in multivariable analysis.  
mAbs : monoclonal antibodies.



Figure 1



\* Excluding B-acute lymphoblastic leukemia (n=2)

Figure 2.

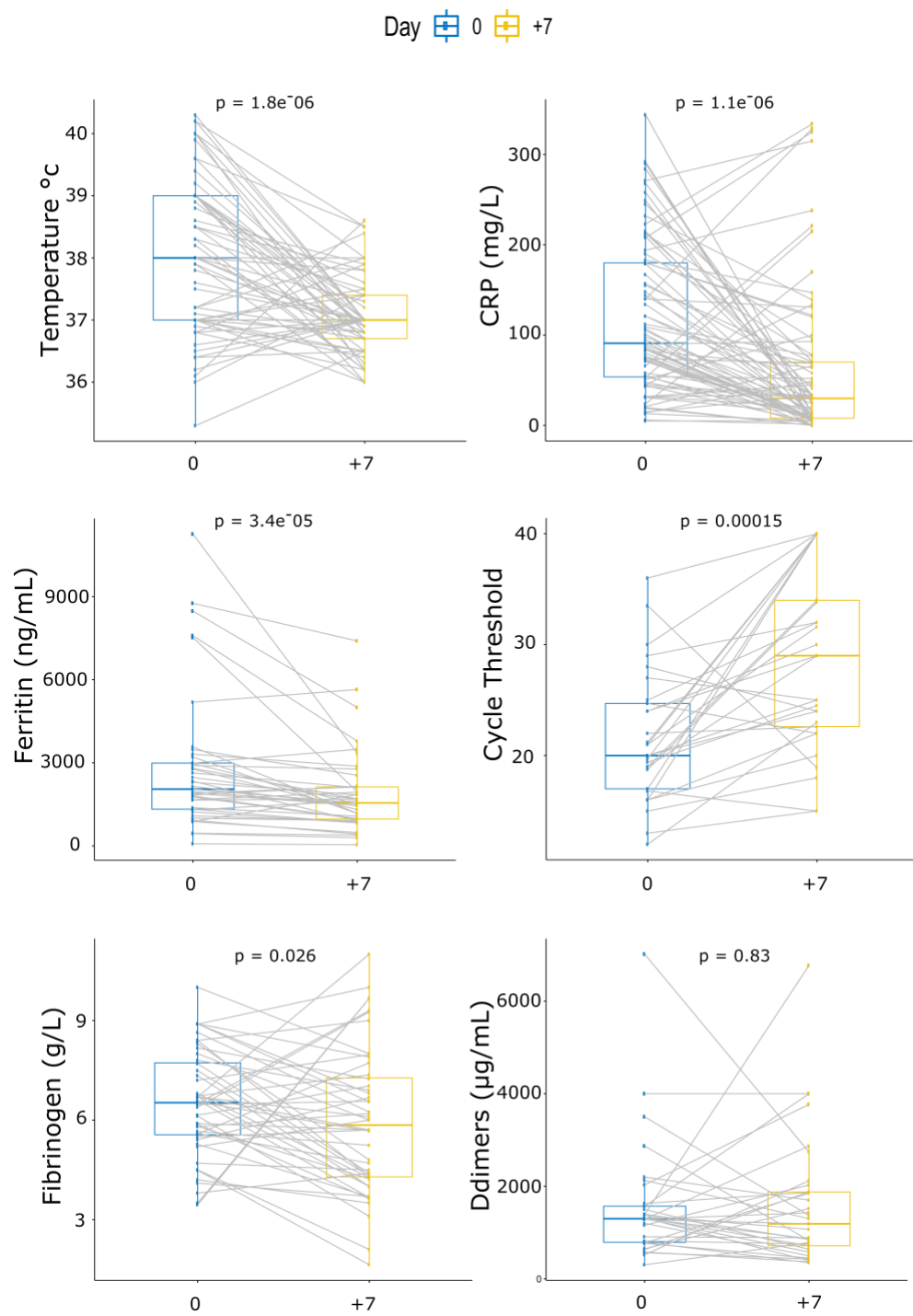


Figure 3.

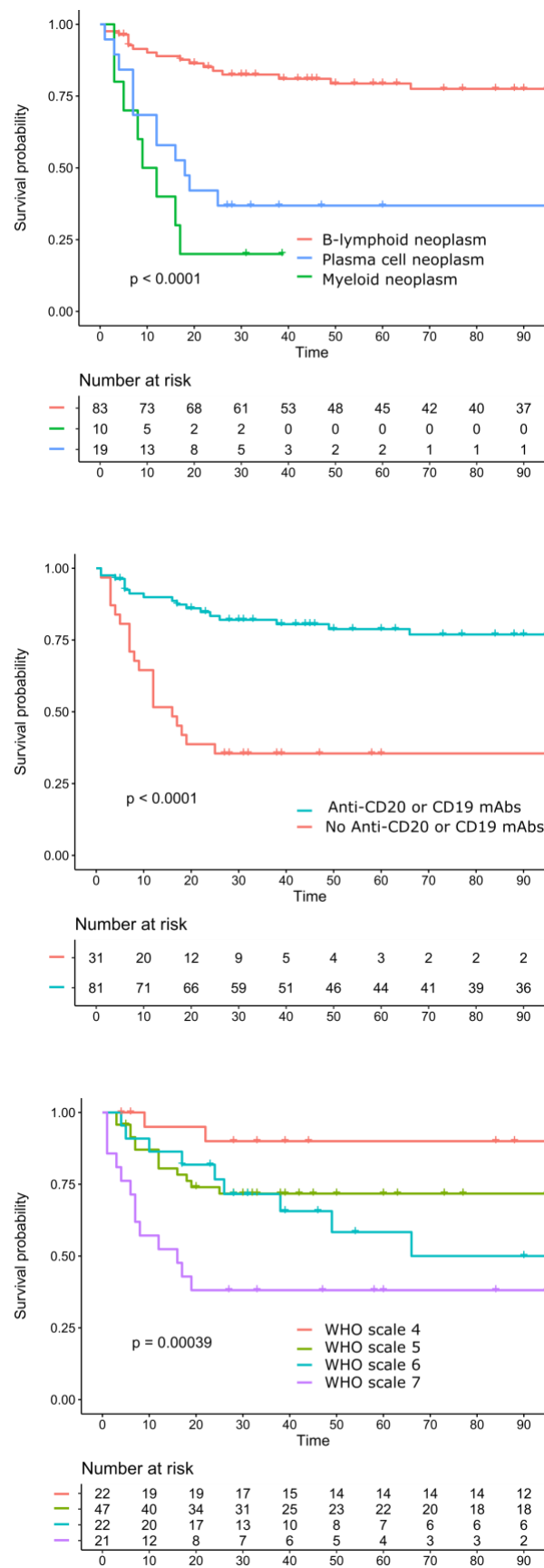
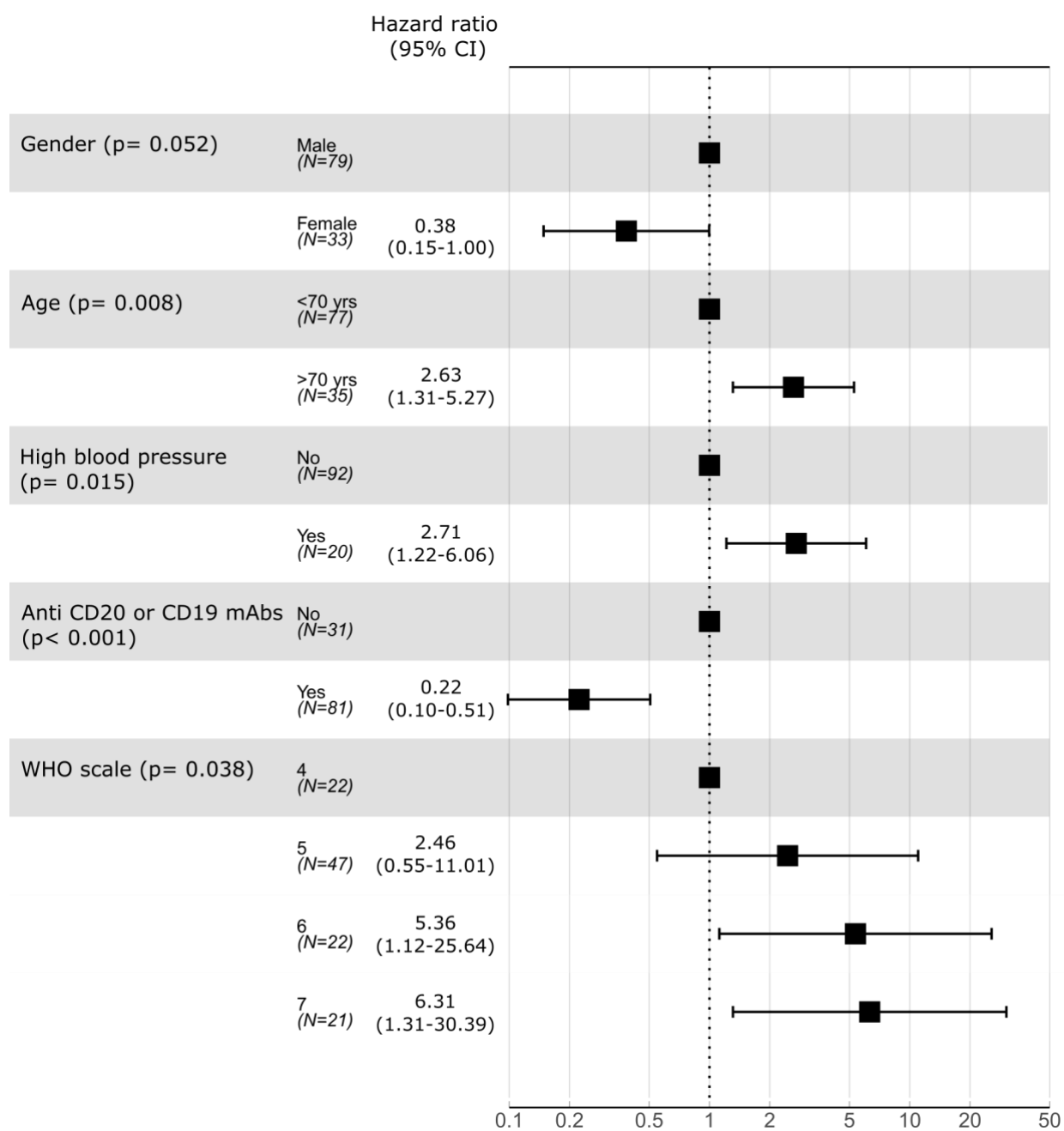


Figure 4.



## Supplementary Tables

	Analysed population									
	RCT-like population		Wave 2-4 population		IdF population		16d population		Anti-CD20 population	
	Group CP+ N (%)	Group CP- N (%)	Group CP+ N	Group CP- N	Group CP+ N	Group CP- N	Group CP+ N	Group CP- N	Group CP+ N	Group CP- N
<b>All</b>	<b>61</b>	<b>76</b>	<b>62</b>	<b>26</b>	<b>33</b>	<b>85</b>	<b>33</b>	<b>139</b>	<b>78</b>	<b>94</b>
<b>Epidemic wave</b>	<b>(100%)</b>	<b>(100%)</b>	<b>(100%)</b>	<b>(100%)</b>	<b>(100%)</b>	<b>(100%)</b>	<b>(100%)</b>	<b>(100%)</b>	<b>(100%)</b>	<b>(100%)</b>
<b>1st 2020,mar-jun</b>	11 (18%)	54 (71%)	0 (0%)	0 (0%)	14 (42%)	62 (73%)	2 (6%)	93 (67%)	19 (24%)	79 (84%)
<b>2nd 2020,jul-oct</b>	19 (31%)	8 (11%)	26 (42%)	10 (38%)	10 (30%)	7 (8%)	8 (24%)	26 (19%)	26 (33%)	3 (3%)
<b>3rd 2020,nov-dec</b>	27 (44%)	10 (13%)	32 (52%)	11 (42%)	8 (24%)	11 (13%)	19 (58%)	18 (13%)	29 (37%)	8 (9%)
<b>4th 2021,jan-apr</b>	4 (7%)	4 (5%)	4 (6%)	5 (19%)	1 (3%)	5 (6%)	4 (12%)	2 (1%)	4 (5%)	4 (4%)
<b>Area</b>										
<b>Paris region</b>	23 (38%)	49 (64%)	19 (31%)	23 (88%)	33 (100%)	85 (100%)	13 (39%)	89 (64%)	32 (41%)	64 (68%)
<b>Grand-Est</b>	6 (10%)	23 (30%)	7 (11%)	0 (0%)	0 (0%)	0 (0%)	2 (6%)	28 (20%)	8 (10%)	26 (28%)
<b>Other</b>	32 (52%)	4 (5%)	36 (58%)	3 (12%)	0 (0%)	0 (0%)	18 (55%)	22 (16%)	38 (49%)	4 (4%)
<b>Gender</b>										
<b>male</b>	41 (67%)	49 (64%)	44 (71%)	14 (54%)	26 (79%)	52 (61%)	19 (58%)	91 (65%)	55 (71%)	57 (61%)
<b>female</b>	20 (33%)	27 (36%)	18 (29%)	12 (46%)	7 (21%)	33 (39%)	14 (42%)	48 (35%)	23 (29%)	37 (39%)
<b>Age (years)</b>										
<b>&lt;55</b>	15 (25%)	10 (13%)	13 (21%)	3 (12%)	5 (15%)	8 (9%)	9 (27%)	19 (14%)	18 (23%)	9 (10%)
<b>55-64</b>	19 (31%)	19 (25%)	19 (31%)	3 (12%)	16 (48%)	27 (32%)	11 (33%)	47 (34%)	27 (35%)	29 (31%)
<b>65-74</b>	19 (31%)	29 (38%)	20 (32%)	12 (46%)	9 (27%)	25 (29%)	10 (30%)	45 (32%)	21 (27%)	30 (32%)
<b>&gt;=75</b>	8 (13%)	18 (24%)	10 (16%)	8 (31%)	3 (9%)	25 (29%)	3 (9%)	28 (20%)	12 (15%)	26 (28%)
<b>BMI (kg/m<sup>2</sup>)</b>										
<b>&lt;18.5</b>	2 (3%)	4 (5%)	1 (2%)	1 (4%)	1 (3%)	5 (6%)	2 (6%)	6 (4%)	3 (4%)	5 (5%)
<b>[18.5;25[</b>	27 (44%)	37 (49%)	28 (45%)	11 (42%)	13 (39%)	43 (51%)	14 (42%)	67 (48%)	32 (41%)	51 (54%)
<b>[25;30[</b>	18 (30%)	22 (29%)	20 (32%)	9 (35%)	12 (36%)	21 (25%)	11 (33%)	37 (27%)	23 (29%)	20 (21%)
<b>&gt;=30</b>	8 (13%)	10 (13%)	8 (13%)	2 (8%)	2 (6%)	12 (14%)	4 (12%)	18 (13%)	8 (10%)	14 (15%)
<b>missing</b>	6 (10%)	3 (4%)	5 (8%)	3 (12%)	5 (15%)	4 (5%)	2 (6%)	11 (8%)	12 (15%)	4 (4%)

<b>Arterial hypertension</b>											
no	50 (82%)	48 (63%)	51 (82%)	17 (65%)	27 (82%)	52 (61%)	28 (85%)	96 (69%)	66 (85%)	56 (60%)	60 (60%)
yes	11 (18%)	28 (37%)	11 (18%)	9 (35%)	6 (18%)	33 (39%)	5 (15%)	43 (31%)	12 (15%)	38 (40%)	40 (40%)
<b>Diabetes</b>											
no	57 (93%)	58 (76%)	58 (94%)	23 (88%)	30 (91%)	65 (76%)	31 (94%)	117 (84%)	73 (94%)	72 (77%)	77 (77%)
yes	4 (7%)	18 (24%)	4 (6%)	3 (12%)	3 (9%)	20 (24%)	2 (6%)	22 (16%)	5 (6%)	22 (23%)	23 (23%)
<b>AH or diabetes or BMI&gt;25kg/m<sup>2</sup> -PS*</b>											
no	28 (46%)	27 (36%)	26 (42%)	10 (38%)	15 (45%)	34 (40%)	14 (42%)	62 (45%)	39 (50%)	37 (39%)	39 (39%)
yes	33 (54%)	49 (64%)	36 (58%)	16 (62%)	18 (55%)	51 (60%)	19 (58%)	77 (55%)	39 (50%)	57 (61%)	61 (61%)
<b>WHO at hospitalization</b>											
missing	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	6 (7%)	0 (0%)	4 (3%)	0 (0%)	3 (3%)	3 (3%)
4	20 (33%)	26 (34%)	15 (24%)	8 (31%)	18 (55%)	21 (25%)	8 (24%)	48 (35%)	28 (36%)	26 (28%)	28 (28%)
5	33 (54%)	42 (55%)	39 (63%)	16 (62%)	13 (39%)	51 (60%)	23 (70%)	72 (52%)	42 (54%)	54 (57%)	57 (57%)
6	6 (10%)	5 (7%)	6 (10%)	2 (8%)	1 (3%)	3 (4%)	2 (6%)	8 (6%)	6 (8%)	5 (5%)	5 (5%)
7	2 (3%)	2 (3%)	2 (3%)	0 (0%)	1 (3%)	4 (5%)	0 (0%)	7 (5%)	2 (3%)	6 (6%)	6 (6%)
<b>Anti-cd20 therapy</b>											
no	3 (5%)	13 (17%)	3 (5%)	11 (42%)	1 (3%)	21 (25%)	1 (3%)	24 (17%)	0 (0%)	0 (0%)	0 (0%)
yes	58 (95%)	63 (83%)	59 (95%)	15 (58%)	32 (97%)	64 (75%)	32 (97%)	115 (83%)	78 (100%)	94 (100%)	100 (100%)
<b>Corticotherapy - PS*</b>											
no	24 (39%)	53 (70%)	16 (26%)	6 (23%)	14 (42%)	54 (64%)	11 (33%)	80 (58%)	29 (37%)	67 (71%)	71 (71%)
yes	37 (61%)	23 (30%)	46 (74%)	20 (77%)	19 (58%)	31 (36%)	22 (67%)	59 (42%)	49 (63%)	27 (29%)	29 (29%)
<b>Tocilizumab</b>											
no	61 (100%)	76 (100%)	60 (97%)	25 (96%)	29 (88%)	80 (94%)	32 (97%)	129 (93%)	72 (92%)	90 (96%)	96 (96%)
yes	0 (0%)	0 (0%)	2 (3%)	1 (4%)	4 (12%)	5 (6%)	1 (3%)	10 (7%)	6 (8%)	4 (4%)	4 (4%)
<b>Azithromycin-hydroxychloroquine</b>											
no	61 (100%)	76 (100%)	62 (100%)	26 (100%)	32 (97%)	78 (92%)	33 (100%)	128 (92%)	76 (97%)	87 (93%)	93 (93%)
yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	7 (8%)	0 (0%)	11 (8%)	2 (3%)	7 (7%)	7 (7%)
<b>Remdesivir</b>											
no	61 (100%)	76 (100%)	55 (89%)	26 (100%)	31 (94%)	82 (96%)	30 (91%)	130 (94%)	69 (88%)	92 (98%)	98 (98%)
yes	0 (0%)	0 (0%)	7 (11%)	0 (0%)	2 (6%)	3 (4%)	3 (9%)	9 (6%)	9 (12%)	2 (2%)	2 (2%)
<b>B-lymphoid neoplasm</b>											
CLL	10 (16%)	11 (14%)	10 (16%)	10 (38%)	5 (15%)	17 (20%)	6 (18%)	21 (15%)	11 (14%)	8 (9%)	9 (9%)



<b>NHL/DLBCL</b>	20 (33%)	35 (46%)	20 (32%)	8 (31%)	15 (45%)	33 (39%)	12 (36%)	50 (36%)	28 (36%)	47 (50%)
<b>NHL/FL</b>	18 (30%)	15 (20%)	18 (29%)	4 (15%)	5 (15%)	14 (16%)	6 (18%)	36 (26%)	23 (29%)	18 (19%)
<b>NHL/LZM</b>	3 (5%)	5 (7%)	3 (5%)	1 (4%)	1 (3%)	11 (13%)	2 (6%)	14 (10%)	3 (4%)	10 (11%)
<b>NHL/MCL</b>	9 (15%)	7 (9%)	10 (16%)	1 (4%)	5 (15%)	7 (8%)	5 (15%)	14 (10%)	11 (14%)	10 (11%)
<b>WM</b>	1 (2%)	3 (4%)	1 (2%)	2 (8%)	2 (6%)	3 (4%)	2 (6%)	4 (3%)	2 (3%)	1 (1%)

Table S1. Characteristics of patients according to analyzed population (other sensitivity analyses). AH : arterial hypertension, BMI: body mass index, PS\*: included in the propensity score, N: number of patients, RCT: randomized control trial, WHO: world health organization.

Variable-modality	Adjusted association		Adjusted association including sex	
	HR of death [95%CI]	p-value	HR of death [95%CI]	p-value
AH or diabete or BMI>25kg/m <sup>2</sup> no vs. yes	0.72 [0.43;1.2]	0.210	0.74 [0.44;1.3]	0.254
Age (years) <65 vs. ≥65	0.50 [0.29;0.85]	0.011	0.50 [0.30;0.86]	0.012
Corticotherapy no vs. yes	0.80 [0.47;1.4]	0.418	0.80 [0.47;1.4]	0.399
Gender female vs. male			0.82 [0.48;1.4]	0.481
Exposure to convalescent plasma yes vs. no	0.46 [0.26;0.84]	0.012	0.45 [0.25;0.83]	0.010

Table S2. Estimation of hazard ratios (HR) of death associated with covariables included in the multivariable model in the overall population and their 95% confidence intervals (CI). AH: arterial hypertension; BMI: body mass index

## Supplementary data – Figures

Figure S1: Overlap between the two distributions of propensity scores according to actual exposure to convalescent plasma allowed the use of propensity score-based method. Distributions of propensity score in the two groups in 16 day-anti-CD20 population (Panel A), in overall population (Panel B), in randomized controlled trial like population (Panel C), in wave 2-4 population (Panel D) , in Paris region population (Panel E) and in 16 day-population (Panel F).

Figure S2: The use of weighted observations succeeded in decreasing the differences between the two groups for variables included in propensity score. Differences between the two groups could remain for variables which were not included in the propensity score since very small number of patients could not fit the positivity assumption and sensitivity analyses were run excluding modalities from these variables. Standardized mean differences between original observations and weighted observations from convalescent plasma (CP)+ and CP- groups in 16day- antiCD20 preexposed population (Panel A), in overall population (Panel B), in randomized controlled trial like population (Panel C), in wave 2-4 population (Panel D) , in Paris region population (Panel E) and in 16day-population (Panel F) for binary variable: wave1: first wave vs. following waves; remdesivir: yes vs. no; AZT\_PLQ: azithromycin/hydroxychloroquine yes vs. no, TOCI\_ANA: Tocilizumab or Anakinra yes vs. no; OMS 5: WHO score 5 vs. <5; Sexe: male vs.female; Diabete: diabetes yes vs. no; HTA: arterial hypertension

Figure S1

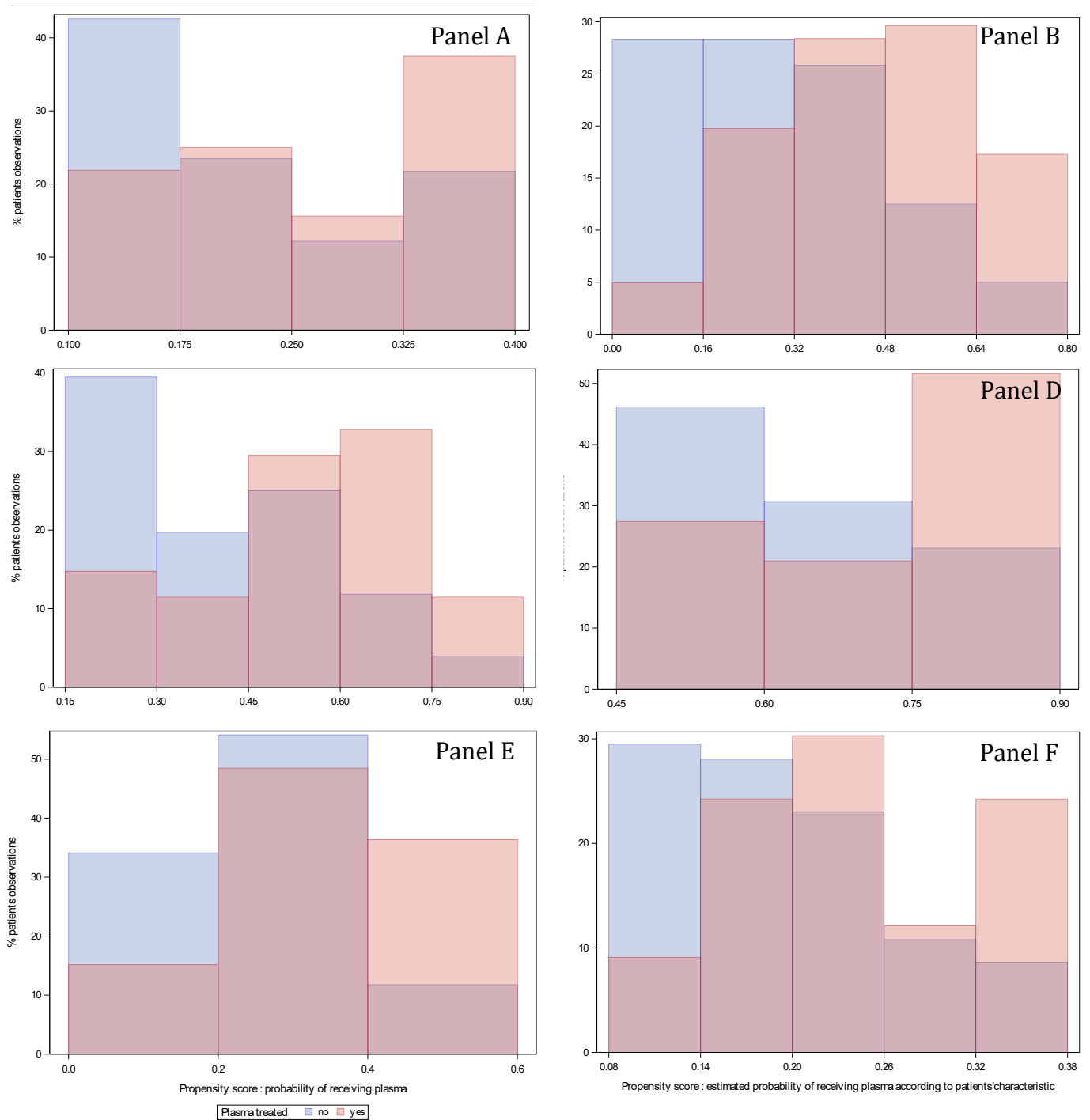


Figure S2

