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Impact of pre-transplant diffusion lung capacity for nitric oxide (DLNO) and of DLNO/pre-transplant diffusion lung capacity for carbon monoxide (DLNO/DLCO) ratio on pulmonary outcomes in adults receiving allogeneic stem cell transplantation for hematological diseases

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1 Letter

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3 **Impact of pre-transplant diffusion lung capacity for nitric oxide (DLNO) and of**
4 **DLNO/pre-transplant diffusion lung capacity for carbon monoxide (DLNO/DLCO)**
5 **ratio on pulmonary outcomes in adults receiving allogeneic stem cell transplantation for**
6 **haematological diseases.**

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30 Incidence of pulmonary damages is high after allogeneic stem cell transplantation
31 (allo-SCT) and accounting for one of the main causes of non-relapse mortality (NRM) and
32 intensive care unit admission. Pre-transplant alteration of the lung function is considered as
33 the most important parameter to take into account to predict pulmonary complications and
34 outcomes.¹ As a consequence, pre-transplant pulmonary function testing (PFT) is required in
35 all patients eligible for an allo-SCT. Diffusion lung capacity for carbon monoxide measured
36 after a 10 second single breath-hold technique (DLCO_{10s}, thereafter DLCO), which reflects the
37 alveolar capillary interface, is considered as one of the key parameters to cancel the allograft.
38 Indeed, reduction of the diffusion capacity has been shown to predict NRM, overall survival
39 (OS) and early respiratory failure after allo-SCT.^{1, 2} Thus, current guidelines suggest that
40 patients with a pre-transplant DLCO < 60% of predicted normal value are not ideal candidates
41 for allo-SCT. However, this recommendation is currently debated, especially since the
42 predominant use of less toxic reduced-intensity conditioning (RIC) regimens.³⁻⁵

43 Other pulmonary parameters may help to discriminate patients at high-risk of severe
44 lung complications. In 1987, Guénard et al, demonstrated that nitric oxide (NO), together with
45 CO, can be used to measure the diffusion pathway from the alveoli to capillary plasma in the
46 lung.⁶ The lung diffusing capacity for NO (DLNO) is considered as a measure of membrane
47 conductance which is less affected by any diffusive resistance associated with capillary
48 erythrocytes, except the presence of free hemoglobin. In fact, DLNO reflects the distance
49 between the alveoli and the capillaries mainly related to the alveolar-capillary membrane and
50 the thickness of the alveolar blood barrier while DLCO rather reflects the capillary blood
51 vessels function.⁷ Also, DLNO/DLCO ratio represents a new index of gas exchange and an
52 alternative way of investigating the alveolar membrane and the blood reacting with the gas.⁸
53 Although explored in many lung diseases,⁹⁻¹² impact of DLNO and DLNO/DLCO ratio has
54 not been yet established in the setting of allo-SCT. It is of particular interest as radiotherapy

55 and chemotherapy used to treat patients with hematological diseases affect mostly the
56 alveolar-capillary membrane, which destruction is more appreciate by DLNO than DLCO
57 measure. In our study, DLNO and DLNO/DLCO ratio seem more appropriate to predict
58 pulmonary complications than DLCO after allo-SCT and therefore should be rather
59 considered to define eligibility for transplant.

60 Between March 2012 and January 2014, 153 adults performed a pre-transplant PFT in
61 our department. Fifty patients were excluded of the study because: 1) no DLNO measure was
62 performed during the pre-transplant PFT (n=30); 2), an unevaluated pre-transplant diffusion
63 lung capacity (n=10); 3) allograft was contra-indicated due to abnormal PFT (n=1),
64 uncontrolled infection (n=4), psychiatric illness (n=1), relapse before transplant (n=3), or
65 death during the conditioning regimen (n=1). Thus, overall, the full PFT data required for the
66 study for each case was available in 103 patients. Characteristics of patients are summarized
67 in Table 1. The study was approved by the Institutional Review Board of the French learned
68 society for respiratory medicine -Société de Pneumologie de Langue Française (ref number
69 CEPRO 2015-025) and patients gave their consents for anonymous use of their data.

70 All PFT were performed in routine at the CHU of Nantes in the same laboratory.
71 Because of faster diffusion, DLNO is measured after a 5 (and not 10) second single breath-
72 hold technique (DLNO_{5s}, thereafter DLNO). DLCO can be measured simultaneously
73 (DLCO_{5s}) for a double diffusion measure, allowing to calculate a DLNO_{5s}/DLCO_{5s} ratio
74 (thereafter DLNO/DLCO). Normal DLCO and DLNO percentage of predicted normal value
75 PNV (>80%) were documented in 48 and 44 patients, respectively but median percentages for
76 the all cohort were below the normal at transplant: DLCO: 78.9%, DLNO: 78.1%. Median
77 DLNO/DLCO ratio was 5.3 (range: 2.7-8.6). Only 6 patients had a pejorative high-risk lung
78 function score (LFS) (between 6 and 9).¹³ Median DLCO was significantly decreased in older
79 patients (>58 years, 75.4% of PNV vs 81.0%, p=0.05), patients with previous documented

80 respiratory events (72.3% vs 81.5%, p=0.001) or previous administration of drugs with
81 cardiac or pulmonary toxicities (74.2% vs 80.6%, p=0.02). Median DLNO was also
82 significantly decreased in patients with previous documented respiratory events (74.3% versus
83 80.9%, p=0.03) and patients with active or history of smoking (75.3% versus 81.8%, p=0.03).
84 Finally, younger patients (≤ 58 years) had a significant lower median DLNO/DLCO ratio (5.2
85 vs 5.5, p=0.04).

86 Median follow up was 21.5 months (range: 3.8-34.7). Two years OS, disease free
87 survival, relapse incidence and NRM were 65.4% (55.2-73.6), 52.5% (42.7-62.2), 31.8%
88 (22.3-41.7) and 15.8% (9.4-23.5), respectively. Cumulative incidence (CI) of acute GVHD
89 grade II-IV and grade III-V were 34% (25-43.2) and 19.4% (12.4-27.6) while CI of overall
90 and extensive chronic GVHD were 25.5% (17.5-34.3) and 14.7% (8.6-22.3), respectively.

91 After transplant, any type of pulmonary event was collected retrospectively from
92 clinical and radiologic data available in medical records. Thus, 77 respiratory events were
93 documented in 53 patients: 27 bronchitis, 22 pneumonia, 14 invasive fungal infection, 4
94 bronchiolitis obliterans syndrome, 2 idiopathic pulmonary fibrosis, 2 pneumothorax, 1
95 tuberculosis, 1 sinusoidal obstruction syndrome, 1 mediastinal lymphoma, 1 acute pulmonary
96 edema, 1 pulmonary embolus, and 1 case with multiple pulmonary nodules of undetermined
97 significance. The median number of pulmonary events per patient after transplant was 1
98 (range: 0-7). Two year CI of severe pulmonary complication (SPC) (defined as any
99 pulmonary complication responsible for hospitalization), acute respiratory distress syndrome
100 (ARDS) and pulmonary related mortality (PRM) were 25.4% (17-34), 7.8% (4-14), and 4.9%
101 (1.8-10.4), respectively. Overall, five patients died of a respiratory complication (1 invasive
102 aspergillosis; 1 CMV pneumonia; 3 bacterial pneumonia in patients with severe acute or
103 refractory chronic GVHD: *pseudomonas aeruginosa*: n=2, *pseudomonas aeruginosa* +
104 *acinetobacter baumannii*: n=1).

105 In univariate analysis, when considering various cut-offs ($\geq 80\%$, 60-80% and $< 60\%$),
106 DLCO was not predictive of any outcomes considered for the analysis: ARDS, SPC, PRM
107 and NRM (Table 2). Conversely, a DLNO value $< 60\%$ was associated with significant higher
108 incidences of SPC ($\geq 80\%$: 20.5% vs 60-80%: 24% vs $< 60\%$: 59.3%, $p=0.02$) and ARDS
109 ($\geq 80\%$: 9.1% vs 60-80%: 2% vs $< 60\%$: 35.6%, $p<0.005$). When considering DLCO and
110 DLNO as continuous variables, lower percentage were associated with higher risk of SPC for
111 both parameters ($p=0.048$ and $p=0.026$, respectively). Also, lower DLNO/DLCO ratio
112 (considered as a continuous variable) was associated with higher PRM ($p=0.04$). Previous
113 history of pulmonary events was associated with higher risk of ARDS (no: 3.1% vs yes:
114 15.8%, $p<0.01$). Among factors related to patient, disease or transplant, only the type of
115 disease impacted on pulmonary outcomes as lymphoid patients were associated with higher
116 risk of ARDS ($p=0.04$), SPC ($p=0.03$) and PRM ($p=0.02$).

117 In multivariate analysis, there was a trend for a significant association between lower
118 value of pre-transplant DLNO ($< 60\%$) and higher risk of ARDS (HR: 3.34, 95%CI: 0.99-
119 11.2, $p=0.05$) and of SPC (HR: 2.5, 95%CI: 0.93-7.12, $p=0.06$).

120 At our knowledge, this is the first series reporting on the impact of pre-transplant
121 DLNO percentage and DLNO/DLCO ratio after allo-SCT. In univariate analysis, lower value
122 of DLNO ($< 60\%$ of PNV) was associated with higher incidence of ARDS and SPC while
123 lower DLNO/DLCO ratio was associated with an increased risk of PRM. Significance was
124 not reached by multivariate analysis probably because of the relative small number of patients
125 of our cohort.

126 Currently, lower pre-transplant DLCO percentage remains generally an excluding
127 criteria when considering the eligibility of a patient for allo-SCT. Guidelines suggest that
128 patients with pre-transplant DLCO $< 60\%$ of PNV should not proceed with the transplant

129 because of an unacceptable increased risk of pulmonary complication and mortality. Here, we
130 found no impact of lower pre-transplant DLCO value, confirming recent results observed in
131 adults as well as in children.³⁻⁵ In fact, DLCO is the most variable parameter in a PFT,
132 particularly when a restrictive or obstructive ventilatory impairment is present, suggesting that
133 lower value in a particular patient may be equivalent to a normal value in another. Thus,
134 DLCO should not be retained anymore as unique criteria to decide or not to perform the graft
135 in patient.

136 In the literature, DLNO/DLCO ratio has been observed between 4.3 and 5.3,⁸ which is
137 in accordance with the median value (4.9±0.6) observed in a cohort of healthy subjects who
138 performed PFT, including both DLNO and DLCO measures, in our department. If the median
139 ratio was higher for haematological patients included in this study, it is difficult to define it as
140 abnormal, as no normal values have been clearly reported currently. Higher median ratio may
141 be the fact of older age of our cohort or higher concentration of free haemoglobin in this
142 population, as it is highly reactive with NO.¹⁴

143 As a conclusion, DLNO and DLNO/DLCO ratio seem more appropriate to predict
144 pulmonary complications than DLCO after allo-SCT and therefore should be rather
145 considered to define eligibility for transplant. However, the number of patients is low in our
146 study and many variables may be involved explaining the results. Then multivariable analysis
147 with a larger patient-group and clear exclusion criteria of transplant patients, who are
148 considered not eligible because of preceding pulmonary problems, should be proposed in the
149 future.

150

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1 **Table 1:** Characteristics of patients (N=103)

Variables	N= 103
Gender: male	68 (66%)
Median age at transplant: years (range)	58 (24-69.1)
Median weight at transplant: Kg (range)	72 (52-105)
Type of diseases:	
-Myeloid diseases: AML/MDS/MF/CML/AA	67 (65%): 47/10/7/2/1
-Lymphoid diseases: ALL/HD/DLBCL/FL/ATCL/PTCL/MCL/CLL/MM	36 (35%): 14/1/5/2/1/2/1/6/4
Status at transplant: CR (CR1/CR2)/PR/active non treated/refractory disease	56 (54.4%) (44/11)/23 (22.3%)/8 (7.8%)/16 (15.5%)
DRI: low/intermediate/high/very high/unavailable	13 (12.6%)/57 (55.3%)/29 (28.2%)/3 (2.9%)/1 (1%)
Type of donor: MRD/haplo-RD/MUD/MisMUD/UCB	35 (34%)/5 (4.9%)/43 (41.7%)/9 (8.7%)/11 (10.7%)
Type of stem cell source: BM/PBSC/UCB	10 (9.7%)/83 (80.6%)/10 (9.7%)

Conditioning regimen:*

-RIC/MAC 85 (82.5%)/18 (17.5%)

-use of ATG: yes/no 85 (82.5%)/18 (17.5%)

-use of TBI>6gy: yes/no 5 (4.85%)/98 (95.15%)

Smoking history:

-active smokers/former smokers/never smoked 17 (16.5%)/36 (35%)/50 (48.5%)

-median number of pack-years/smokers (range) 22 (2-45)

Previous administration of therapeutic with cardiac or pulmonary toxicities

-previous graft: autograft/allograft 16 (15.5%)/5 (4.8%)

- bleomycin/methotrexate/anthracyclin/cyclophosphamide 2 (1.9%)/9 (8.7%)/82 (79.6%)/41 (39.8%),

-median number of drugs administered per patient (range) 1 (0-5)

- number of drugs administered per patient: <2 vs ≥2 63 (61.2%)/40 (38.8%)

Previous pulmonary events:

-no/yes: (pulmonary embolism/bronchitis/bacterial pneumonia/IFI/
asthma/emphysema or COPD/pneumothorax/pleural effusion/ sarcoidosis/

65 (63.1%)/38 (36.9%) : (5/1/12/16/5/3/1/1/1/3)

Pulmonary involvement of the haemopathy)

HCT-CI: low risk (0)/intermediate risk (1-2)/high risk (≥ 3)

37 (35.9%)/37 (35.9%)/29 (28.2%)

2 AA : aplastic anemia, ALL: acute lymphoid leukemia, AML: acute myeloid leukemia, ATCL : angio-immunoblastic T-cell lymphoma,
3 ATG: antithymocyte globulin, BM: bone marrow, COPD: chronic obstructive pulmonary disease, CLL : chronic lymphoid leukemia, CML:
4 chronic myeloid leukemia, CR : complete remission, DLBCL : diffuse large B-cell lymphoma, DRI: Disease risk index,¹⁵ FL : follicular
5 lymphoma, IFI: invasive fungal infection, haplo-RD : haploidentical related donor, HD : hodgkin disease, HCT-CI: Hematopoietic Cell
6 Transplantation-Comorbidity Index ,² MAC: myeloablative conditioning, MCL : mantle-cell lymphoma, MDS, myelodysplastic syndrome, MF:
7 myelofibrosis, MM : multiple myeloma, MRD : matched related donor, MUD : matched unrelated donor, MisMUD: mismatched unrelated
8 donor, PBSC: peripheral blood stem cell, PR : partial remission, PTCL : peripheral T-cell lymphoma, RIC: reduced intensity regimen, UCB:
9 umbilical cord blood. *GVHD prophylaxis consisted of cyclosporine (CsA) alone or CsA + mycophenolate mofetyl after RIC allo-SCT using a
10 sibling donor or an unrelated donor, respectively. Standard combination of CsA + short course of low dose methotrexate was used after MAC.
11 Granulocyte-colony-stimulating factor was administered during aplasia only in patients receiving a cord blood transplant.

1 **Table 2** : Univariate analysis

	NRM		PRM		Severe pulmonary complication*		ARDS	
	%	p-value	%	p-value	%	p-value	%	p-value
DRI: low-risk + intermediate vs high-risk+very-high risk	14.4 (7.4-23.4) vs 9.4 (2.3-22.6)	0.25	5.8 (1,8-13.1) vs 3.1 (0.2-14.2)	0.56	25.9 (16.2-36.7) vs 25.0 (11.5-41.1)	0.55	10.1 (4.4-18.5) vs 3.1 (0.2-14.2)	0.16
Disease: lymphoid vs myeloid	19.8 (8.6-34.4) vs 9.0 (3.6-17.3)	0.04	11.4 (3.5-24.4) vs 1.5 (0.1-7.2)	0.02	39.7 (23.5-55.5) vs 17.9 (9.8-28.0)	0.03	14.2 (5.1-27.8) vs 4.5 (1.2-11.4)	0.04
HCT-CI: 0 vs ≥ 1	8.3 (2.1-20.2) vs 15.2 (7.7-24.9)	0.14	0.0 (0.0-0.0) vs 7.6 (2.8-15.6)	0.09	21.7 (10.0-36.3) vs 27.3 (17.1-38.4)	0.39	2.7 (0.2-12.3) vs 10.6 (4.6-19.5)	0.11

Previous pulmonary event: no vs yes	9.4 (3.8-18.1) vs 18.4 (8.0-32.4)	0.5	3.1 (0.6-9.8) vs 7,9 (2.0-19.4)	0,28	21.8 (12.6-32.6) vs 31.6 (17.5-46.7)	0.28	3.1 (0.06-0.09) vs 15.8 (6.3-29.2)	<0.01
Age: < vs ≥ median (58y)	15.6 (7.2-26.9) vs 9.8 (3.6-19.9)	0.57	3.9 (0.7-12.0) vs 5,9 (1.5-14.8)	0.65	26.8 (15.5-39.3) vs 24.0 (13.2-36.6)	0.94	7.6 (2.4-16.8) vs 8.0 (2.5-17.7)	0.76
Conditioning Regimen: RIC vs MAC	10.7 (5.2-18.4) vs 22.2 (6.6-43.6)	0.11	5.9 (2.2-12.5) vs 0.0 (0.0-0.0)	0.29	24.9 (16.2-34.6) vs 278 (9.6-49.6)	0.97	5.9 (2.2-12.5) vs 16.7 (3.9-37.2)	0.18
Use of ATG: yes vs no	9.5 (4.4-16.9) vs 27.8 (9.7-49.5)	0.12	3.6 (0.9-9.3) vs 11.1 (1.7-30.5)	0.18	23.7 (15.2-33.2) vs 33.3 (13.0-55.3)	0.52	5.9 (2.2-12.4) vs 16.7 (3.9-37.3)	0.18
LFS: 2 vs ≥ 3	12.7 (5.1-23.9) vs 12.7	0.79	4.3 (0.8-13.0) vs 5.5	0.76	19 (9.3-31.3) vs 30.9 (0.2-	0.06	6.4 (1.6-15.8) vs 9.1 (3.3-18.5)	0.40

	(5.5-23.0)		(1.4-13.8)		0.4)			
DLCO _{10s} % of predicted normal value: > 80% vs 60-80% vs < 60%	12.7 (5.1-23.9) vs 12.8 (5.1-24.1) vs 12.5 (0.4-45.3)	0.95	4.3 (0.8-13.0) vs 4.3 (0.8-13.0)	0.57	19.0 (9.3-31.3) vs 27.7 (15.7-41.0) vs 50.0 (12.2-79.6)	0.06	6.4 (1.6-15.8) vs 6.4 (1.6-15.9) vs 25.0 (3.0-57.9)	0.20
DLNO % of predicted normal value: > 80% vs 60-80% vs < 60%	18.2 (8.4-30.9) vs 8.0 (2.5-17.7) vs 11.1 (0.5-40.9)	0.26	9.1 (2.8-19.9) vs 0.0 (0.0-0.0) vs 11.1 (0.5-40.9)	0.07	20.5 (10.0-33.5) vs 24.0 (13.2-36.6) vs 59.3 (13.0-87.4)	0.02	9.1 (2.8-19.9) vs 2.0 (0.2-9.3) vs 35.6 (5.7-68.8)	<0.005

	HR	p-value	HR	p-value	HR	p-value	HR	p-value
DLCO _{10s} % of	1.0 (1.0-1.1)	0.94	1.0 (0.9-1.0)	0.23	1.0 (0.9-1.0)	0.04	1.0 (0.9-1.0)	0.13

predicted normal
value^s

DLNO % of	1.0 (0.9-1.0)	0.35	1.0 (0.9-1.1)	0.45	2.0 (1.1-3.7)	0.02	1.0 (0.9-1.0)	0.17
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predicted normal
value^s

DLNO/DLCO	0.9 (0.5-1.6)	0.7	1.6 (1.0-2.6)	0.04	0.9 (0.5-1.7)	0.78	1.6 (0.6-4.0)	0.34
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ratio^s

2 *defined by complication requiring hospitalization, ^s: analysis considering continuous variables, ARDS: acute respiratory distress syndrome,
3 ATG: antithymocyte globulin, DLCO: diffusion capacity for carbon monoxide (with correction for hemoglobin concentration), DLNO: diffusion
4 capacity for nitric oxide, DRI: disease risk index,¹⁵ LFS: lung function score,¹³ MAC: myeloablative conditioning, NRM : cumulative incidence
5 of non-relapse mortality, PRM : cumulative incidence of pulmonary related mortality, RIC: reduced intensity regimen, vs: versus

