

Risk factors for a severe form of COVID-19 after allogeneic haematopoietic stem cell transplantation: a Société Francophone de Greffe de Moelle et de Thérapie cellulaire (SFGM-TC) multicentre cohort study

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1 **Risk factors for a severe form of COVID-19 after allogeneic haematopoietic stem cell**
2 **transplantation: an SFGM-TC multicentre cohort study**

3

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1 **Running title:** COVID-19 in alloHSCT recipients

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1 COVID-19, caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), emerged in
2 China at December 2019 and rapidly spread worldwide. Epidemiological studies in the general
3 population (1–3) identified older age, diabetes, obesity, hypertension, cardiovascular diseases, chronic
4 lung diseases, end-stage renal and liver diseases, cancer and haematological malignancies, as risk
5 factors for severity and mortality. Allogeneic hematopoietic stem cell transplantation (alloHSCT)
6 recipients were also considered at risk of severe COVID-19, as respiratory viral infections in
7 alloHSCT recipients associate with significant morbidity and mortality.(4,5)

8 During the first European peak, SFGM-TC and EBMT issued recommendations(6) to postpone
9 alloHSCT whenever feasible. However, many alloHSCT could not be delayed, and all previously
10 transplanted patients were considered at risk of severe COVID-19. Although alloHSCT recipients
11 were advised to limit social interactions, several were still infected. The SFGM-TC conducted a
12 multicentre study of COVID-19 alloHSCT recipients, aiming to identify risk factors for severity and
13 mortality.

14
15 All SFGM-TC centres were invited to report alloHSCT recipients diagnosed with COVID-19 in
16 France, Belgium and Switzerland from February 2020. Only patients with laboratory-confirmed
17 SARS-CoV-2 infection (RT-PCR performed on nasopharyngeal swab) were included. Data were
18 retrospectively collected from the patients' charts and the ProMISe database. Biological data were
19 collected at COVID-19 diagnosis. Most chest CT scans were collected and reviewed by two
20 researchers (HS, MLCC), combining visual and automated analysis of the extension of the COVID-
21 19-related opacities, thanks to a prototype software (Siemens Healthineers®). Radiological patterns
22 were classified as previously published.(7) Conditioning regimen was considered myeloablative or
23 reduced-intensity / non-myeloablative as previously published.(8) Graft-versus-host disease (GVHD)
24 was considered acute before day 100 and chronic after. **Pneumonia was defined according to the**
25 **ECIL-4 guidelines for the definition of community-acquired respiratory viruses-attributable**
26 **pneumonia (clinical symptoms and signs of low respiratory tract infection, virus detected in**
27 **nasopharyngeal swab), and considered probable in case of infiltrates on imaging or hypoxemia,**
28 **and possible in their absence.**(9) Patients transferred to an intensive care unit (ICU) or deceased due

1 to COVID-19 were classified as severe, and non-severe in other cases.(10) All patients gave their
2 written consent for data collection. The study followed the Declaration of Helsinki.

3 Continuous variables are expressed as median (range) or mean (\pm standard deviation, SD) and
4 compared using students or Mann-Whitney tests for normally and abnormally distributed data,
5 respectively. Categorical variables are expressed as frequencies (percentages) and compared using χ^2
6 or Fisher's tests when appropriate. Risk factors of severe COVID-19 were assessed using both
7 univariate and multivariate logistic regressions. All analyses were performed using SAS version 9.4.6
8 (SAS Institute Inc., Cary, NC, USA). A two-tailed significance level $p < 0.05$ was used.

9

10 Fifty-four alloHSCT recipients were diagnosed with COVID-19 between March and May 2020. The
11 incidence was 0.40% in all 25 participating centres and 0.64% for the 14 centres with patients. Centres
12 reported a median of 2.5 patients (range: 1-9). Cases were mostly diagnosed in Ile-de-France (44.4%)
13 and in the East of France (31.5%). The incidence varied among centres (0.14%-1.50%), even within
14 the same region.

15 Patient characteristics are described in **Supplementary table 1**: 21 (38.8%) experienced severe
16 COVID-19, including 13 transferred to ICU and 8 deceased from COVID-19 outside of ICU
17 (**Supplementary Figure 1**). Overall survival is shown in **Figure 1**. The breakdown of severe and non-
18 severe cases according to time from alloHSCT to COVID-19, **and in patient receiving or not**
19 **immunosuppressive treatment** are shown in **Supplementary Figures 2A and 2B**. Biological data at
20 COVID-19 diagnosis, available for a subset of patients, are shown in **Supplementary table 1**.
21 **Radiological findings are described in Supplementary material 1.**

22

23 Haematological characteristics did not vary between patients with severe or non-severe forms of
24 COVID-19 (**Supplementary table 1**). **Univariable and multivariable analyses of risk factors for**
25 **severe COVID-19 are shown in Table 1A: probable pneumonia, symptoms other than**
26 **respiratory and immunosuppressive treatment were associated with severity in multivariable**
27 **models.** Risk factors for death from COVID-19 (**Table 1B**) were older age at alloHSCT, shorter time

1 from alloHSCT to COVID-19 diagnosis, probable pneumonia, co-infection during the course of
2 COVID-19, and lower platelet count.

3

4 This international study is the first to describe risk factors for severe infection and death from COVID-
5 19 in alloHSCT recipients. AlloHSCT recipients are at high risk of COVID-19 severity and mortality,
6 with a fatality rate of 25%. **Previous studies of haematological malignancies patients with COVID-
7 19 reported fatality rate of 39 to 61%.**(11–13) The lower mortality rate in our study might be related
8 to the young age of our patients, as well as the inclusion of non-hospitalized patients, with milder
9 forms of COVID-19. **In our study, as previously seen in haematology patients**(2,13), the risks of
10 severity and death were not associated with the factors seen in the general population (male sex,
11 diabetes and obesity). **Probable pneumonia was the only factor associated with severity and
12 death. Immunosuppressive treatment was a risk factor for severity but not for death: the impact
13 of immunosuppression on the course of COVID-19 in alloHSCT recipients is difficult to
14 determine. Recent** studies reported the efficacy of steroids and/or tocilizumab in the treatment of
15 severe COVID-19.(14,15) Immunosuppression may be an aggravating factor (decreasing the ability to
16 control viral replication), but may also be a protective factor (decreasing the inflammatory phase).
17 Unfortunately, we were not able to perform longitudinal cytokines and immunological analyses over
18 the course of COVID-19. Concerning biological data, only a low platelet count but not a low
19 lymphocyte count was associated with poorer outcomes in our population. However, the lymphocyte
20 count was low in the entire population, as expected in alloHSCT recipients.

21 The central review of CT scans showed that atypical lesions were not rare, so COVID-19 should not
22 be ruled out on the sole basis of radiological findings in alloHSCT recipients. Bronchiectasis within
23 opacities may alert us to the risk of further onset of fibrotic lesions. Indeed, respiratory viruses
24 infections can be a trigger for pulmonary chronic GVHD(16), and alloHSCT recipients who survived
25 COVID-19 should be closely monitored and evaluated for the development of pulmonary GVHD.

26 The total number of COVID-19 among all centres of the SFGM-TC was lower than could have been
27 feared, probably related to the education of alloHSCT recipients: alloHSCT recipients probably

1 applied the instructions of social distancing, mask wearing and handwashing better than the general
2 population. Some nosocomial clusters have been reported (11), but none found in participating centres.
3 Our study has limitations: due to the retrospective data collection, not all biological and clinical data
4 could be fully exhaustive. Patient collection was prospective, so no case should have been missed in
5 the participating centres, **but we cannot exclude an underestimation of the true incidence of**
6 **COVID-19 among alloHSCT recipients if pauci-symptomatic patients did not report to their**
7 **transplant centre.**

8 To date, no vaccine against SARS-CoV-2 is yet commercially available and the vaccination in
9 alloHSCT recipients has limited efficacy. As SARS-CoV-2 continues to spread internationally,
10 alloHSCT recipients should maintain a high level of awareness to avoid contamination.

11

12

1 **Declarations**

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3 AX, CX, MDA, HS, JOB, MR, SNGQ and MTR participated in research design, data analysis and
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6

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13

14

15 *Competing interests*

16 The authors declare that they have no competing interests.

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16

- 1 **Figure legends**
- 2 **Figure 1: Survival curve after COVID-19 diagnosis**
- 3
- 4 **Supplementary figure 1: Flow chart**
- 5 **Supplementary figure 2A: Proportion of severe and non-severe cases, according to time from**
- 6 **alloHSCT to COVID-19 diagnosis**
- 7 **Supplementary figure 2B: Breakdown of cases of COVID-19 by severity and immunosuppressive**
- 8 **treatment**
- 9

1 **Table 1A: Univariable and multivariable logistic regression analyses for association with a severe**
 2 **form of COVID-19**

Characteristic	Univariable ^a		Multivariable ^{a,b}	
	OR (95% CI)	p value	OR (95% CI)	p value
Time between alloHSCT and COVID-19 diagnosis ^a				
Quartile 1 (11d-211d)	Ref		Ref	
Quartile 2 (212d-1.1y)	0.49 (0.09-2.57)	0.40	2.33 (0.15-36.81)	0.55
Quartile 3 (1.4y-3.7y)	0.11 (0.02-0.70)	0.02	0.14 (0.01-3.44)	0.23
Quartile 4 (4.5y-18.8y)	0.10 (0.01-0.69)	0.02	0.13 (0.01-3.16)	0.21
Probable pneumonia	14.18 (1.63-123.20)	0.02	45.20 (1.33 -999.99)	0.03
Possible and probable pneumonia	20.78 (2.42-178.42)	0.006		
Other symptoms ^c	3.40 (1.01-11.52)	0.05	20.89 (1.41-309.62)	0.03
Any IS treatment	5.11 (1.32-19.77)	0.02	16.37 (1.25-215.00)	0.03
Any comorbidity	3.24 (0.86-12.24)	0.08	0.05 (0.01-2.11)	0.12
Co-infection	6.34 (1.71-23.51)	0.006	14.80 (0.70-311.44)	0.08
Platelets (G/L)				
Tertile 1 (11-79)	13.33 (1.78-100.13)	0.01		
tertile 2 (95-189)	3.12 (0.47-20.58)	0.24		
Tertile 3 (221-781)	Ref			

3 ^a Adjusted for age at COVID-19 and sexe

4 ^b Due to the low number of patients, multivariate analysis was performed considering only clinical
 5 factors (excluding platelet count)

6 ^c Other symptoms: asthenia (n=5), neurologic symptoms (n=4), myalgia (n=2), dysgeusia (n=1), skin
 7 lesions (n=1), arthralgia (n=1), other (n=3)

8 Abbreviations: d: days, y: years, IS: immunosuppressive, G/L: giga/liter

9 **Excluding patients younger than 15 from analysis did not modify the results. Due to the low**
 10 **number of patients, multivariable analysis was performed considering only clinical factors**
 11 **(excluding platelet count).**

12

13 **Table 1B: Univariable logistic regression analysis for association with death from COVID-19**
 14 **(dead=13, alive=33)**

Characteristic	Univariable ^a	
	OR (95% CI)	p value
Time between alloHSCT and COVID-19 diagnosis ^a		
Quartile 1 (54d-216d)	Ref	0.02
Quartile 2 (234-1.4y)	0.61 (0.09-4.07)	0.61
Quartile 3 (1.4y-3.7y)	0.16 (0.02-1.35)	0.09
Quartile 4 (4.5y-18.8y)	0.05 (0.01-0.73)	0.03
Probable pneumonia	9.97 (1.09-91.57)	0.04
Possible and probable pneumonia	6.62 (0.70-62.36)	0.10
Other symptoms ^b	2.35 (0.56-9.86)	0.24
Any IS treatment	2.93 (0.69-12.50)	0.15
Any comorbidity	3.27 (0.58-18.34)	0.18

Co-infection	12.04 (1.84-78.87)	0.01
Platelets (G/L)		
Tertile 1 (11-79)	21.37 (1.71-267.11)	0.01
Tertile 2 (95-189)	2.97 (0.23-39.30)	0.41
Tertile 3 (221-781)	Ref	
Age at alloHSCT (years)^c		
Quartile 1 (2.4-35.0)	ref	
Quartile 2 (37.4-54.7)	0.80 (0.04-15.35)	0.89
Quartile3 (55.6-63.4)	4.21 (0.38-46.11)	0.24
Quartile 4 (63.7-74.1)	12.81 (1.19-137.34)	0.04

1 ^a Adjusted for age at COVID-19 and sexe

2 ^b Other symptoms: asthenia (n=5), neurologic symptoms (n=4), myalgia (n=2), dysgeusia (n=1), skin
3 lesions (n=1), arthralgia (n=1), other (n=3)

4 ^c Adjusted for sexe

5 Abbreviations: d: days, y: years, G: giga, L: liter

6 **Excluding patients younger than 15 from analysis did not modify the results. The effective included
7 in the analysis does not allow to perform multivariate analysis.**

8

9

1 Supplementary table 1: Characteristics of the 54 patients

		All (n=54)	Severe (n=21)	Non-severe (n=33)	p value
General characteristics					
Sex	Male	31 (57.4%)	13 (61.2%)	18 (54.6%)	0.59
Centres					
	Besançon	6	3	3	
	Brussels	2	0	2	
	Geneva	3	0	3	
	Institut Gustave Roussy (Villejuif)	5	0	5	
	Liège	4	3	1	
	Lille (pediatric)	1	0	1	
	Montpellier	1	1	0	
	Nancy	8	4	4	
	Nice	2	2	0	
	Pitié-Salpêtrière (Paris)	9	4	5	
	Robert-Debré (Paris)	1	1	0	
	Saint-Louis (Paris)	9	3	6	
	Strasbourg	1	0	1	
	Strasbourg (pediatric)	2	0	2	
Haematological disease characteristics					
Median age at diagnosis (years) (range)		52.6 (0.0-73.5)	53.2 (3.2-73.5)	43.6 (0.0-72.0)	0.21
Age < 15 at diagnosis		4 (7.4%)	1 (4.80%)	3 (9.10%)	1.00
Disease					0.65
	AML	21 (38.9%)	9	12	
	ALL / biphenotypic	7 (13.0%)	3	4	
	NHL	7 (13.0%)	3	4	
	MDS	6 (11.1%)	1	5	
	MPN	4 (7.4%)	3	1	
	Chronic lymphoproliferative disease	4 (7.4%)	1	3	
	Non-malignant ^a	5 (9.3%)	1	4	
Median age at HSCT (years) (range)		55.1 (2.4-74.1)	58.8 (5.5-74.1)	44.8 (2.4-74.1)	0.18
Previous HSCT		10 (18.5%)	4 (19.1%)	6 (18.2%)	0.95
Type	Autologous	9 (90.0%)	4	5	
	Allogeneic	1 (10.0%)	0	1	
Myeloablative conditioning		18 (33.3%)	5 (23.8%)	13 (39.4%)	0.24
Complete remission at HSCT ^b		35 (71.4%)	15 (75.0%)	20 (69.0%)	0.78
Donor type					0.24
	Identical sibling	21 (38.9%)	6 (28.6%)	15 (45.5%)	
	Matched unrelated	19 (35.2%)	11 (52.4%)	8 (24.2%)	
	Haplo-identical	7 (13.0%)	2 (9.5%)	5 (15.2%)	
	Mismatched unrelated	7 (13.0%)	2 (9.5%)	5 (15.2%)	
Stem cell source					0.15
	Bone marrow	10 (18.5%)	2 (9.5%)	8 (24.2%)	

Cord blood	1 (1.9%)	1 (4.8%)	0 (0.0%)	
Peripheral blood	43 (79.6%)	18 (85.7%)	25 (75.8%)	
HCT-CI at alloHSCT				0.85
0	23 (42.6%)	9 (42.9%)	14 (42.4%)	
1	7 (13.0%)	4 (19.1%)	3 (9.1%)	
2	5 (9.3%)	2 (9.5%)	3 (9.1%)	
≥3	18 (33.3%)	6 (28.6%)	12 (36.4%)	
Unknown	1 (1.9%)	0 (0.0%)	1 (3.0%)	
Karnofsky score at HSCT				0.68
90-100	36 (66.7%)	14 (66.7%)	22 (66.7%)	
70-80	13 (24.1%)	6 (28.6%)	7 (21.2%)	
Unknown	5 (9.3%)	1 (4.5%)	4 (12.1%)	
Acute GVHD	32 (59.3%)	14 (66.7%)	18 (56.3%)	0.45
Chronic GVHD	21 (38.9%)	6 (28.6%)	15 (45.5%)	0.21
Relapse	8 (14.8%)	3 (15.0%)	2 (17.2%)	0.54
COVID-19 characteristics				
Time between transplant and COVID-19 diagnosis (years) (range)	1.3 (11d-19y)	0.78 (11d-9y)	2.1 (54d-19y)	0.01
Median age at COVID-19 diagnosis (years) (range)	57.4 (5.5-80.4)	60.5 (5.6-74.9)	56.7 (5.5-80.4)	0.32
Age < 15 years at COVID-19 diagnosis	3 (5.6%)	1 (4.8%)	2 (6.1%)	1
Symptoms	48 (88.9%)	21 (100%)	27 (81.8%)	0.04
Fever	39 (72.2%)	17 (85.0%)	22 (66.7%)	0.14
Upper respiratory symptoms	24 (44.4%)	10 (47.6%)	14 (42.4%)	0.6
Probable pneumonia	36 (66.7%)	20 (95.2%)	16 (48.5%)	<0.001
Possible and probable pneumonia	39 (72.2%)	20 (95.2%)	19 (57.6%)	0.002
Digestive symptoms	10 (18.5%)	5 (23.%)	5 (15.1%)	0.49
Other ^c	17 (31.5%)	10 (47.6%)	7 (21.2%)	0.04
Any IS treatment	33 (61.1%)	17 (81.0%)	16 (48.5%)	0.02
Steroids	14 (25.9%)	6 (28.6%)	8 (24.2%)	0.66
Calcineurin inhibitors	12 (22.2%)	7 (33.3%)	5 (15.1%)	0.17
Ruxolitinib	5 (9.3%)	2 (9.5%)	3 (9.1%)	0.87
Other ^d	7 (13.0%)	5 (23.8%)	2 (6.1%)	0.09
Reason for IS treatment				
Primary GVHD prophylaxis	4 (11.8%)	2 (9.5%)	2 (6.1%)	0.64
Acute GVHD	9 (26.5%)	6 (28.6%)	3 (9.1%)	0.13
Chronic GVHD	20 (60.6%)	9 (42.9%)	11 (33.3%)	0.48
Comorbidities	35 (64.8%)	17 (80.9%)	18 (54.5%)	0.05
Cardiovascular risk factors	21 (38.9%)	8 (38.1%)	13 (39.4%)	0.92
Hypertension	13 (24.1%)	6 (33.3%)	7 (21.2%)	0.2
Other ^e	8 (14.8%)	1 (4.8%)	7 (21.2%)	0.1
Diabetes	10 (18.5%)	4 (19.0%)	6 (18.2%)	1

BMI ≥ 30	7 (13.0%)	5 (23.8%)	2 (6.1%)	0.1
COPD, BOS, pulmonary GVHD	4 (7.4%)	2 (9.5%)	2 (6.1%)	0.89
Co-infection (all types)	18 (33.3%)	11 (52.4%)	7 (21.2%)	0.001
Supplemental oxygen	28 (51.8%)	21 (100.0%)	7 (21.2%)	<0.001
ICU	13 (24.1%)			
Median time between Covid-19 diagnosis and ICU transfer (days) (range)		1 (0-20)		
Median time in ICU (days) (range)		14 (1-77)		
Deceased		14 (25.9%)		
Cause of death				
COVID-19	13 (92.9%)			
Septic shock	1 (7.1%)			
Median follow-up time from COVID-19 diagnosis (range) (days)	46.5 (3-122)			

Biological characteristics

	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	p value
Neutrophils (G/L)	33	4.47 ± 3.69	14	3.76 ±3.43	19	5.00 ±3.87	0.35
Lymphocytes (G/L)	34	1.04 ± 0.87	14	1.008 ±0.506	20	1.064 ±0.646	0.86
Haemoglobin (g/dL)	36	10.56 ± 1.96	15	10.33 ±2.11	21	10.73 ±1.89	0.56
Platelets (G/L)	36	172.86 ± 150.60	15	98.53 ±74.87	21	226.0 ±148.90	0.01
C-reactive protein (mg/L)	34	91.25 ± 92.05	13	106.9 ±90.54	21	81.58 ±20.48	0.44
Creatinine (µmol/L)	34	121.46 ± 111.82	15	116.2 ± 70.51	19	125.6 ±137.9	0.80
AST (IU/L)	33	51.55 ± 45.62	15	42.67 ± 26.96	18	58.94 ±56.49	0.29
ALT (IU/L)	32	55.97 ± 67.60	15	36.07 ±28.24	17	73.5 ±86.36	0.11
Bilirubin (µmol/L)	32	9.57 ± 10.11	14	7.65 ±4.2	18	11.07 ±12.94	0.30
D-dimers (ng/L)	16	1084.81 ± 600.52	4	1048.0 ±269.8	12	1097.1 ±686.5	0.89
LDH (IU/L)	31	436.06 ± 280.50	15	530.5 ±327.2	16	347.5 ±200.4	0.07

1
2 ^a Non-malignant diseases: bone marrow failure (n=1), haemoglobinopathies (n=2), primary immune
3 deficiency (n=2)

4 ^b Only for malignant diseases (n=49)

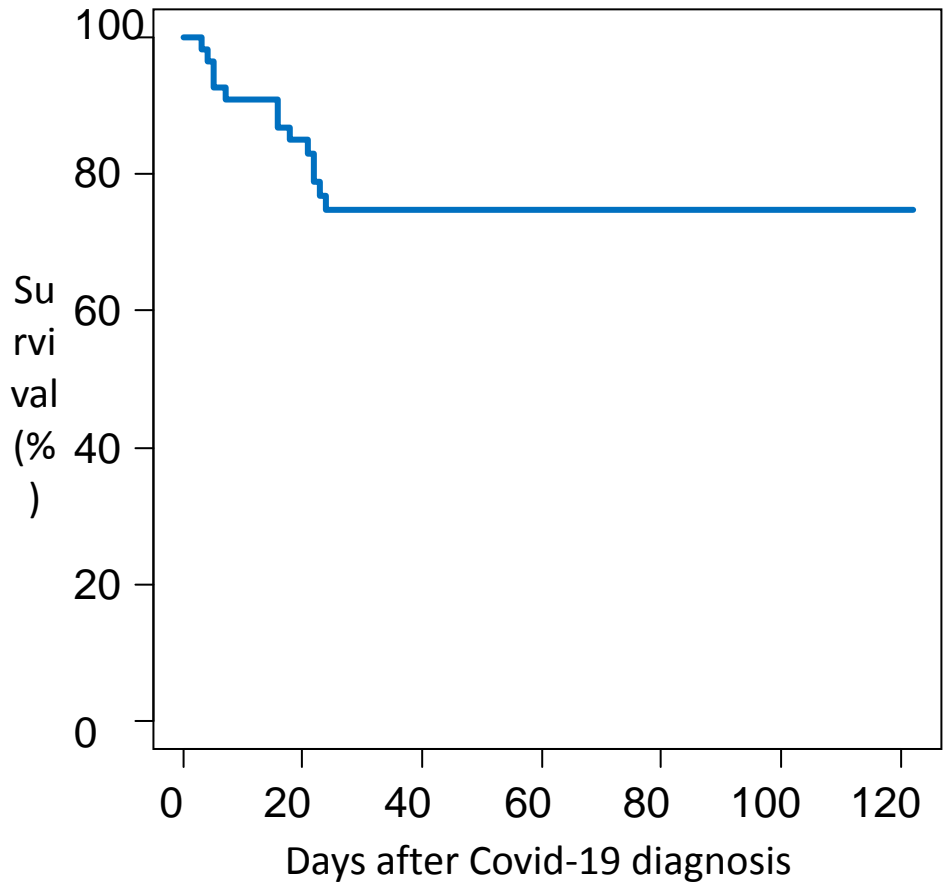
5 ^c Other symptoms: asthenia (n=5), neurologic symptoms (n=4), myalgia (n=2), dysgeusia (n=1), skin
6 lesions (n=1), arthralgia (n=1), other (n=3)

7 ^d Mycophenolate mofetil (n= 3), imatinib, methotrexate, mycophenolic acid, rapamycin (n= 1 each)

8 ^e Other cardiovascular pathologies: coronaropathy, chronic cardiac failure, myocardial infarction,
9 pericarditis, cardiomyopathy

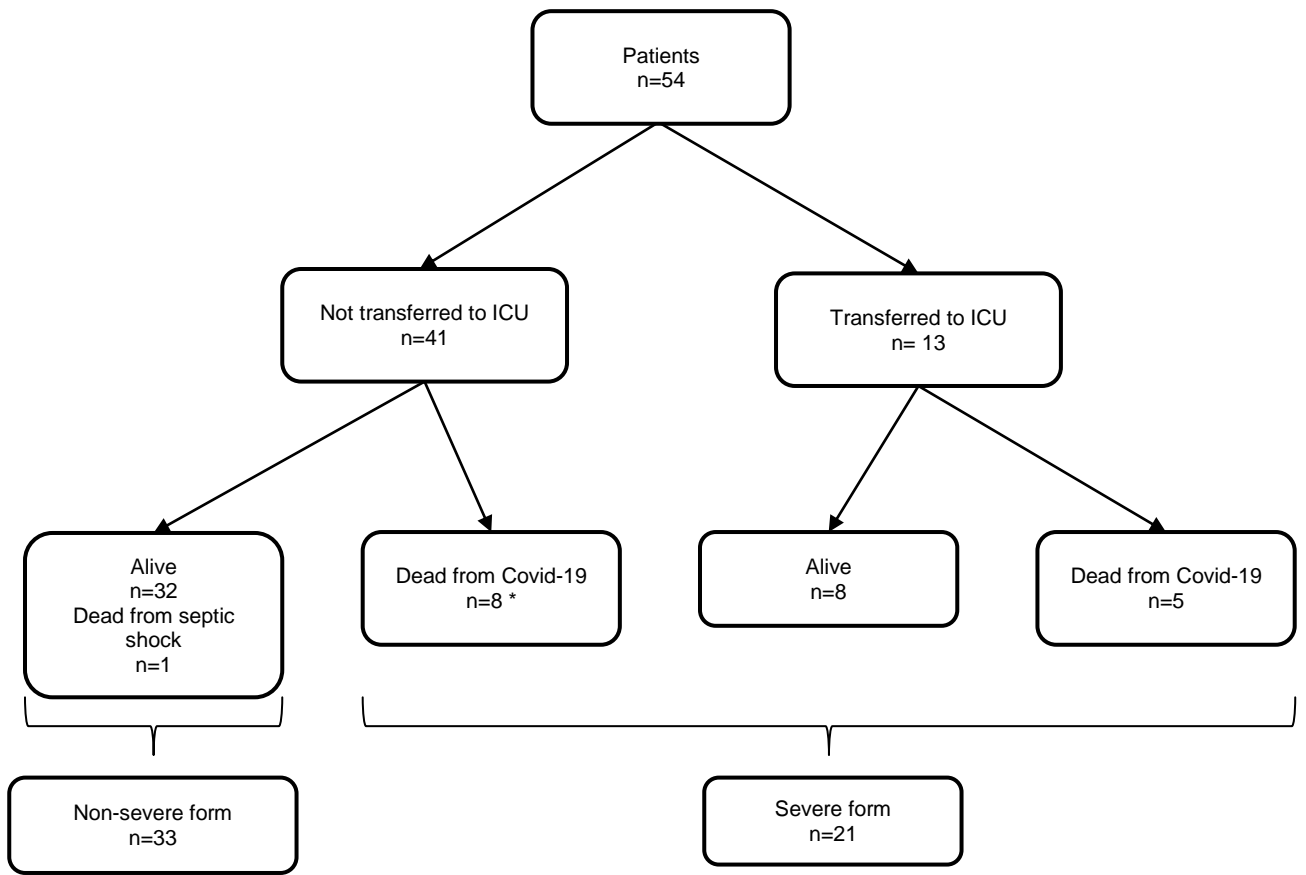
10 Abbreviations: AML: acute myeloid leukaemia, ALL: acute lymphoblastic leukaemia, NHL: non-
11 Hodgkin lymphoma, MDS: myelodysplastic syndrome, MPN: myeloproliferative neoplasms, HSCT:
12 hematopoietic stem cell transplantation, HCT-CI: hematopoietic cell transplantation comorbidity
13 index, GVHD: graft-versus-host disease, IS: immunosuppressive, BMI: body mass index, COPD:
14 chronic obstructive pulmonary disease, BOS: bronchiolitis obliterans syndrome, ICU: intensive care
15 unit; G: giga, L: liter, dL: deciliter, mg: milligram, µmol: micromole, AST: aspartate transaminase, IU:
16 international unit, ALT: alanine transaminase, ng: nanogram, LDH: lactate dehydrogenase

1 **Figure 1: Survival curve after COVID-19 diagnosis**



2

1 **Supplementary figure 1**



2

3

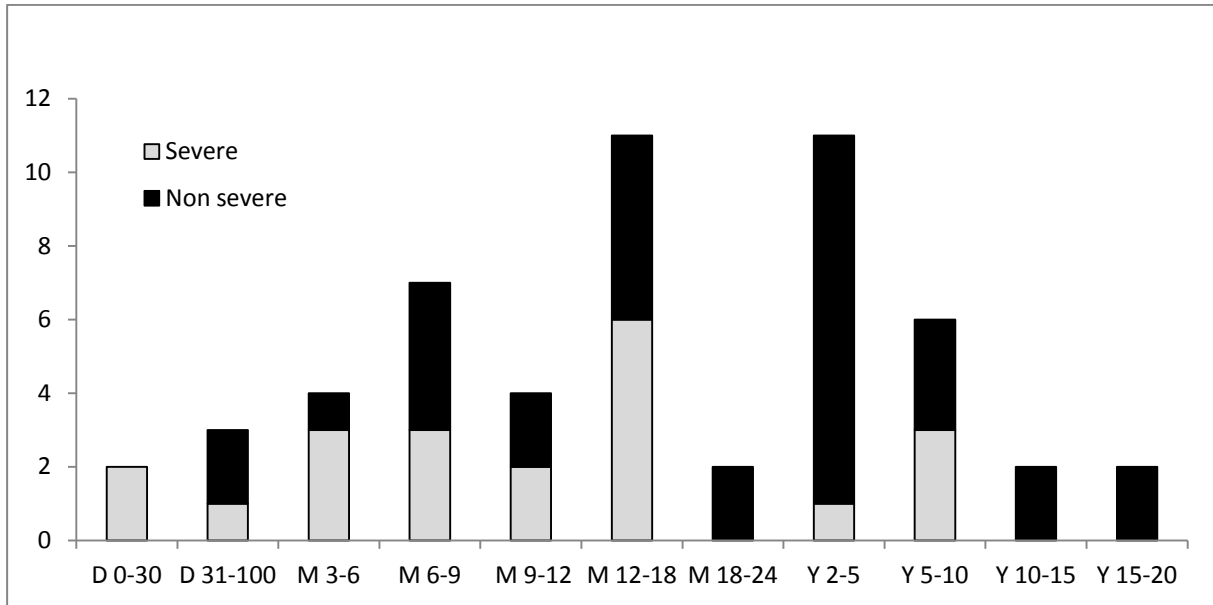
4 **(*) Patients were not transferred to ICU because of relapse (n=3), poor underlying condition (n=2),**
5 **steroid-resistant GVHD (n=2) or patient's choice (n=1).**

6

7

1 **Supplementary figure 2A**

2

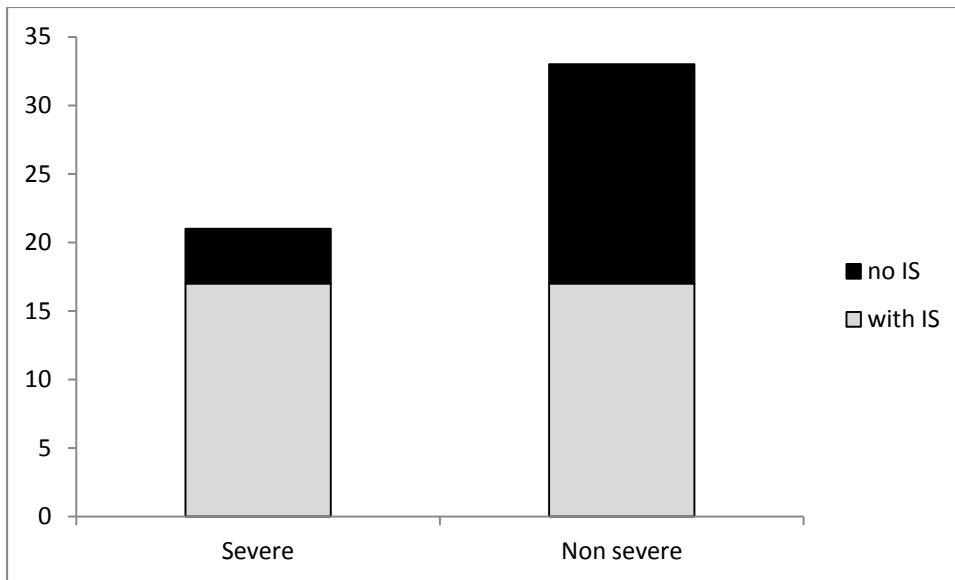


3

4 **54.8% of the patients diagnosed within 18 months after alloHSCT had severe COVID-19, while**
 5 **82.6% of the patients diagnosed more than 18 months after alloHSCT were non-severe.**

6

7 **Supplementary figure 2B**



8

9 **80% of severe COVID-19 patients were receiving immunosuppressive treatment, versus 50% of**
 10 **non-severe patients.**

11

1 **Supplementary material 1 (radiological findings)**

2

3 Thirty-eight chest CT scans were available for 27 patients (50%), including 27 performed at diagnosis:
4 19 showed typical radiological findings (ground glass opacities (100%), condensations (59%) and
5 crazy paving (41%)), five atypical (bronchiectasis within newly-onset opacities (33%), pleural and/or
6 pericardial effusion (26%), nodules and micronodules (19%), septal thickening (15%), pneumothorax
7 (4%)) and three were not determined. Lesions were both peripheral and central in 70% and exclusively
8 peripheral in 22%. Opacities were diffuse in 52% and predominant in the lower lobes in 33%, equally
9 symmetrical (41%) or predominantly in the right lung (44%). The extension of lesions was less than
10 10% in nine cases (33%), 10-25% in four cases (14.8%), 25-50% in eight cases (29%), 50-75% in four
11 cases (14.8%) and >75% in two cases (7%). Eight patients had another CT scan during the course of
12 their disease: lesions worsened in five and improved in three (including one early onset of fibrotic
13 lesions).

14

15