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Rare indications for a lung transplant. A European Society of Thoracic Surgeons Survey

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Abstract

OBJECTIVES: The European Society of Thoracic Surgeons Lung Transplantation Working Group promoted a survey to evaluate overall survival in a large cohort of patients receiving lung transplants for rare pulmonary diseases.

METHODS: We conducted a retrospective multicentre study. The primary end point was overall survival; secondary end points were survival of patients with the most common diagnoses in the context of rare pulmonary diseases and chronic lung allograft dysfunction (CLAD)-free survival. Finally, we analysed risk factors for overall survival and CLAD-free survival.

RESULTS: Clinical records of 674 patients were extracted and collected from 13 lung transplant centres; diagnoses included 46 rare pulmonary diseases. Patients were followed for a median of 3.1 years. The median survival after a lung transplant was 8.5 years. The median CLAD-free survival was 8 years. The multivariable analysis for mortality identified CLAD as a strong negative predictor [hazard ratio (HR) 6.73)], whereas induction therapy was a protective factor (HR 0.68). The multivariable analysis for CLAD occurrence identified induction therapy as a protective factor (HR 0.51). When we stratified patients by CLAD occurrence in a Kaplan–Meier plot, the survival curves diverged significantly (log-rank test: $P < 0.001$). Patients with rare diseases who received transplants had chronic rejection rates similar to those of the general population who received transplants.

CONCLUSIONS: We observed that overall survival and CLAD-free survival were excellent. We support the practice of allocating lungs to patients with rare pulmonary diseases because a lung transplant is both effective and ethically acceptable.

Keywords: Lung transplant • Rare diseases • Lung diseases • Respiratory insufficiency

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Key question

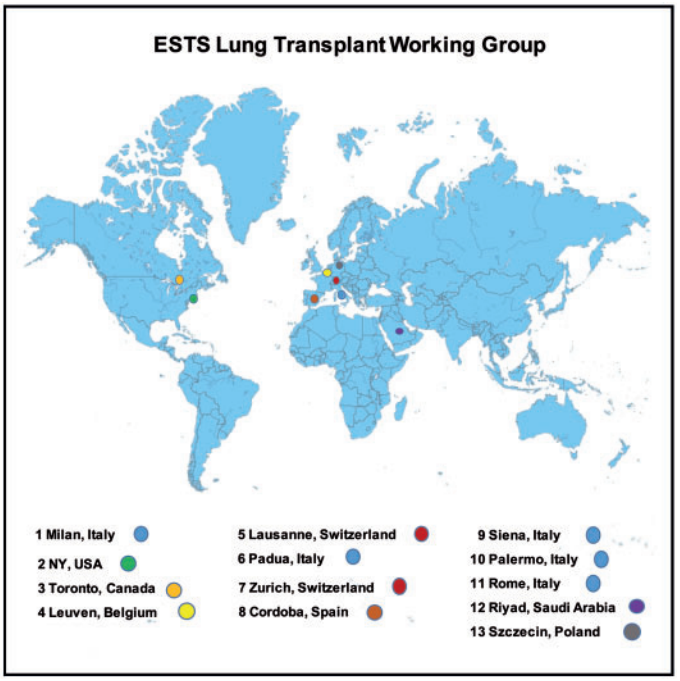
Is it fair to allocate a lung for a lung transplant to a patient with a rare pulmonary disease?

Key finding(s)

Despite limited knowledge of most pulmonary diseases, overall survival and chronic lung allograft dysfunction-free survival were excellent.

Take-home message

We support the practice of allocating lungs to patients with rare pulmonary diseases because a lung transplant is an effective treatment.



INTRODUCTION

A lung transplant is the only treatment available for selected patients with end-stage respiratory insufficiency. A report of the registry of the International Society for Heart and Lung Transplantation (ISHLT) identified chronic obstructive pulmonary disease (COPD), including α1-antitrypsin deficiency, as the most common primary indication for a lung transplant, comprising 32.7% of the procedures between 2004 and 2015 [1]. In the same period, the second most common indication was idiopathic pulmonary fibrosis (26.6%), followed by cystic fibrosis (15.4%). A few of the additional 73 primary indications listed in the ISHLT report reached or exceeded 1% the percentage point; at most, there were a few dozen patients for each diagnosis. In the USA, a rare (orphan) disease is defined as one that affects fewer than 200 000 individuals (roughly 625 individuals per million); therefore, a lung transplant itself could be defined as a 'rare procedure', considering the rate of 3.19 procedures per million inhabitants performed in the USA in 2018. In Western Europe, the annual lung transplant rate is similar to that in the USA; thus, knowledge about patients with rare pulmonary diseases who receive transplants is relatively poor. In this scenario, the scarcity of organs prompts an ethical dilemma: Is it fair to allocate a lung to a patient with a rare disease considering that the outcome is uncertain? To answer this question, the European Society of Thoracic Surgeons (ESTS) Lung Transplantation Working Group (chaired by I.I.) promoted a survey to evaluate current outcomes in a large cohort of patients with rare pulmonary diseases receiving lung transplants.

MATERIALS AND METHODS

Study design

This retrospective multicentre study was conducted by the ESTS Lung Transplantation Working Group. The study was established during the 26th ESTS conference (Ljubljana, Slovenia, 27–30 May 2018); the study was open to non-European centres; the principal investigator was an ESTS member.

Outcomes and study definitions

The primary end point was overall survival; secondary end points were survival of patients with the most common diagnoses in the context of rare pulmonary diseases and chronic lung allograft disease (CLAD)-free survival. Finally, we analysed risk factors for overall survival and CLAD-free survival.

Rare pulmonary diseases were defined as uncommon illnesses or syndromes causing respiratory insufficiency. The list of diagnoses included all the rare pulmonary diseases reported in the 33rd adult lung transplant report on the ISHTL registry [1]. Diagnoses were established before the transplant or made after the transplant by histopathological examination of the explanted lungs; in both cases, the diagnoses were attributed independently by each centre.

According to the ISHLT consensus report, CLAD was defined as a persistent forced expiratory volume in 1 s decline of ≥20% compared with baseline [2].

Data source

Data for this study were obtained from the archives of the participating centres; anonymized files were collected in a dedicated database after a data transfer accord was signed (when required). The dedicated database included patient demographics, diagnoses and information on the type of transplant, induction therapy and follow-up.

A record was eligible for inclusion if the patient received the first lung transplant for a rare pulmonary disease. No time limits were imposed. Exclusion criteria were a paediatric transplant, combined transplant and transplant for 'common diseases'

Table 1: Clinical variables

	Overall	Sarcoidosis	Scleroderma
Number of patients	674	114	100
Female gender	354 (52.5)	54 (47.4)	60 (60)
Age (years)	52.0 (43–59)	54.3 (47.6–60.0)	53.1 (49.0–58.1)
FEV1%	44.0 (29.0–62.0)	45.0 (26.8–59.8)	55.0 (41.0–65.0)
FVC%	52.0 (39.0–67.0)	53.0 (40.0–65.0)	51.5 (40.0–64.8)
Bilateral transplant	482 (71.5)	96 (84.2)	81 (81)
Induction therapy	398 (59.1)	69 (60.5)	34 (34)
Follow-up (years)	3.1 (1.0–6.6)	4.8 (1.3–8.0)	3.1 (1.2–6.6)
CLAD (yes)	214 (31.8)	48 (42.1)	33 (33)
Retransplant	16 (2.4)	4 (3.5)	1 (1)

Data are presented as *n* (%) or median (first quartile to third quartile).
CLAD: chronic lung allograft dysfunction; FEV1%: percentage of preoperative predicted forced expiratory volume in 1 s; FVC%: percentage of preoperative predicted forced vital capacity.

(COPD including α1-antitrypsin deficiency, idiopathic interstitial pneumonia, cystic fibrosis, idiopathic pulmonary arterial hypertension, graft-versus-host disease or a retransplant). The study was approved by the institutional review board (749_2016bis; Milan 2).

Statistical analyses

Continuous data are presented as mean and standard deviation or median and first to third quartile. Categorical variables are shown as absolute and percentage frequencies. Time-to-event data are displayed using a non-parametric Kaplan–Meier estimator; analysis of survival and freedom from CLAD were performed using the log-rank test. In addition to the overall survival analysis, we made a comparison between eras. The hazard ratio (HR) was computed using the multivariable Cox regression model with the Breslow approximation stratified by underlying disease; a robust sandwich variance estimator was adopted to account for correlated groups of observations given by the multicentre nature of the data. The proportional hazards assumption was checked using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals. To detect non-linearity in the relationship between the log hazard and the covariates, we plotted the Martingale residuals against continuous covariates, inspecting the functional form. Influential observations were checked by graphical inspection of deviance residuals. The adjusted smooth hazard function was estimated non-parametrically using B-splines from the perspective of generalized linear mixed models [3]. The Simon and Makuch model was used to evaluate the covariate status of the patients remaining at risk at each event time [4]. Confidence intervals (CIs) were computed at 95%, and side *P*-values were considered significant when <0.05. All analyses were carried out using R-Cran software, version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) [5].

RESULTS

Ten European and 3 non-European lung transplant centres participated in the study; the list of centres is shown in Supplementary Material, Table S1. Clinical records of 674 patients were extracted and collected; baseline demographic and clinical data are shown in Table 1. The list of diagnoses included 46 rare pulmonary diseases; in addition, 14 patients were classified as 'other'. The list of the primary indications for a lung transplant is reported in Supplementary Material, Table S2. Some diagnoses were more frequent: 114 patients had sarcoidosis and 100 had scleroderma. Table 1 shows the clinical data of patients with those diseases. Overall, patients with rare conditions who received transplants accounted for ∼10% of the total volume of transplants performed by the participating centres (range among centres: 1.5–21.5%; median: 8.7%).

Patients were followed for a median of 3.1 years. Overall, the median survival after a lung transplant was 8.5 years (Fig. 1); the overall mortality hazard rates graph is shown in Supplementary Material, Fig. S1. The median survival for patients with sarcoidosis and scleroderma was 7.2 (95% CI 6.6–8.8) and 6.4 (95% CI 4.3–7.4) years, respectively. We divided the study period into 2 eras by following the partition performed by the ISHLT registry: in the first era (1992–2008: 221 patients, 149 events), the median survival was 6.6 years; in the more recent era (2009–2019: 453 patients, 128 events), the median survival was 9.0 years. The

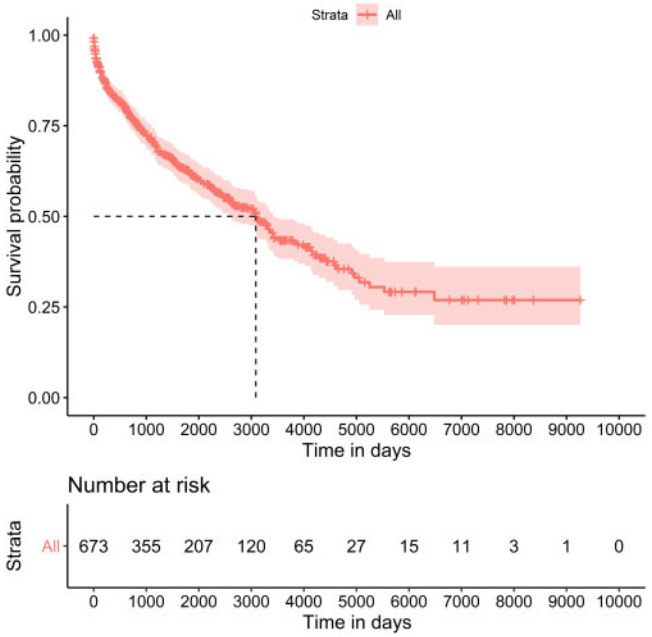


Figure 1: Kaplan–Meier survival curve after lung transplants for patients with rare pulmonary diseases.

Table 2: Hazard ratio for mortality

	Hazard ratio (95% confidence interval)	*P*-value[a]
Male gender[b]	1.12 (0.83–1.52)	0.45
Age (years)	1.01 (0.99–1.02)	0.11
Bilateral transplant[b]	0.86 (0.64–1.16)	0.32
Induction therapy[b]	0.68 (0.51–0.90)	0.007
CLAD[b]	6.73 (4.83–9.38)	<0.001

[a]Schoenfeld test: $P = 0.30$.
[b]References: female, single transplant, no induction therapy, no CLAD.
CLAD: chronic lung allograft dysfunction.

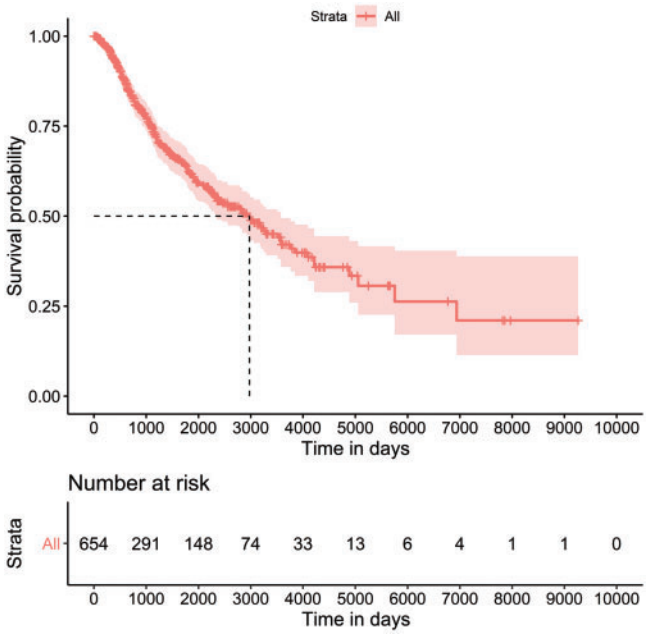


Figure 2: Kaplan–Meier chronic lung allograft dysfunction-free survival curve after lung transplants.

multivariable analysis for mortality identified CLAD as a strong negative predictor (HR 6.73), whereas induction therapy was a protective factor (HR 0.68) (Table 2).

Nearly 32% of patients developed CLAD during their post-transplant course (Table 1). The median CLAD-free survival was 8 years (Fig. 2); the CLAD hazard rates graph is shown in Supplementary Material, Fig. S2. In the first era, 46% of patients received induction therapy versus 65.7% of patients in the most recent era ($P < 0.001$). The multivariable analysis for the occurrence of CLAD identified induction therapy as a protective factor (HR 0.51) (Table 3). When we stratified patients by the occurrence of CLAD in a Kaplan–Meier plot, the survival curves diverged significantly (log-rank test: $P < 0.001$) (Fig. 3).

Table 3: Hazard ratio for chronic lung allograft dysfunction

	Hazard ratio (95% confidence interval)	*P*-value
Male gender[a]	1.04 (0.74–1.76)	0.83
Age (years)	0.99 (0.98–1.02)	0.87
Bilateral transplant[a]	0.78 (0.55–1.13)	0.19
Induction therapy[a]	0.51 (0.029–0.91)	0.023

[a]References: female, single transplant, no induction therapy; Schoenfeld test: $P = 0.19$.

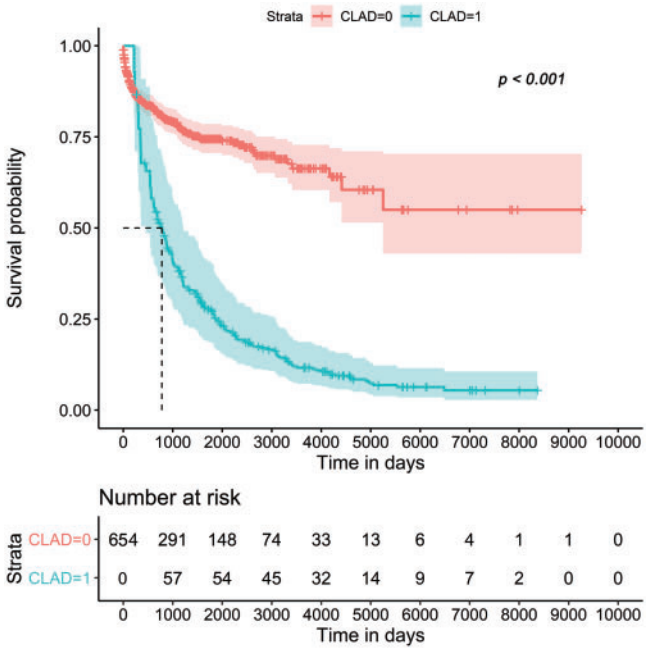


Figure 3: Kaplan–Meier survival curves stratified by occurrence of CLAD. CLAD: chronic lung allograft dysfunction.

DISCUSSION

Although this survey comprised a large number of patients, we observed that a lung transplant for a rare disease remains a marginal procedure. Given that only 10% of lung transplants performed in the participating centres involved rare diseases, worries related to indications and outcomes are understandable. To the best of our knowledge, there are no papers that specifically address the problem of rare indications for lung transplants. Few articles address some of the most frequent diagnoses (e.g. scleroderma and lymphangioleiomyomatosis), often reporting limited monocentric experiences [6–9]. Taken together, rare indications for lung transplants comprise a heterogeneous cohort; we identified 46 different diseases, with a median of 4 patients per diagnosis (range 1–114). Despite the heterogeneity and the limited knowledge about most of the diseases, the overall survival was very satisfactory: A median survival of 8.5 years in our cohort versus a median survival of 6.0 years in the 1990–2015 ISHLT report is extremely encouraging [10]. Considering that some of the rare diseases have extrapulmonary manifestations, which could potentially limit survival, our good survival results are probably related to particularly selective criteria adopted from the participating centres for listing patients with uncommon illness. The excellent overall survival observed in our study can satisfy the ethical principles for organ allocation stated by the Organ Procurement and Transplantation Network/United Network for Organ Sharing Ethics Committee in the 'Ethical Principles in the Allocation of Human Organs' document (https://optn.transplant.hrsa.gov/resources/ethics/): utility, justice and respect for persons. The principle of utility is satisfied because good overall survival after a lung transplant maximizes 'the expected net amount of overall good', which included patients and graft survival. Justice in the allocation of benefits is respected by the survival of patients with rare diseases that was equal, if not superior, to that of patients with common diseases as reported by ISHLT. The principle of respect for the person is also satisfied: Our study supports access to lung transplants for patients with rare diseases. Therefore, these patients are not discriminated against because of the rarity of their disease, giving free expression to their autonomous request for treatment.

It is interesting to note that the number of patients with rare diseases who underwent lung transplants has more than doubled from the period 1992–2008 to the period 2009–2019. Conversely, the number of patients referred to in the ISHLT

Register increased in a less impressive way, moving from 31 462 in the period 1990–2008 to 28 531 in the period 2009–2016. Therefore, we could speculate that the propensity of the centres to offer lung transplants to patients with rare diseases has grown over time and/or the pulmonologists increasingly consider a lung transplant to be a therapeutic option for diseases not previously considered. In any case, survival after a lung transplant for rare diseases seems to have definitely improved in the comparison between the 2 eras. The significant increase in the use of induction therapy may have played a role. In addition, innovative therapies able to limit the systemic effects of some diseases, better surgical techniques and medical treatment of post-transplant complications may have contributed to the improved survival [11].

The mortality hazard rates curve shows that patients with rare diseases who received a transplant had a higher risk of death in the immediate postoperative period; then, the hazard rates curve decreased abruptly until it reached stability beyond 2 years after surgery (Supplementary Material, Fig. S1). This hazard rates profile is not dissimilar from that known for all patients receiving lung transplant. Our multivariable analysis of mortality included a limited number of variables; CLAD was confirmed as the factor that most often limits survival, given that it leads to an increase in mortality almost 7 times that in our cohort. On the contrary, the administration of induction therapy seems to decrease the risk of mortality by 40% (Table 2).

When we examined the most 'frequent' rare diseases, we observed that the survivals are satisfying: Patients with sarcoidosis had a median survival of 7.2 years in our cohort versus 5.8 years in a large cohort from the Organ Procurement and Transplantation Network database [12]. The Working Group on Heart/Lung Transplantation in Systemic Sclerosis, which collected 90 patients, published a 5-year survival of 61% that is close to the 56% in our cohort[7].

A subgroup of patients who require special attention is the cohort who receives a transplant for low-grade pulmonary neoplasms (Supplementary Material, Table S2); these 15 patients had a median survival of 13.6 years (5-year survival: 68%). We do not intend to support lung transplants in patients with low-grade pulmonary neoplasms, but it is clear that reconsideration is necessary, also in light of the indications reported in the 2014 ISHLT consensus statement on recommendations for referral and listing for lung transplants [13].

Approximately 32% of the patients in our cohort developed CLAD. The CLAD-free median survival was 8 years; considering that the cumulative morbidity rate for bronchiolitis obliterans syndrome within 5 years is 41.1% in the ISHLT registry versus 33.8% in our cohort, we can assume that patients who received transplants for rare diseases had similar, if not lower, chronic rejection rates than the general population who received transplants [14]. As expected, the hazard rates curve for CLAD shows a peak at 3 years after the transplant (Supplementary Material, Fig. S2). A solid endorsement of induction therapy with lung transplants comes from evidence associated with kidney and heart transplants. However, nearly 50% of lung transplant centres have not given their general patients induction agents, partly for fear of infections and partly because of the lack of concrete evidence [15]. Indeed, induction therapy appears to be a significantly protective factor for the development of CLAD in our peculiar cohort of patients (Table 3). Once manifested, CLAD heavily influenced survival, as can be seen from Fig. 3.

Limitations

The present study has several limitations: Primarily, it has the common drawbacks of retrospective studies even though the data were originally collected prospectively. Each centre autonomously formulated the diagnoses; centralized pathological and/or clinical reviews were lacking. The volume of activity of the transplant centre is known to impact clinical results; therefore, the different sizes of the participating centres constituted a limitation that we tried to compensate for with the use of a robust sandwich variance estimator.

The distribution of the different diagnoses among the transplant centres was inhomogeneous; this fact derives from the specific prevalence of some diseases in certain geographical areas as well as from the ability of some centres to attract specific pathological entities. Considering that this study includes a large number of different diseases as well as different geographic areas, their inhomogeneity should be considered uncorrectable. We recognize that the waiting time is an important issue, but, given the different allocation systems of the centres, we considered that collecting waiting times was futile; this is another limitation of the study. A further limitation concerns CLAD: Each centre used its own criteria and timing for the diagnosis of CLAD; moreover, knowledge about and definitions of CLAD have changed over time. This inhomogeneity must be considered in the interpretation of the results. A cohort of patients without transplants with similar diagnoses that could act as a control arm was absent. The present study highlights a possible protective role of induction therapy on the incidence of CLAD and therefore on survival. Unfortunately, the centres used several drugs, which prevented an accurate analysis; assuming that this study was not designed to investigate induction therapy, we observed that basiliximab had a positive impact on survival.

CONCLUSION

This ESTS Lung Transplantation Working Group study is the first to discuss the issues related to lung transplants for patients with a rare pulmonary disease. In a large cohort, we observed that overall survival and CLAD-free survival were excellent. We support the practice of allocating lungs to patients with a rare pulmonary disease because a lung transplant is an effective and an ethically acceptable treatment.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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Conflict of interest: none declared.

Author contributions

Mario Nosotti: Conceptualization; Data curation; Formal analysis; Investigation; Supervision; Visualization; Writing—original draft. **Frank D'Ovidio:** Conceptualization; Data curation; Investigation; Supervision; Writing—review &

editing. **Miguel Leiva-Juarez:** Conceptualization; Data curation; Investigation; Writing—review & editing. **Shaf Keshavjee:** Conceptualization; Data curation; Investigation; Supervision; Writing—review & editing. **Mindaugas Rackauskas:** Conceptualization; Data curation; Investigation; Writing—review & editing. **Dirk Van Raemdonck:** Conceptualization; Data curation; Investigation; Supervision; Writing—review & editing. **Laurens J. Ceulemans:** Data curation; Investigation; Writing—review & editing. **Thorsten Krueger:** Data curation; Investigation; Writing—review & editing. **Audrey Roth:** Data curation; Investigation; Writing—review & editing. **Marco Schiavon:** Data curation; Investigation; Writing—review & editing. **Federico Rea:** Data curation; Investigation; Supervision; Writing—review & editing. **Ilker Iskender:** Data curation; Investigation; Writing—review & editing. **Paula Moreno:** Data curation; Investigation; Supervision; Writing—review & editing. **Antonio Alvarez:** Data curation; Investigation; Writing—review & editing. **Luca Luzzi:** Data curation; Investigation; Writing—review & editing. **Piero Paladini:** Data curation; Investigation; Supervision; Writing—review & editing. **Lorenzo Rosso:** Data curation; Investigation; Visualization; Writing—review & editing. **Alessandro Bertani:** Data curation; Investigation; Supervision; Writing—review & editing. **Federico Venuta:** Data curation; Investigation; Supervision; Writing—review & editing. **Ylenia Pecoraro:** Data curation; Investigation; Writing—review & editing. **Khaled Al-Kattan:** Data curation; Investigation; Supervision; Writing—review & editing. **Bartosz Kubisa:** Data curation; Investigation; Supervision; Writing—review & editing. **Ilhan Inci:** Conceptualization; Data curation; Investigation; Supervision; Writing—review & editing.

Reviewer information

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