Improving lung transplant outcomes in France: the high emergency lung transplantation programme

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Prioritisation programmes for lung transplant like the high emergency lung transplantation programme in France have the potential to increase transplants in high-risk groups without worsening post-transplant outcomes https://bit.ly/3w1p8es

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With the advancement in diagnostics, therapeutics and dietary programmes, outcomes in cystic fibrosis (CF) have significantly improved for individuals fortunate enough to have access to care [1–4]. However, mortality in advanced CF remains high for those who do not receive lung transplant [5]. Efforts to increase access to lung transplant and/or reduce waitlist times are important. Retrospective observational analyses of single-centre cohorts demonstrate that lung transplant improves survival in persons with CF with advanced lung disease [6, 7]. Given the age and relative lack of co-morbidities of CF lung transplant recipients, outcomes tend to be superior in CF when compared with other end-stage lung diseases [8, 9]. As lung transplant is resource intensive and limited, countries and institutions have adopted varying strategies to prioritise patients for lung transplant listing [10–13].

In this issue of the *European Respiratory Journal*, Coriati *et al.* [14] address this important area of need. Their study assesses how one prioritisation strategy, named the high emergency lung transplantation (HELT) programme, impacted health outcomes in France for persons with CF. The HELT programme prioritises highest need patients for lung transplant [12]. The programme is focused on disease processes leading to end-stage lung disease including CF, bronchiectasis, idiopathic pulmonary fibrosis and pulmonary hypertension [14]. Within these disease groups, individuals suffering from hypoxaemic or hypercarbic respiratory failure and at risk for imminent death are considered for the programme. In CF, for example, candidates for HELT may include those receiving mechanical ventilation or extracorporeal membrane oxygenation (ECMO), or those at risk of impending intubation (*e.g.* on non-invasive ventilation >18 h per day for at least 3 days with arterial carbon dioxide tension (P_{aCO_2}) >80 mmHg) [14]. Enrolment allows two experts to review and, if approved, list the individual. Once listed, individuals remain in the programme for 8 days and can be renewed once. Coriati *et al.* [14] examined health outcomes in CF before and after HELT was introduced in France and, to account for temporal trends, used data from the Canadian CF Registry as a comparator where no similar prioritisation programme has yet been adopted.

The authors found that the HELT programme was associated with an increased number of lung transplants in France. During the post-HELT period, the number of lung transplants increased in both France and Canada, but more so in France. They also found that in the post-HELT period, the risk of death without lung transplant was lower and that the HELT programme did not negatively impact survival post-transplant.

This study was a natural experiment (in a pre–post design with an external control (Canada) to address temporal changes) comparing outcomes before and after a structured programme was instituted to expedite transplant listing for high emergency cases (France), and also comparing both pre- and

post-implementation outcomes to a structure of prioritisation of the sickest patients that is not based on a national programme (Canada). Similar studies have been done in a number of clinical settings, including lung transplantation [15, 16], to provide insight on the impact of large-scale administrative changes to health systems [17, 18]. One of the challenges of addressing clinical questions of this kind relate to a concept of "ecological fallacy". Ecological fallacy exists when studies employing aggregate data to assess a change in outcome due to a change in the environment neglect the potential confounders that could account for the change. Group level changes are erroneously attributed to changes experienced at the individual level [19, 20]. If one looks solely at a population, inferences made about a natural experiment in a location (in this case France, but not Canada) can lead to false inferences. This challenge is especially acute when one infers individual effects from group effects. One could envision looking at group level proportions (*e.g.* ratio of transplants to pre-transplant deaths) and infer that the difference is due to a large-scale ecological experiment. The solution to such a problem is to augment such analyses with individual level data, as was done by the authors leveraging two large national registries.

Another challenge that the authors overcame was addressing multiple outcomes (death without transplant or transplant) that compete and cannot both occur. They did this by employing a competing risk regression model, an analysis that allows assessment of the probability of one event (death without transplant) in the setting of a competing event (transplant) [21, 22]. Such approaches can be challenging to interpret: the interpretation of covariates' associations of the event of interest (transplant), depending on the choice of model, may differ substantively [23]. For example, in cause-specific hazard modelling, covariates in the model only reflect the association with the primary event of interest (in this example, transplant in the absence of death without transplant) [24]. However, ignoring competing risks using all-cause mortality limits one's ability to fully understand treatment effects when competing risks exist [23]. While all analytic approaches have both strengths and weaknesses, all observational data can suffer from bias or unmeasured confounding. The goal of the reader should be to consider these potential factors when interpreting an analysis.

The most prominent limitation of the work by Coriati *et al.* [14] is the potential that other factors are temporally linked to the introduction of the HELT programme but cannot be accounted for. Increasing organ availability, improving transplant referrals, improving clinical management of end-stage disease, or increased access to highly effective CF therapeutics occurring in France but not Canada might pose a challenge to the interpretation of the data. There is no clear evidence that any of these co-interventions were occurring at that time, but they remain potential confounders.

Studying transplant outcomes in CF has historically proved difficult as many available CF registries lack physiological variables that are present in lung transplant registries. There is a growing effort to integrate physiological data (*e.g.* 6-min walk, P_{aCO_2}, echocardiogram, cardiac index) into CF registries and/or study these outcomes with merged registries between CF and transplantation entities. In considering areas of further investigation posed by the authors, some additional questions should be considered. Given HELT was associated with increased lung transplants in CF, how did the HELT programme affect lung transplant rates and outcomes for other lung diseases in France? Did the number of referrals or evaluations for transplant in severe CF change as a result of the HELT programme (although the authors acknowledge the French CF registry does not capture referral data)? The authors also acknowledge that a limitation is not having access to the listing data, and thus not being able to delineate pre-transplant waitlist deaths from pre-listing deaths. Perhaps most importantly, as these questions are explored, the effects of cystic fibrosis transmembrane conductance regulator (CFTR) modulators will be central in future CF-related work.

Overall, improving access to lung transplant and improving prioritisation to decrease death on the list is a laudable goal. Having systematic approaches to ensure access to organs for the most in need is critical. Also critical is ensuring that changes to enhance access do not impact the outcomes of the procedure. Taking a societal perspective, one would ideally prioritise those most in need while ensuring that overall survival benefit of the procedure is either maintained or improved. It appears that France has succeeded in this key task, as shown by Coriati *et al.* [14]. Prioritisation in lung transplant has been an ongoing area of focus for this reason. This is of particular relevance as certain prioritisation structures may not be optimised to specific patient groups, like CF, leading to longer waitlist times and/or limiting lung transplant [25]. For example, in the USA where, between 2018 and 2020, over 7700 lung transplants were performed, the Lung Allocation Score (LAS) is used to prioritise selection by assigning scores to patients by disease characteristics and severity [11, 13]. However, common predictors of death without transplant for persons with CF are not represented in the LAS [26]. Thus, further studies on how varying lung transplant prioritisation structures impact outcomes in CF are needed.

It is interesting that the HELT programme did not impact post-transplant survival. Progressing to more advanced disease can potentially affect post-transplant outcomes, as has been shown in the CF population where higher LAS scores at the time of transplant predicts worse outcomes [27]. Confidence intervals were not included in the post-transplant survival analyses of the present study. Including these may provide further clarification in future studies. Also, the selection process for HELT, such as how many were receiving mechanical ventilation or ECMO, how patient level data may have influenced outcomes, and/or how existing structured programmes for prioritisation (*e.g.* HELT, LAS) compare, with regards to timing for transplant and post-transplant survival, will be important areas of future investigation.

In summary, the HELT programme was associated with increased lung transplants in France without adversely affecting post-transplant survival outcomes. Overall, this topic is important and these data reflect the need for further investigation into lung transplant prioritisation programmes. Waitlist mortality is high for CF and efforts that expand access to lung transplant without negatively impacting post-transplant outcomes need to be a focus for the CF and lung transplantation communities.

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