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Abstract (199 words)

Carriers of germline telomerase-related gene (TRG) mutations can show poor prognosis, with an increase in common hematological complications after lung transplantation (LT) for pulmonary fibrosis. The aim of this study was to describe the outcomes after LT in recipients carrying a germline TRG mutation and to identify predictors of survival.

In a multicenter cohort of LT patients, we retrospectively reviewed those carrying pathogenic TRG variations (n=38; *TERT*, n=23, *TERC*, n=9, *RTEL1*, n=6) between 2009 and 2018. The median age at LT was 54 years (interquartile range [IQR] 46-59); 68% were male, and 71% had IPF. At diagnosis of pulmonary fibrosis, 28 (74%) had a hematological disease, including 8 with myelodysplasia. After a median follow of 26 months (IQR 15-46), 38 patients received LT.

The overall post-LT median survival was 3.75 years (IQR 1.8-NA). Risk of death after LT was increased for patients with myelodysplasia (HR 4.1 [95%CI 1.5-11.5]) or short telomere (HR 2.2 [1.0-5.0]) before LT. After LT, all patients had anemia, 66% thrombocytopenia, and 39% neutropenia. Chronic lung allograft dysfunction frequency was 29% at 4 years.

The present findings support the use of LT in TRG mutation carriers without myelodysplasia. Hematological evaluation should be systematically performed before LT.

Short title: Lung transplantation with telomere syndrome

Keywords: idiopathic pulmonary fibrosis; genetics; familial; thrombocytopenia; myelodysplastic syndrome, interstitial lung disease

Words: 3105

List of abbreviations

IPF: idiopathic pulmonary fibrosis

ILD: interstitial lung disease

FPF: familial pulmonary fibrosis

LT: lung transplantation

CLAD: chronic lung allograft dysfunction

TRG: telomerase-related gene

WHO: world health organization

IU: international unity

NGS: next generation sequencing

MDS: myelodysplasic syndrome

FCV: forced vital capacity

ATS : American Thoracic society

ERS : European Respiratory Society

JRS : Japonese Respiratory Society

ALAT : Latin American Thoracic Society

AP-HP: Assistance Publique-Hôpitaux de Paris

CMV: cytomegalo virus

EBV: Epstein-Barr virusECMO: Extra-corporal membrane oxygenation

Introduction

The prevalence of idiopathic pulmonary fibrosis (IPF) is estimated at 1/2500 to 1/7000, but 10% of IPF patients have at least one family member with an interstitial lung disease (ILD)[1]. Genetic analysis led to the identification of telomere-related genes mutations in familial and sporadic pulmonary fibrosis (FPF) (TRGs: *TERT, TERC, RTEL1, NAF1, PARN, DKC1, NHP2, NOP10, TINF2, ZCCHC8*) [2,3,4(p2),5]. In addition to ILD, TRG mutations may be associated with liver disease, bone-marrow failure, or immunodeficiency accounting for the so-called telomere syndrome [6,7].

IPF is a rare, heterogeneous, progressive and fatal disease [1]. Lung transplantation (LT) is the only curative therapy and should be offered to selected patients [1,8]. Because of their young age, TRG mutation carriers are frequently candidates for LT [8]. However, the first reported cohorts suggested increased risk of hematological complications and poor survival after LT [9,10]. In addition, reduced telomere length has been associated with reduced overall survival and increased risk of chronic lung allograft dysfunction (CLAD) [11].

The aim of this study was to describe the outcomes and identify predictors of survival after LT in TRG mutation carriers.

Methods

Patients

In this retrospective, observational, non-interventional study, all lung transplant centers from France, Brussels (Belgium), and Lausanne (Switzerland) identified patient carriers of TRG mutations referred for LT between 2008-2018. In addition, cases were cross-identified by the laboratory of genetics in Bichat hospital and by OrphaLung.

We included all patients with ILD who underwent LT in France, Mont-Godinne (Belgium) and Lausanne (Switzerland). Included patients carried a TRG variant interpreted as pathogenic (hereafter called a mutation) according to the international guidelines [12]. Patients who underwent LT for ILD during the same period from the same centers and were not carrier of TRG mutation with next generation sequencing (NGS) analysis were included as a first control group. *Patients who underwent LT for lung fibrosis during the same period from the same centers without genetic analysis were selected from the CRISTAL database*[13] and included as a second control group. The study was approved by local ethics committees (CPP IDF1, 0811760 and CERC-SFCTCV-2016-3-23-16-35-3-MoPi).

Outcomes of interest

ILD was classified according to the 2018 official ATS/ERS/JRS/ALAT statement for IPF and the revised classification of idiopathic interstitial pneumonia [14,15]. Haematogical manifestations were classified according to the 2017 WHO classification [16]. Liver disease was considered with any reported liver abnormality: elevated serum transaminase levels > 30 International Unity (IU)/Liter, abnormal liver imaging (hepatic dysmorphia, signs of portal hypertension, hyperechogenicity), hemochromatosis, hepatopulmonary syndrome, or histological abnormality [17]. Data were collected before, during and after LT including acute cellular rejection episodes [18], and CLAD (stage 1 or higher) [19]. The burden of acute cellular rejection was assessed as reported previously [20].

Genetic analysis

Exons, intron-exon junctions and promoters of *TERT*, *TERC*, *RTEL1*, *NAF1*, *PARN*, *DKC1*, *NHP2*, *NOP10*, *TINF2*, *ZCCHC8* were sequenced by Sanger or NGS and compared to the reference sequences in the genetics laboratory of AP-HP Bichat Hospital, Paris, France). Signed informed consent was obtained for all patients.

Telomere length analysis

Measurement of telomere length was performed using quantitative real-time PCR (qPCR) as previously described and expressed as telomere to single copy gene (T/S) ratio[21].

Statistical analysis

Categorical variables are expressed as number (%). Survival was estimated by the Kaplan-Meier method, and Cox models were used to analyze which factors present at the time of LT impacted overall survival. Statistical significance was set at $p<0.05$. Analyses involved the use of R software version 3.5.3 (The R Project for Statistical Computing; http://www.r-project.org/).

Results

Clinical features before LT

We identified 38 patients (68% men) who were carriers of a TRG mutation and underwent LT from 2009 to 2018, including 10 patients previously reported [9,22](Tables 1 and S1). The median age at ILD diagnosis was 51 years (IQR 43-56). The most frequent ILD diagnosis was IPF (n= 27, 71%).

At ILD diagnosis, median forced vital capacity (FVC) was 61 (IQR 50-77) %predicted and median diffusing capacity of lung for carbon monoxide (DLCO) was 41 (31-52) %predicted. Thirty-seven (97%) patients received specific ILD therapy before LT including corticosteroids (n=31, 82%), antifibrotics (n=13, 34%: pirfenidone n=12, 31%; nintedanib n=6, 16%), immunosuppressants (n=19, 50%: azathioprine n=9; 24%, cyclophosphamide n=8; 21%, mycophenolate mofetil n=2, 5%).

The median delay between ILD diagnosis and LT was 26 months (IQR 15-46) (Table 2). Every patient eventually showed decreased pulmonary function. The last FVC before LT was 46% (39-57) and last DLCO was 20% (16-31) (Table 2), corresponding to a mean FVC decline of 461 mL/year (242-779).

Most patients (n=36, 95%) had extra-pulmonary features suggestive of a TRG mutation at ILD diagnosis: mucocutaneous abnormalities (n=16, 41%); liver disease (n=7, 18%,) or hematologic abnormalities (n=28, 74%). During the follow-up before LT, liver abnormalities developed in 14 patients, and hematological disease in 4. Eventually 21 (55%) patients had a diagnosis of liver disease and 33 (87%) a diagnosis of hematological disease before LT (Table 2).

Sixteen patients had a pre-LT bone-marrow cytologic examination because of macrocytosis (n=5), thrombocytopenia (n=9), or despite normal cell count (n=2). Eight had a normal result and 8 (all with abnormal blood cell count), had a diagnosis of myelodysplastic syndrome

(MDS): all had refractory cytopenia with unilineage or multilineage dysplasia, without blast excess and with a normal karyotype. Among 8 patients with pre LT myelodysplasia, 4 previously received immunosuppressive therapy (cyclophosphamide n=2, azathioprine n=2), and 7 received corticosteroids: 4 as maintenance therapy and 3 only briefly for an ILD exacerbation

Among the 21 patients with pre-LT liver disease, a liver biopsy was performed in 4 patients, and showed sinusoidal dilatation (n=2) with superimposed perisinusoidal fibrosis (n=1) or isolated mild portal inflammation (n=1). One patient had systematic pre-LT liver biopsy without increased liver enzyme dosage, and showed normal liver architecture.

Genetic analysis

Genetic results were available before LT for 22 (58%) patients and after LT for 16 (42%), including 5 with results available only after death. The indication for genetic analysis was a family history of ILD (n= 18, 47%), extra-pulmonary signs suggestive of TRG mutation (n=13, 34%) or family history of hepatic or hematological diseases (n=7, 18%). Ten (26%) patients had both family history of ILD and extra-pulmonary signs suggestive of TRG mutation. Mutations were detected in the following genes: *TERT* (n=23, 60%), *TERC* (n=9, 24%) and *RTEL1* (n= 6, 16%) (Table 1 and supplementary table 1).

The median telomere length (T/S) measured on blood leucocytes was reduced in all patients (median : 0.45 (IQR 0.20-0.80)).

Lung transplantation

In the TRG mutation carrier group, the median age at LT was 54 years (IQR 46–59). The non-TRG mutation group included 28 patients (75% men); the median age at LT was 58 years (IQR 48-62, p=0.56). After the exclusion of patients with available genetic analysis, the CRISTAL database included 541 patients with pulmonary fibrosis (70% men), median age at LT was 58 years (IQR 50-62) (Table 3).

In the TRG mutation carrier group, 18 (47%) patients underwent LT as a high emergency procedure, a procedure available for patients with a life expectancy<2 weeks Table 2)[13]; 22 (57%) had double LT, including 2 with combined liver transplantation. Twenty-two patients (58%) were CMV positive before LT and 7 (18%) more patients had a CMV mismatch with a negative recipient and positive donor. Thirteen (34%) patients received induction therapy: 10 (26%) with basiliximab, and 3 (8%) with thymoglobulins (Table 2).

Extra-corporal membrane oxygenation (ECMO) was used for 10 patients before LT because of acute respiratory failure, 15 more patients required an ECMO during the LT procedure. ECMO was removed at the end at the surgery for 13 patients and still required for 12, including 4 patients with ECMO before LT. One patient required an ECMO after the LT because of primary graft dysfunction.

Every patient received an immunosuppressant after LT: low level of corticosteroids (n=38, 100%), anticalcineurin inhibitor (n=38, 100%; ciclosporin, n=9; 23%; tacrolimus n= 36, 95%), mycophenolate mofetil (n=25, 92%) or everolimus (n=12, 32%). Nine patients received everolimus in addition to an anticalcineurin inhibitor and 3 were switched from an anti-calcineurin inhibitor. Seventeen patients received more immunosuppressant for acute cellular rejection and 6 for acute antibody mediated rejection.

Overall, 31 patients received cotrimoxazole for primary prophylaxis: 12 were switched to atovaquone and 1 to pentamidine because of cytopenia (Table 4).

Hematological complications

Excluding the first 3 months after LT, every patient had at least one episode of anemia, 25 (66%) had at least one episode of thrombocytopenia (platelet count: 67-107 G/L) and 15 (39%) at least one episode of neutropenia (neutrophil count: 0.8-1.2 G/L). Thrombocytopenia required platelet transfusion in 6 (16%) patients. Neutropenia required an adjustment in

immunosuppressive treatment and/or injection of granulocyte colony stimulating factor in 11 patients (29%).

After a median delay of 4 months, 4 patients had a diagnosis of thrombotic microangiopathy, related to everolimus (n=3) or tacrolimus (n=1), which persisted despite plasmapheresis and drug withdrawal. Thrombotic microangiopathy was concomitant to CMV viremia in all cases. Among the 4 patients, 3 had a mismatch CMV.

In addition to the 8 patients with myelodysplasia before LT, 6 patients had a diagnosis of myelodysplasia confirmed with bone-marrow cytology (multilineage dysplasia, n=5; unilineage megakaryocytic dysplasia, n=1) after a median delay of 21 months after LT. The karyotype was abnormal in 2 cases (del20q and t(1 ;21)). All 6 patients had hematological abnormalities before LT (thrombocytopenia, n=3; anemia, n=3; macrocytosis, n=2), although only one underwent bone-marrow cytolology pre-LT, which was normal.

Liver and kidney complications

Four patients showed a severe liver disease after a median delay of 12 months: secondary haemochromatosis because of repeated transfusion (n=1), portal hypertension (n=2), and liver fibrosis (n=1) with portal hypertension suspected. None had a liver biopsy.

None of the patients had renal insufficiency before LT. After LT, 18 (47%) patients showed chronic renal failure with median creatinine clearance 50 μmol/L/min/1.73m^2 (IQR 47-57) at a median delay of 6 months (IQR 5.5–9); none required chronic renal replacement therapy.

Infectious diseases

A total of 25 (66%) patients had opportunistic infection: invasive aspergillosis (n=5, 13%), pneumocystosis (n=3, 8%), nontuberculous mycobacteria (n=2, disseminated *Mycobacterium avium* infection, *M. chimaera* pulmonary infection), pulmonary tuberculosis (n=1), human HHV6 encephalitis (n=1), CMV infection or CMV disease (n=17, 45%).

Twenty-four of the 29 CMV positive patients initially received valganciclovir as a primary prophylaxis in median for 3.0 months (1.6-5.1) after LT. Seventeen (59%) had at least one episode of CMV viremia, none with valganciclovir, including 5 with severe organ diseases: colitis (n=2), pneumonia (n=2), and severe retinitis (n=1). Four patients with severe CMV organ disease were from the group of 7 CMV mismatch.

Acute cellular rejection and CLAD

During the first year after transplant, 13 patients had at least one episode of acute cellular rejection (ACR), including 4 patients with 2 episodes.

Participants alive at 1 year after LT (n=29, 76%) were screened for CLAD. CLAD was detected in 7 patients (restrictive allograft syndrome, n=1; bronchiolitis obliterans syndrome, n=6) in a median of 2.1 years (IQR 1.0-3.36). The rate of CLAD at 2, 3, and 4 years after LT was 21%, 26%, and 29%, respectively. The median CLAD free survival was 2.2 years (IQR 1.0-NA).

Survival

After a median follow-up of 39.4 months (IQR 16-46.6), 20 (52.6%) patients had died. Deaths were related to an infectious disease in 10 patients: pneumonia (n= 5), septicemia (n=2), disseminated aspergillosis (n=1), human herpesvirus 6 encephalitis (n=1), candidemia (n=1). Other deaths were related to hematological complications (n=2; thrombotic microangiopathy, n=1; gastrointestinal bleeding, n=1), ischemic cardiomyopathy (n=1), pulmonary embolism (n=1), fall (n=1), post-operative hemorrhage (n=1), acute graft rejection (n=1), CLAD (n=1), and unknown (n=2).

The median survival after LT was 3.75 years (IQR 1.8-NA) in the TRG mutation carrier group and did not differ from the group without TRG mutation (3.0 years, (IQR 1.4-NA), p=0.36) or from the CRISTAL database (4.4 years, (IQR 3.74-5.91) p=0.6) (Figure 1).

The 1-, 2- and 5-year median survival in the TRG mutation group after LT was significantly different according to the presence of an MDS before LT: 79.9 % (66.7-95.7), 71.0% (55.7-18.3) and 36.4% (18.3-72.4) in absence of MDS vs 37.5 % (15.3-91.7), 37.5% (15.3-91.7) in presence of MDS (non calculable at 5-year, Figure 2).

On univariate analysis, a diagnosis of myelodysplasia before LT (hazard ratio 4.1 [95% confidence interval 1.5-11.5]) and a reduced telomere length (2.2 [1.0-5.0]) before LT in TRG mutation carriers were the only factors significantly associated with overall survival (Table 5, Figure 2). Age, thrombocytopenia before LT, bilateral transplantation or the gene involved was not significantly associated with survival.

Discussion

In this series of 38 patients with a TRG mutation who underwent LT**,** the median survival after LT was 3.75 years and did not differ from the observed overall survival in France after LT for ILD. A pre-LT characteristic, MDS, was associated with survival and should be considered when LT is being planned. We confirm that LT is hazardous but might be offered to TRG mutation carriers.

The first cohorts raised concerns about hematological risk in this patients [8,10,22]. TRG mutations were first described in hematological diseases and subtle hematological abnormalities (macrocytosis, thrombocytopenia) are associated with a high prevalence of TRG mutation among ILD patients [3,23]. Indeed, cytotoxic drugs may be harmful in TRG mutation carriers [8–10,22]. A recent cohort of 31 patients suggested that hematological complications after LT were not more frequent in TRG mutation carriers [24]. These different outcomes may reflect the difference in genotypes included in these cohorts (Table S2). Indeed, 32/38 (84%) patients from these series were carriers of a *TERT* or *TERC* mutation as compared with 13/31 (42%) of the later cohort [24]. Though the number of unique mutations does not authorize a genotype/phenotype correlation, *PARN* and *RTEL1* mutations seem associated with older age at disease onset, less extra-pulmonary diseases at ILD diagnosis and long telomere length [25,26(p1)]. Indeed, 14 patients from this series had a diagnosis of myelodysplasia after LT, so hematological risk is a probable specific complication of TRG mutation, maybe more frequent with *TERT* or *TERC* than with *RTEL1* or *PARN* mutations [26(p1)].

The survival impact of myelodysplasia suggests evaluating hematological disorders in TRG mutation carriers. George et al.[27] reported a bone-marrow screening in patients with short telomeres, showing abnormalities in 8/13 (61.5%): hypocellular marrow (n=4), early myelodysplastic syndrome (n=2), hypocellular marrow with decreased megakaryocyte lineage

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(n=1), and increased plasma cells (n=1) [27]. Immunosuppressants before LT may have confounded the analysis of MDS. Moreover, a cohort of 18 TRG mutation carriers with MDS or acute myeloid leukemia showed poor outcome with a mean survival of only 15 months after hematological diagnosis [28]. All patient who developed MDS after LT had pre LT hematological abnormalities, though only one had bone marrow evaluation without MDS. This result suggests a bone-marrow evaluation for every patient with blood cell count abnormalities before LT, but should be evaluated in the absence of hematological abnormalities.

Liver and kidney have been of particular focus in TRG mutation carriers [6,10]. Four patients showed severe liver disease after LT; none had a full specific check-up for hepatic liver disease before LT and none had screening for portal hypertension or hepatocellular carcinoma. Thus, we should carefully monitor hepatic disease in TRG mutation carriers, including hepatic ultrasonography and gastric endoscopy before LT and liver biopsy might be discussed in selected patients [27]. In the subset of patients with established liver and lung disease, a combined liver–LT might be considered. However, only 2 patients of this cohort with limited follow-up received combined liver–LT. Further studies are needed for this indication.

Renal manifestations are rare in TRG mutation carriers, although a specific renal disease has been suggested, as 2/92 patients with chronic kidney disease had pathogenic *PARN* mutations [29]. Moreover 4/8 patients of the first reported cohort required dialysis, and chronic renal failure developed in 18 (47%) patients of this series, although none required chronic renal replacement therapy. Because of the relatively low number of patients a specific renal risk could not be demonstrated in this study. These results agree with a reported cohort of 31 patients with TRG mutations without increased risk of renal disease as compared with non-TRG mutation carriers[24].

The rate of CLAD in this series was similar to the general population of LT recipients. Previous studies provided inconsistent data. Swaminathan observed a high rate of CLAD (62% estimate at 5 years), whereas Tokman did not (4/12, 33.3%) [22,24]. In a cohort of LT, telomere length < 10th percentile was associated with the development of CLAD [11]. Due to the limited follow-up and high 1-year mortality, the number of CLAD and the CLAD free survival analysis is limited in our study.

Opportunistic infections with a special focus on CMV are a concern after LT. IPF LT recipients are at high risk of CMV viremia after LT (69%), and patients with the shortest telomere have the highest risk of complications [8]. Because of pre-existing and induced cytopenia, doses of several antimicrobial agents such as ganciclovir or cotrimoxazole must be adapted and may be below their therapeutic range. Moreover, IPF patients with short telomeres show impaired *in vitro* CMV-specific T-cell effector [8], and some TRG mutations have been associated with specific immunodeficiency [7,8]. At least 10 patients from this series died of infectious disease, and 17 (45%) showed CMV infection, which suggests that in addition to hematological risk, patients with TRG mutations may have increased risk of opportunistic infection. Offering the less cytotoxic among antimicrobial agents should be the rule. Drugs such as brincidofovir should be evaluated in this population. The usefulness of immunodeficiency detection before LT (CMV-specific proliferative responses, T-cell effector functions) needs to be evaluated [8].

Our study has several limitations. It is retrospective with limited number of patients without TRG mutation after genetic analysis. The clinical care is heterogeneous: treatment, pre-LT process (bone-marrow or hepatic evaluation or not). Because of the low number of patients, we did not realise a multivariate analysis and did not evidence usual post LT prognosis factors. There may have been other uncaptured LT recipients with TRG mutations because of the screening rules. This series is representative of the reality of LT in this

particular population but might be biased by a high prevalence of pre- or post-LT hematological disease that led to the genetic analysis. Finally, although we were able to compare the survival of TRG mutation carriers with the overall French survival of ILD patients (CRISTAL database), none of them had a genetic or telomere length analysis.

Patients with TRG mutation present the same overall survival after LT than the whole population of ILD patients. However, severe complications may occur in carriers of TRG mutation after LT. We suggest a careful immune-hematologic evaluation before LT and discourage LT in patients with established myelodysplasia. Prospective study is needed to evaluate pre-LT systematic evaluation and post-LT immunosuppressive treatment.

Acknowledgments

The authors report no funding.

Author contributions:

RB had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. RB and MPH contributed to drafting the manuscript. CG and GW contributed to the statistical analysis. HM, VC, FSF, SS, JFM, SH, AR, LWS, JLP, CP, SMA, AF, RL, JMN, SJ, HN, MRG, ALB, DB, CB, BC, MPH, RB contributed to data analysis and interpretation. IB and CK contributed to the genetic analysis.

Other contribution

The authors would like to thank Francois Philit, Gaelle Dauriat, Michael Tamm, Kathleen Jahn, the patients and all the physicians.

Figures

Figure 1. Overall survival after lung transplantation for pulmonary fibrosis in 2008-2018 in the telomere related gene (TRG) mutation carrier group (n=38, red), in patients without TRG mutation identified (blue, n=28), in patients with ILD without genetic analysis in 2008-2018 (whole French cohort: CRISTAL database, green, n=541). The 3 groups did not show a survival difference, *according to Kaplan-Meier analysis.*

Figure 2. Survival according to the diagnosis of myelodysplasia before lung transplantation in TRG mutation carriers (n=38). Patient without myelodysplasia (n=30, red) at the time of lung transplantation had a better overall survival after lung transplantation (*Kaplan-Meier analysis*, p=0.007).

Table 1: Main characteristics of patients at interstitial lung disease (ILD) diagnosis (n=38)

Age at pulmonary fibrosis diagnosis, years	51 (43-56)
Male, n (%)	26 (68)
Ever smoking	23 (61)
Pulmonary function test	
FVC %	61 (50-77)
DLCO %	41 (31-52)
ILD diagnosis	
IPF	27 (71)
Unclassifiable fibrosis	4 (10)
Pleuroparenchymal fibroelastosis	3 (8)
Chronic hypersensitivity pneumonitis	2 (5)
Pneumoconiosis	1 (3)
Non-specific interstitial pneumonitis	1 (3)
Hematological abnormalities	28 (74)
Anemia	9 (24)
Thombocytopenia	17 (45)
Macrocytosis	15 (39)
Bone-marrow analysis	16 (32)
Myelodysplastic syndrome	8 (21)
Cutaneous abnormalities	16 (42)
Premature hair greying	7 (18)
Cutaneous carcinoma	1 (3)
Nail dystrophy	4 (11)
Lichen	2 (5)
Cutaneous dyschromia	3 (8)
Liver abnormalities	7 (18)
Unexplained elevated liver enzymes	3 (8)
Hepatic dysmorphia	2 (5)
Portal hypertension (portal cavernoma)	1 (3)
Previous liver transplantation for nodular regenerative hyperplasia	1 (3)
Gene mutation	
TERT	23 (60)
TERC	9 (24)
RTEL1	6 (16)
Telomere Length (T/S)	0.45 (0.20-0.80)

Data are median (interquartile range) or no. (% of available data). Forced vital capacity (FVC) and diffusing lung capacity for carbon monoxide (DLCO) are expressed as % predicted value.
* Idiopathic pulmonary fibrosis (IPF), or probable IPF or possible IPF diagnosis based on CT scan and histology. Patients with a working diagnosis of IPF after multidisciplinary discussion are classified as IPF.

Table 2: Main characteristics of the patients at lung transplantation (LT) (n=38)

Age at LT, years	53.6 (45.8-59.3)
Pulmonary function test	
FVC %	46 (39-57)
DLCO %	22 (16-31)
Hematological abnormalities	33 (87)
Anemia	14 (37)
Thombopenia	18 (47)
Macrocytosis	15 (39)
Bone-marrow analysis	16 (32)
Myelodysplastic syndrome	8 (21)
Cutaneous abnormalities	16 (42)
Liver abnormalities	21 (55)
Unexplained elevated liver enzymes	11 (29)
Steatohepatitis	9 (24)
Hepatic dysmorphia	4 (11)
Portal hypertension	2 (5)
Previous liver transplantation for nodular regenerative hyperplasia	1 (3)
Hemochromatosis	1 (3)
Lung transplantation	
High emergency LT	18 (47)
ECMO	25 (66)
ECMO pre LT	10 (26)
ECMO during surgery	25 (66)
ECMO after surgery	13 (34)
Bilateral LT	22 (58)
LT combined with liver transplantation	2 (5)
Induction therapy, n (%)	13 (34)
Thymoglobulins	3 (8)
Basiliximab	10 (26)

Data are median, [interquartile range] or no. (% of available data). Forced vital capacity (FVC) and diffusing lung capacity for carbon monoxide (DLCO) are expressed as % predicted value.
ECMO: extra-corporal membrane oxygenation

Table 3 Main characteristics at LT of the patients with TRG mutation, without TRG mutation and from the control CRISTAL database with unknown genetic status

	TRG mutation carriers N=38	No TRG mutation carriers N=28	Cristal database: N=541	P*
Age years	54 (46 – 60)	58.3 (48-62)	58 (50-62)	0.045
Male, n (%)	26 (68)	16 (57)	378 (70)	0.99
Time on waiting list (days)	26 (9-77)	32 (16-98)	45 (15-119)	0.08
FVC, % pred	48.3 (41-57)	40 (33-53)	46 (36-59)	0.4
DLCO, % pred	22 (16-31)	20 (15-27)	24 (19-32)	0.32
High emergency transplantation	18 (47)	9 (32)	166 (31)	0.051
Bilateral lung transplantation	22 (58)	20 (71)	278 (51)	0.55
Cardiopulmonary support	26 (68)	23 (82)	241 (44)	0.006

Median (IQR) or Count (%). * Statistical analysis between the TRG mutation carriers group and the CRISTAL database

Table 4: Main complications after LT

Hematological abnormalities	
Anemia	38 (100)
Thrombocytopenia	25 (66)
Neutropenia	15 (39)
Bone marrow analysis	13 (34)
Myeldoysplastic syndrome	6 (16)
Thrombotic microangiopathy	4 (11)
Infectious diseases	25 (66)
Invasive aspergillosis	5 (13)
Pneumocystosis	3 (8)
Nontuberculous mycobacteria	2 (5)
Pulmonary tuberculosis	1 (3)
HHV6 encephalitis	1 (3)
CMV infection	17 (45)
Liver disease	4 (11)
Portal hypertension	2 (5)
Liver fibrosis	1 (3)
Hemochromatosis	1 (3)
Kidney insufficiency	18 (47)
Malignancies	2 (5)
Vulva squamous cell carcinoma	1 (3)
Cutaneous carcinoma	1 (3)

CMV, cytomegalovirus; HHV6, human herpesvirus 6

Table 5: Univariate analysis of pre-LT characteristics associated with post-LT survival

	HR	95% CI	P-value
Thrombocytopenia	2.5	0.5–3.9f	0.07
Myelodysplasia	4.1	1.5–11.5	0.007
Emergency procedure	1.6	0.6–4.0	0.32
Age < 54 years	0.8	0.3-1.9	0.57
TERT vs other genes	0.9	0.3–2.1	0.74
Telomere Length	2.25	1.01-5.01	0.048

HR, hazard ratio; 95% CI, 95% confidence interval

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