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ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
ΣΤΗ ΔΗΜΟΣΙΑ ΥΓΕΙΑ
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“Τεχνητή Νοημοσύνη και Μεταμοσχεύσεις Καρδιάς και Πνεύμονα: Διερεύνηση και Ανάλυση των Επιπτώσεων στην Υγεία και Ποιότητα ζωής των Ασθενών - Συστηματική Βιβλιογραφική Ανασκόπηση”

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SPECIALIZATION:
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Master Thesis

“Artificial Intelligence and Heart - Lung Transplantations: Processing and Analysis of the Impact on Patient’s Health and Quality of Life - Systematic Literature Review”

George- Chrysovalantis Sargiotis
Registration Number: mdy21080

Supervisor: Kostas Athanasakis
Assistant Professor

Athens, 2024

ΠΑΝΕΠΙΣΤΗΜΙΟ ΔΥΤΙΚΗΣ ΑΤΤΙΚΗΣ
ΣΧΟΛΗ ΔΗΜΟΣΙΑΣ ΥΓΕΙΑΣ
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Μέλη Εξεταστικής Επιτροπής συμπεριλαμβανομένου και του Επιβλέποντα

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Ο κάτωθι υπογεγραμμένος Γεώργιος - Χρυσοβαλάντης Σαργιώτης του Δημητρίου, με αριθμό μητρώου mdy21080. φοιτητής του Προγράμματος Μεταπτυχιακών Σπουδών στη Δημόσια Υγεία του Τμήματος Πολιτικών Δημόσιας Υγείας της Σχολής Δημόσιας Υγείας του Πανεπιστημίου Δυτικής Αττικής, δηλώνω ότι:

«Είμαι συγγραφέας αυτής της μεταπτυχιακής εργασίας και ότι κάθε βοήθεια την οποία είχα για την προετοιμασία της, είναι πλήρως αναγνωρισμένη και αναφέρεται στην εργασία. Επίσης, οι όποιες πηγές από τις οποίες έκανα χρήση δεδομένων, ιδεών ή λέξεων, είτε ακριβώς είτε παραφρασμένες, αναφέρονται στο σύνολό τους, με πλήρη αναφορά στους συγγραφείς, τον εκδοτικό οίκο ή το περιοδικό, συμπεριλαμβανομένων και των πηγών που ενδεχομένως χρησιμοποιήθηκαν από το διαδίκτυο. Επίσης, βεβαιώνω ότι αυτή η εργασία έχει συγγραφεί από μένα αποκλειστικά και αποτελεί προϊόν πνευματικής ιδιοκτησίας τόσο δικής μου, όσο και του Ιδρύματος.

Παράβαση της ανωτέρω ακαδημαϊκής μου ευθύνης αποτελεί ουσιώδη λόγο για την ανάκληση του πτυχίου μου».

Ο/Η Δηλών/ούσα

Γεώργιος Χρυσοβαλάντης Σαργιώτης

Ψηφιακή υπογραφή επιβλέποντα

ΚΩΝΣΤΑΝΤΙΝΟΣ ΑΘΑΝΑΣΑΚΗΣ

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Η παρούσα διπλωματική εργασία εκπονήθηκε στο πλαίσιο των απαιτήσεων του Προγράμματος Μεταπτυχιακών Σπουδών στη Δημόσια Υγεία του Τμήματος Πολιτικών Δημόσιας Υγείας της Σχολής Δημόσιας Υγείας του Πανεπιστημίου Δυτικής Αττικής. Η έγκρισή της δεν υποδηλώνει απαραιτήτως και την αποδοχή των απόψεων του συγγραφέα εκ μέρους του Τμήματος Πολιτικών Δημόσιας Υγείας.

Βεβαιώνω ότι η παρούσα Διπλωματική Εργασία είναι αποτέλεσμα προσωπικής μου εργασίας και δεν αποτελεί προϊόν αντιγραφής. Στις δημοσιευμένες ή μη δημοσιευμένες πηγές που αναφέρω έχω χρησιμοποιήσει εισαγωγικά όπου απαιτείται και έχω παραθέσει τις πηγές τους στο σχετικό τμήμα της βιβλιογραφίας.

Υπογραφή

Γεώργιος Χρυσοβαλάντης Σαργιώτης

Προτεινόμενη Βιβλιογραφική Αναφορά: Σαργιώτης Γ.Χ., Σεργεντάνης Θ., Πάβη Ε., Αθανασάκης Κ. Τεχνητή Νοημοσύνη και Μεταμοσχεύσεις Καρδιάς και Πνεύμονα: Διερεύνηση και Ανάλυση των Επιπτώσεων στην Υγεία και Ποιότητα ζωής των Ασθενών - Συστηματική Βιβλιογραφική Ανασκόπηση. Διπλωματική εργασία ΠΜΣ «Δημόσια Υγεία». Τμήμα Πολιτικών Δημόσιας Υγείας. ΠΑΔΑ. Ιούλιος 2024.

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Περίληψη

Εισαγωγή: Η αποτελεσματικότητα και η ικανότητα των μοντέλων τεχνητής νοημοσύνης να προβλέπουν τα μετα-μεταμοσχευτικά αποτελέσματα υγείας, είναι υπό αμφισβήτηση. Το αντικείμενο αυτής της συστηματικής ανασκόπησης ήταν να αξιολογηθεί η απόδοση διαφορετικών μοντέλων τεχνητής νοημοσύνης στην πρόβλεψη των αποτελεσμάτων υγείας μετά τη μεταμόσχευση καρδιάς ή πνευμόνων.

Μέθοδοι και Υλικά: Ερευνήθηκαν διαδικτυακές βάσεις δεδομένων, συγκεντρώθηκαν και αναλύθηκαν δεδομένα σχετικά με τις μετρήσεις απόδοσης των μοντέλων τεχνητής νοημοσύνης σε μεταμοσχεύσεις καρδιάς ή πνευμόνων. Επιπλέον, διενεργήθηκε μελέτη αξιολόγησης του κινδύνου μεροληψίας.

Αποτελέσματα: Από τις 122 αρχικές μελέτες, 15 μελέτες συμπεριλήφθηκαν στην ανάλυση. Τα μοντέλα τεχνητής νοημοσύνης έδειξαν υψηλή απόδοση, με μετρήσεις για τη διάκριση, όπως η περιοχή κάτω από την καμπύλη ROC που κυμαίνεται από 0,620 έως 0,921 και καλή βαθμονόμηση για μακροπρόθεσμα αποτελέσματα. Τα μοντέλα Random Forest και Extreme Gradient Boosting ξεπέρασαν τα άλλα μοντέλα και ιδιαίτερα τα παραδοσιακά γραμμικά μοντέλα. Το κυρίαρχο επιμέρους δείγμα ήταν λευκοί άντρες από τις ΗΠΑ, ενώ οι παιδιατρικοί πληθυσμοί εξαιρέθηκαν από την ανάλυση. Οι περισσότερες από τις μελέτες κατέδειξαν υψηλό συνολικό κίνδυνο μεροληψίας, ενώ η εφαρμοσιμότητα στα ερευνητικά ερωτήματα έδειξε χαμηλό κίνδυνο μεροληψίας.

Συμπεράσματα: Τα μοντέλα μηχανικής μάθησης αποδίδουν αρκετά καλά στην πρόβλεψη των αποτελεσμάτων υγείας μετά τη μεταμόσχευση, αν και είναι σημαντικό να ληφθούν υπόψη οι προκαταλήψεις και τα ηθικά διλήμματα που προκύπτουν από τις εφαρμογές των μοντέλων τεχνητής νοημοσύνης σε μεταμοσχεύσεις, προκειμένου να εξαχθούν ασφαλή συμπεράσματα.

Λέξεις-κλειδιά: μεταμόσχευση καρδιάς, μεταμόσχευση πνεύμονα, μηχανική μάθηση, τεχνητή νοημοσύνη, αποτελέσματα υγείας

Abstract

Background: Artificial Intelligence models' efficacy and capacity to predict post-transplant health complications have been disputed over the last few years. The scope of this systematic review was to assess the performance of different AI models in the prediction of heart and lung post-transplant health outcomes.

Methods and Materials: Online databases have been researched. Data about performance metrics of AI applications in heart and lung transplantations have been gathered and analyzed. Additionally, a risk of bias assessment was conducted.

Results: Of the 122 initial studies, 15 studies were included in the synthesis. The AI models showed high performance, with metrics for discrimination such as the Area Under the Receiver Operating Curve ranging from 0.620 to 0.921, and good calibration for long term outcomes. Random Forest and Extreme Gradient Boosting models outperformed other models and especially traditional linear models. North-American, white people were the predominant subsample and pediatric populations were excluded from the analysis. Most of the studies demonstrated a high overall risk of bias, while applicability to research questions showed low risk of bias.

Conclusions: Supervised Machine Learning models perform pretty well in predicting post-transplant health outcomes, though it is critical to consider the biases and ethical concerns that arise from the applications of AI models in transplantations, in order to draw safe conclusions.

Keywords: heart transplantation, lung transplantation, machine learning, artificial intelligence, health outcomes

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Preface

Writing about transplantations and artificial intelligence wasn’t an easy job. Due to the rise of scientific interest in Artificial Intelligence, I thought that it was a good chance for me to “meddle” with this field; I had no clue or knowledge, and it really demanded a lot of time studying about algorithms, their use, and their applications in healthcare. Specifically, solid organ transplantations is a subject that I always wanted to do research on due to my personal experience with Cystic Fibrosis. My first thoughts and motivations to address that issue were about questioning whether my co-patients would have a different life if AI had been applied during their operation or if it had warned their doctors before their health got worse. In addition, I was wondering whether an AI approach would have changed the way organs are allocated or patients are monitored after transplantation and what the benefits or risks of such a great innovation would be. I had many concerns about either the morality of applying AI machines to the place of a doctor or if I could trust a machine that would tell me whether I needed a transplant or not. It’s true that we have already been using machines for many years, and we have been sharing our personal data without limitations or legal obstacles, but nowadays, due to the prevalence of technological methods in our lifestyle, things have changed. Given that health services like transplanting an organ to a patient require that clinicians obey the ethical principles of beneficence and non-maleficence, safety, privacy, and autonomy of patients, AI applications need to be adjusted. So, we need legal frameworks and guidelines that would protect patients, we need standardized procedures to ensure patients’ best quality of life and to minimize human errors. To achieve that, we need to do research beforehand and give answers to unresolved and unmet issues. These are the reasons why I decided to deal with that subject, in order to give my answers to the justification of using AI models in transplantations and what the impact would be on patients' lives.

In this journey, I wouldn’t be able to complete this work without the guidance and help of my professor, Dr. Kostas Athanasakis, whom I thank a lot for the trust he showed me and the insightful advice he has been giving me all this time.

Introduction

Solid organ transplantations are an essential part of public health policies, considering a great number of heart or lung disease-related patients are waiting on a pretransplant list or have already had a transplant; thus, they are in constant need of medical assistance, follow-up, guidance throughout their lives, and treatment of complications in order to have a good quality of life. The research subject of the present systematic review is the evaluation of Artificial Intelligence applications in Heart or Lung Transplantations, especially in the post-transplant phase, assessing the AI models' performance and their impact on transplant patients' lives and health outcomes. The originality of this study lies in the inclusion and analysis of data from both types of heart or lung transplant studies that previous scientists like Naruka et al. 2022, Gholamzadeh et al. 2022, and Palmieri et al. 2023 haven't done in their reviews. The scope of the studies was to investigate the use of AI models in the prediction of health outcomes after heart or lung transplantation.The absence of a qualitative analysis of studies that present results about AI applications in heart or lung transplantations was the main reason that led to the development of the present review.

In the following chapters, there is described in detail a thorough presentation of the pathological conditions of the heart and lungs that lead to transplantation, the transplantation procedures, some basic knowledge about artificial intelligence and its applications in healthcare and transplants, and the findings and conclusions of the analysis of reviewed studies. Specifically, the first chapter refers to the pathology of heart and lung diseases, whose last and main treatment is organ transplantation, as well as epidemiologic data about the prevalence, incidence of diseases, mortality, and quality of life of patients. In addition, there is an extended section for transplantations, like the legal framework that encompasses it, organ donation, preservation, and pair matching, as well as post-transplant information like follow-up procedures, complications and treatments provided, rehabilitation techniques, and the quality of life of post-transplant patients. Chapter two is dedicated to an insightful demonstration of Artificial Intelligence and its applications in healthcare. In Chapter 3, the rationale, scope, and objectives of the present systematic review, the methodology, the results of the analysis of the included studies, and the discussion and commentary of the results and conclusions drawn regarding the performance of AI models used in transplantation procedures, the significance of certain variables in the prediction of health outcomes, and the ethical considerations of AI implementations are presented, as well as the limitations and future considerations for future research.

Chapter 1
Heart and Lung Transplantations

1.1 Pathological Conditions

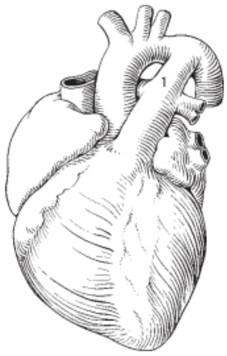
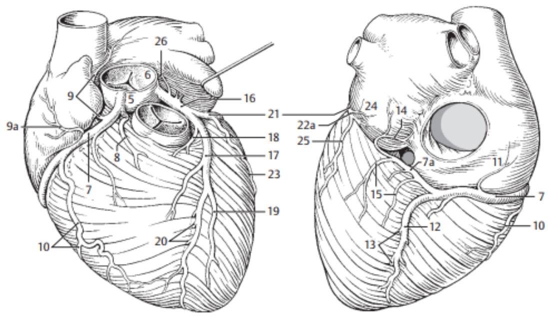
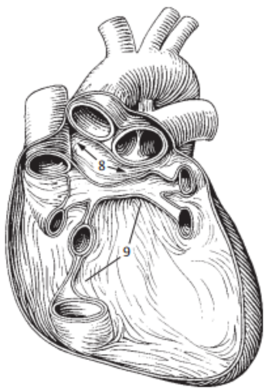
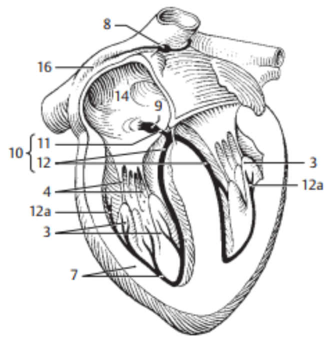
1.1.1 Heart

Don't let heart failure stop you[1]

Heart has been vastly considered the epicenter of life, the reason animals like humans live and the reason they die when the heart stops unexpectedly. It was praised for its beating rhythm, connected with love, eros, and pathos, while being extensively studied over the years for its functions. Its work is mainly to keep stable the circulation of blood to and from the periphery and provide cells with nutrients, hormones, and other substances while mediating for the transfer of oxygen (O2) and carbon dioxide (CO2) from and to the lungs, respectively, and the circulation of subproducts from cells to metabolic sites in the body for their excretion. The heart has a complex mechanism of function that comprises an autonomous electric signal pathway that regulates the movement of the heart, the blood flow, and the force with which the heart pumps the blood. Unfortunately, it's impossible yet to cease or reverse the inevitable decline deriving through time from natural causes or underlying diseases (Chaudhry et al. 2022).

[1] Global Heart Hub Awareness Campaign Logo, 2021

Despite the implementation of several therapeutic advances, a great number of congenital or acquired heart diseases are the reason for end-stage patients, around the world, to wind up in transplantation (Houyel et al. 2017, Attenhofer Jost et al. 2013).

Image 1.1 Heart and Cardiovascular Anatomy	
 Fetal Heart	 Cardiovascular system anterior view (left), posterior view (right)
 Pericardium with great vessels	 Internal conduction system of heart
Feneis, H., et al., Chapter 10 - Heart, Chapter 11- Arteries, in Pocket Atlas of Human anatomy- Based on the International Nomenclature, pp. 184–193.	

Some of these pathological conditions are either congenital, like:

- Hypoplastic left heart syndrome (HLHS): It is a heart condition where the left side of the heart, including the ventricle and the atrium, is underdeveloped due to aortic or mitral valve stenosis or atresia. Either the decreased flow into or the decreased outflow from the left ventricle leads to its hypoplasia and complete dependence on systemic and pulmonary circulation on the right ventricle, which gathers de- and oxygenated blood and pumps it through pulmonary veins to the pulmonary circulation and through patent ductus arteriosus into the aorta to the systemic circulation. After birth, when those two holes, patent ductus arteriosus and patent foramen ovale close, the systemic circulation lacks oxygenated blood in neonates with HLHS (Kritzmire et al., 2023, Bahaaldin Alsoufi et al. 2016).

- Transposition of the great arteries (TGA): During the evolution of the embryo, the aorta and pulmonary arteries pathologically shift positions, resulting in oxygenated blood flowing from the left ventricle to pulmonary circulation and deoxygenated blood outflowing from the right ventricle to systemic circulation (Song et al., 2014,Muñoz-Guijosa, C. et al., 2009, M. Hegarová et al. 2015).
- Tetralogy of Fallot: Four pathologic features characterize this heart deficiency, which are a) a hole in the septum that divides the two ventricles, b) a slightly shifted aorta found above the hole of the septum, c) pulmonary artery stenosis and d) right ventricle hypertrophy (Diaz-Frias J et al. 2022).
- Eisenmenger syndrome: It arises when pulmonary artery pressure rises, affecting lung vessels and finally destroying them. The rise of pressure occurs in many heart deficiencies, like when blood flows from the left to right side of the heart (left-to-right shunt)(Rajan A.G. Patel et al. 2008, Basit H et al. 2023).
- Arrhythmogenic right ventricular dysplasia (ARVD) or cardiomyopathy (ARVC): it is a hereditary disease caused by gene alterations that contribute to accumulation of fatty or fibrous tissue in the heart muscle. In this condition, mostly the right ventricle, in the beginning, appears to have arrhythmogenic cardiomyopathy and progressively the left ventricle might be affected (McNally E et al. 2005, Shah SN et al. 2023).

Or acquired, like

- Dilated cardiomyopathy: the enlargement of myocardial tissue of one or both ventricles, leads to arrhythmias and heart failure (Mahmaljy H et al. 2023)
- Ischemic cardiomyopathy: when coronary vessels’ epithelial get covered with lipid plaques, then some regions of the heart do not receive the right amount of nutrients and oxygen, ending up to ischemia and eventually cardiomyopathy, that is the difficulty of heart to pump blood out of ventricles to circulation (Bhandari B. et al. 2023)

- Restrictive cardiomyopathy: it’s a rare acquired condition caused by infiltrative diseases like amyloidosis, sarcoidosis, etc. that provoke myocardial diastolic dysfunction (Brown KN et al. 2023)
- Congestive heart failure: in this incidence, the heart due to structural or functional irregularities, is unable to provide the whole body with the blood, oxygen and nutrients that are required for the continuing of life. The source of this deficiency might be diabetes mellitus, ischaemic infarctions, or hypertension (Malik A et al. 2022)

Prevalence and Incidence

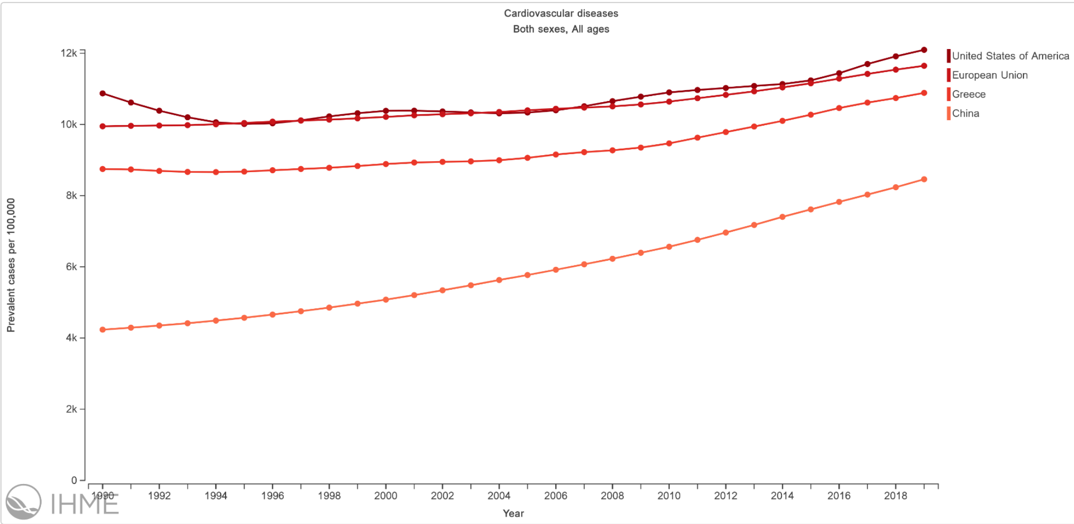
Due to poor lifestyle choices, the prevalence of heart diseases such Coronary Heart Disease has increased since the first decades of the 20th century. People started monitoring their health status and making dietary and lifestyle changes, mostly in high-income nations that led to less hospitalizations, acute coronary episodes and deaths, in the USA (Dalen JE et al. 2014). However, as it seems in Figure 1.1, the prevalence of cardiovascular diseases has been escalating over the last two decades, despite the entrance of new and innovative medications that have entered the market.

A vulnerable social group like pregnant women have a higher risk, almost 50% rise, of developing a heart disease like Acute Myocardial Infarction or Ischemic Heart Disease, due to the many alterations that happen in their bodies. During gestation, increased hormone levels affect the vessels' elasticity, metabolism of glucose and lipids profoundly change, ending up in either coronary artery dissections, atherosclerosis, followed by acute myocardial infarctions. Lower-income and black women appear to have a higher incidence of such heart diseases that remain after delivery and affect women's lives in a severe way (Gédéon T, et al. 2022, Gibson P, et al. 2017, Baris L, et al. 2020).

Many patients with congenital heart diseases nowadays have improved quality of life and a longer lifespan thanks to new protocols, medications, and treatments. This is the reason why the prevalence of many congenital diseases has risen over the last decades (Ávila P et al. 2014). Prevalence is the rate of people with the disease in a population at a specific time frame (Tenny S et al. 2023), that means more people alive with a disease accounts for higher prevalence.

Acute or chronic heart diseases greatly affect the population and have an enormous impact on their health and quality of life. Over the last decades, the incidence and prevalence of coronary heart diseases escalated, despite all the primary and secondary prevention measures that national and international organizations have taken and implemented.

Figure 1.1 Prevalence per 100,000 of Cardiovascular diseases,both sexes, all ages, in the European Union, Greece, China and the U.S.A., 1990-2019



Data from Global Burden of Disease, Institute for Health Metrics and Evaluation (Accessed 06/11/2023)

Mortality rate

The mortality rate of Cardiovascular Diseases varies among people of different genders, ages, regions, and ethnicities (C.J. McAloon et al. 2016). High systolic blood pressure, diets deficient in whole grains, fruit, vegetables, and seeds, high BMI, and tobacco use all contribute significantly to the rise in heart illnesses, particularly coronary heart disease, in the majority of the world 9P.E. Puddu et al. 2018). Compared to lifetime non-drinkers, heavy alcohol usage and previous usage (above 36 grams of pure alcohol per day) have been associated with an elevated risk of IHD (Roerecke M et al.2014).

Inequalities in healthcare access due to lack of infrastructure, medication shortage, and high-cost treatments, as well as other critical absences, are one of the major determinants of high mortality rates in vulnerable communities, like Black and

Hispanic people (Tran R et al., 2022). Knowledge and awareness of CVD play a significant role in dealing with the disease and managing health, by evolving literacy skills, which results in lower death rates, especially in women (Martin LT et al. 2011).
Globally, death rates by cardiovascular diseases decreased at a slow pace, but they remain at the top of the leading causes of death. In 2019, Greece's death rate increased to 540.97 deaths per 100,000, outgrowing the European Union (389.44 deaths) and China (322.3 deaths), with ischemic heart disease and stroke being the predominant reasons for death. Regarding heart diseases, ischemic or coronary heart disease constitutes the major cause of death, with 252.9 deaths per 100,000 in Greece in 2019 (IHME 2023).
Table 1.1 presents the mortality rate by heart diseases, like ischemic cardiomyopathies and acute myocardial infarctions, in Greece, Europe, and the USA during the period 2016 to 2020.

Table 1.1 Deaths by Heart Diseases, ischemic cardiomyopathy, acute myocardial infarction, 2016-2020, in Greece, Europe* & United States of America (U.S.A.) (number of deaths)

Year	Country/Continent	Other heart diseases **	Ischemic Cardiomyopathy (I20–I25)	Acute Myocardial Infarction (I21–I22)
2020	Greece	10,576	13,947	6,693
	Europe	398,518	551,121	183,619
	U.S.A.	232,176	382,820	109,199
2019	Greece	10,388	13,827	6,633
	Europe	408,516	527,627	180,411
	U.S.A.	228,946	360,900	104,280
2018	Greece	12,575	12,808	6,652
	Europe	430,282	539,703	187,020
	U.S.A.	226,036	365,744	108,610
2017	Greece	13,103	7,973	6,959

	Europe	427,750	556,652	192,734
	U.S.A.	223,441	365,914	110,346
2016	Greece	12,323	11,783	6,225
	Europe	426,469	543,938	194,468
	U.S.A.	218,766	363,452	111,777

*27 countries
**ICD10 for other heart diseases Greece, Europe (I30-I51), U.S.A. (I26-I51)
Data extracted from EUROSTAT for Greece and Europe and from National Vital Statistics Reports, by National Center for Health Statistics for U.S.A. / Date: 27-28/10/2023

Quality of Life

Quality of Life is the concept of evaluating one's life based on the positive and negative situations or events they have encountered, the burden of diseases and the health outcomes. Because of the variety and variability of factors included in its measurement, such as health, social status, work, freedom, and so on, QoL can be described as a very complicated assessment indicator (Teoli D et al. 2023). In health, different metrics have been used to estimate someone's quality of life, like DALY's, QALE, QALY's, etc. Besides its strong impact on research as an indicator of someone's life status, different metrics have been used as predictors of outcomes like survival, mortality, disability (Haraldstad K et al. 2019).

Disability-adjusted life Years (DALYs) is an assessment indicator for general populations of the years spent with a disability (YLD) or in a non-healthy state, plus the years of life lost (YLL) due to premature death caused by this disease (L. Ferrucci et al. 2007). DALY's are used more frequently in the evaluation of the burden of a disease or in cost-effectiveness analysis of an intervention and as a measure includes disability and age-weighting factors which vary across the lifespan of a person. On the other hand, QALY's or QALE are used in the assessment of enhancement of quality adjusted life years or life expectancy of a person during or after the implementation of an intervention. Due to changes in the age-weighting

variable, research indicates that the age at which the disease initially presents can be a significant determinant for assessing quality of life (Sassi, F 2010).
On a global level, male individuals appear to have more DALY's than females, relating to increased ischemic heart disease incidence in this gender (C.J. McAloon et al., 2016). It is commonly known that ischemic heart disease, which has an average incidence appearance age of 67.4 years for both sexes, has been the leading cause of death worldwide (Jacqueline Müller-Nordhorn et al. 2017) (Miller Dylan V et al. 2018). Considering the disparities in the provision of healthcare, income, lifestyle, and dietary choices, among countries of the world, life expectancy and the evolution of a disease are directly impacted. Besides Ischemic Heart Disease (IHD), almost every cardiovascular disease has a great impact on people's lives, resulting in a high percentage of life years lost due to disability and premature death (C.J. McAloon et al, 2016).
In Table 1.2 and Figures 1.2, 1.3, it is shown the Disability-Adjusted Life Years lost, in Europe and the USA for the period 2016-2019. Notably, DALY's for patients with ischemic heart disease have increased the most in Eastern Europe over the years. In Eastern Europe and mainly in its Northern part, higher rates of unhealthy habits like smoking or acquired diseases like diabetes are some of the causes of the higher incidence of IHD (Edina Cenko et al. 2023) .

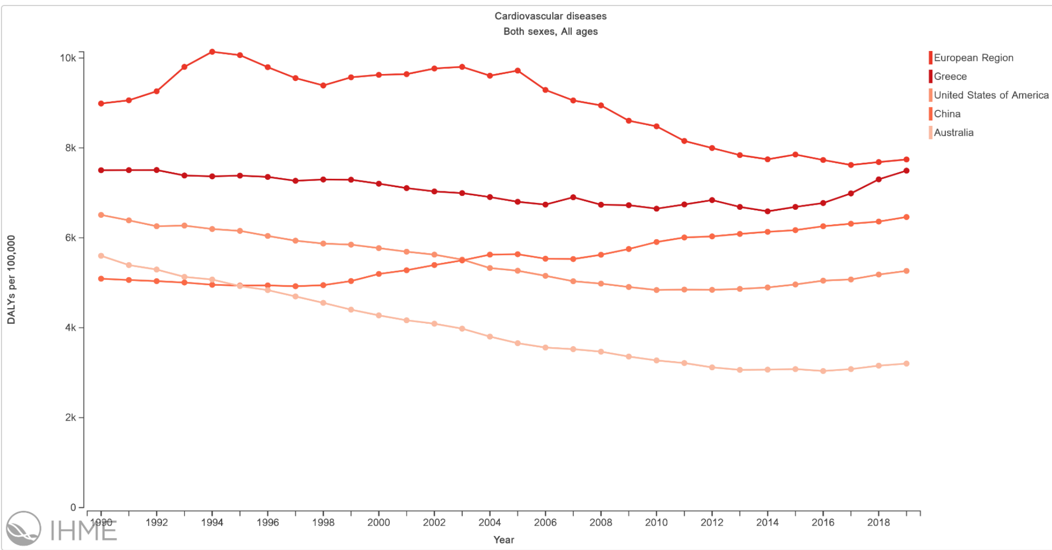
Table 1.2 Disability-Adjusted Life Years (DALY's)

Year	Region	Ischemic heart disease	Cardiomyopathy and myocarditis	Atrial fibrillation and flutter	Endocarditis
2016	WE	8,699,768.42	703,266.03	1,313,421.32	192,086.88
	CE	5,344,188.02	514,944.26	289,619.76	23,770.70
	EE	17,603,689.95	2,458,882.91	462,306.39	84,018.80
	USA	8,409,870.12	762,366.89	862,192.28	145,374.02
2017	WE	8,806,654.59	715,631.52	1,328,851.17	191,456.62
	CE	5,386,276.79	522,305.83	295,371.61	23,564.61

	EE	16,897,847.26	2,364,659.30	465,666.84	80,312.02
	USA	8,483,075.76	774,149.37	885,515.12	145,240.66
2018	WE	8,978,868.09	727,834.79	1,344,293.46	192,207.33
	CE	5,452,900.15	526,347.06	300,364.60	23,439.18
	EE	16,992,266.25	2,359,551.80	473,842.63	79,886.45
	USA	8,749,762.09	788,280.46	920,175.78	147,050.38
2019	WE	9,125,379.54	739,475.81	1,347,219.73	193,128.10
	CE	5,471,195.31	529,593.71	302,864.50	23,256.89
	EE	17,082,364.87	2,360,896.35	481,405.89	79,479.53
	USA	8,948,088.72	797,275.52	955,312.32	148,628.26

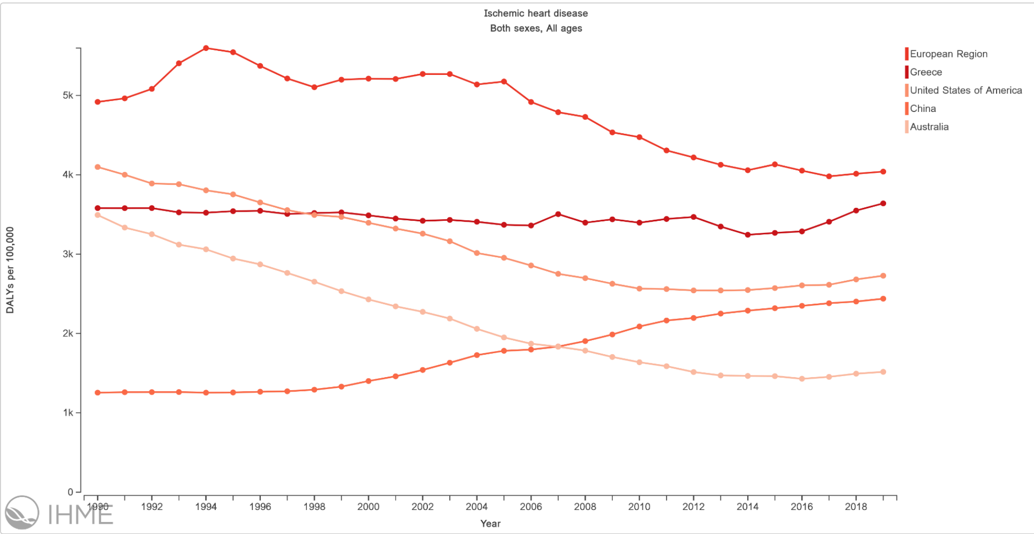
WE: Western Europe, CE: Central Europe, EE: Eastern Europe, USA: United States of America
*Data extracted from EUROSTAT and IHME (Institute for Health Metrics and Evaluation)/Date: 28/10/2023

Figure 1.2 DALY's per 100,000 for Cardiovascular Diseases, both sexes, all ages, 1990-2019



Data for Greece, European Region, U.S.A., China and Australia, Global Burden of Disease, IHME, (Access: 31/10/2023)

Figure 1.3 DALY's per 100,000 for Ischemic Heart Disease, both sexes, all ages, 1990-2019



Data for Greece, European Region, U.S.A., China and Australia, Global Burden of Disease, IHME, (Access: 31/10/2023)

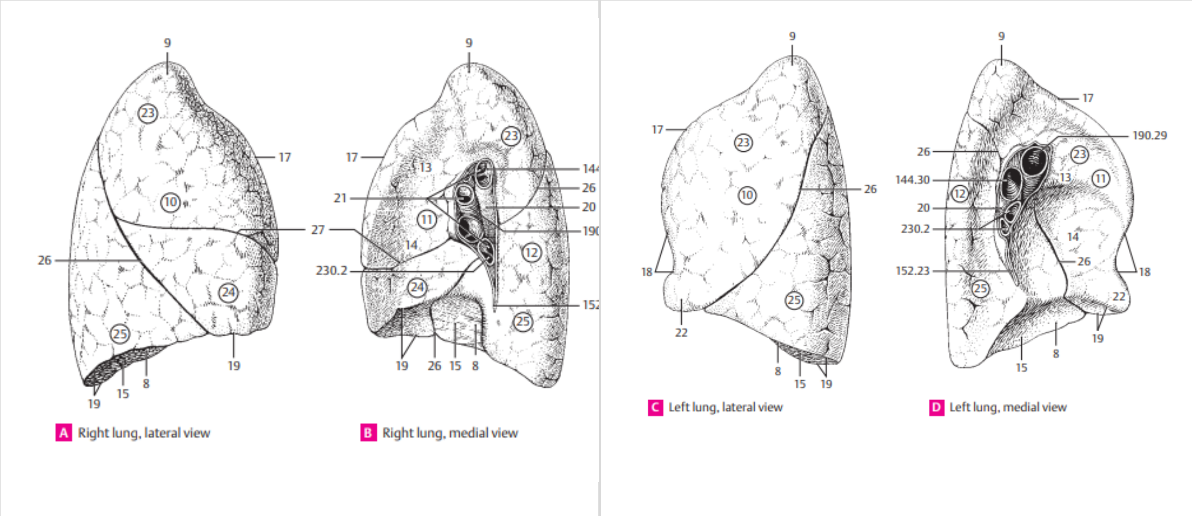
1.1.2 Lungs

Each Breath a Step Closer to Our Dreams[2]

Lungs are an essential part of the body, providing oxygen that is utterly necessary for many internal functions, like cellular respiration, substance degradation, etc. and contributing to excretion of carbon dioxide (CO_2), which is a side product of different cellular processes. As an organ, it consists of two parts, the right and left lobes. The right lobe is divided into three parts and the left into two by crevices. In the inspiration and expiration process, a few muscles play a significant role, like the diaphragm (Chaudhry R et al. 2023).

Image 1.2 Lungs Anatomy (lateral and medial view of the right and the left lobe)

[2] Hellenic Cystic Fibrosis Association Awareness Campaign Logo, 2012-2016



Feneis, H., et al., ‘Chapter 6- Digestive and respiratory system’, in Pocket Atlas of Human anatomy- Based on the International Nomenclature, pp. 134–153.

In many critical conditions or end-stage lung diseases, transplantation is the last decision to keep the patient alive. Some of the pathological lung conditions, whose last resort is transplantation, are:

- Chronic Obstructive Pulmonary Disease (COPD) /emphysema: COPD is a chronic disease of lungs caused by constant exposure to harmful substances, like the ingredients of cigarettes, which provoke chronic inflammation, excretion of sputum, and airflow limitation. Acute episodes are characterized by dyspnea, wheezing, and increased cough. COPD can lead progressively to lung failure. Emphysema is a form of COPD that is caused by chronic inflammation and the rupture of alveoli sacks, resulting in the creation of a larger air pocket (Agarwal AK et al. 2023, Schrijver J et al. 2022).
- Idiopathic Pulmonary Fibrosis (IPF): Of unknown reasons (viral or bacterial infections, exposure to chemical substances, tobacco, metals), IPF constitutes a progressive inflammatory disease which scars the pneumonic parenchyma and replaces it with fibrous tissue. Dyspnoea and cough are some of the major symptoms. Some of the complications are thromboembolism, pulmonary hypertension, acute coronary syndrome (Krishna R et al. 2023).
- Cystic Fibrosis: It is a rare congenital disease affecting multiple organs, like the lungs, pancreas, stomach, intestine, upper air tract, exocrine glands, and

reproductive system. Its cause is the deficient expression of CFTR protein, an ion channel that controls the circulation of Chlorine and Bicarbonate ions in and out of the cell, due to mutations to the CFTR gene. As a result, a thick mucus is produced, filling the lumens and provoking progressive obstruction, fibrosis, and organ failure (Savant A et al. 2001).

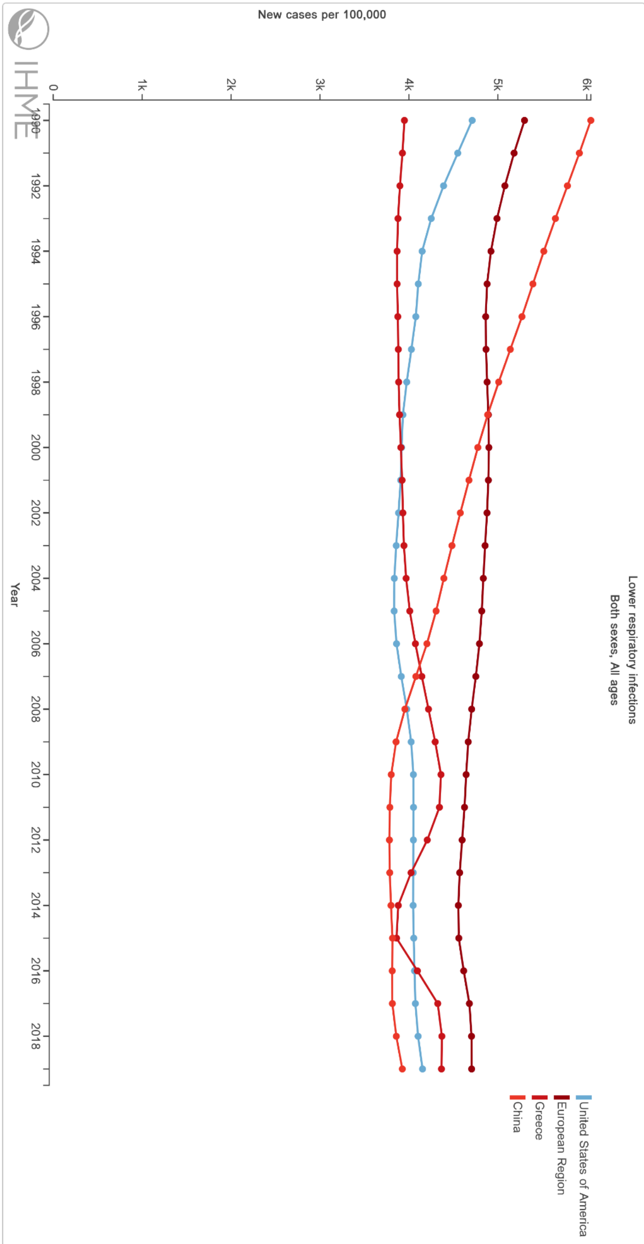
- Alpha - 1 Antitrypsin Deficiency (AAT): it's a hereditary condition that affects the production of the Alpha-1 antitrypsin protein, which opposes the neutrophil elastase enzyme. Deficiency of AAT causes lung elastin to be degraded by the released elastase enzyme, ending up in fibrosis and alveoli destruction. Whereas AAT protein is abundantly accumulated in the hepatocytes, which are deeply disintegrated (Meseeha M et al. 2023, Stoller JK et al. 2006).
- Idiopathic Pulmonary Arterial Hypertension (IPAH): the hypertension of pulmonary arteries due to elevated vasoconstriction leads to gradual obstruction and destruction of vessels. The reason for IPAH is a combination of genetic susceptibility and environmental factors (Krowl L et al. 2023).
- Sarcoidosis: The disease is primarily asymptomatic and is brought on by an idiopathic build-up of immune cells, such as leukocytes, macrophages, and histiocytes, mostly found in the skin and lungs lymph nodes, where they form granulomas. In the end stage of the disease, transplantation may be required (Bokhari SRA et al. 2023).
- Bronchiectasis: It is a chronic disease that is a result of continuous airway inflammations, or an evolving stage of other acquired or congenital diseases. Its features are increased sputum production, accompanied by hemoptysis, dilation of bronchi, and lack of lumina tapering (that is a gradual lumen diameter decrease from larger bronchi to smaller alveoli), bronchial wall thickening, that lead to the obstruction of small airways (Bird K et al. 2023, Grenier PA et al. 2019).

Prevalence and Incidence

Over the last decades, lower respiratory infections have been on the top of the rank of communicable diseases (Figure 1.4). During COVID-19 pandemic, it was noticed that the non-pharmacological treatments like hand washing, environmental measures, social distancing and movement restrictions had a major effect on the reduction of viruses' circulation in the population and presumably contributed on the increase of the incidence when the measures were no longer in action (Principi N et al. 2023). In the rank of non-communicable diseases, the only chronic respiratory condition that holds a high position is Chronic Obstructive Pulmonary Disease (Data from GBD, IHME, 2023).

The extreme climate events that hit our planet have established new and unpleasant alterations in the biosphere and the ecosystem of different regions of the world. As a result, plants and their pollen have invaded virgin places, air-borne vectors have traveled to the northern hemisphere transferring infectious diseases, which were unknown to the natives, and high proliferation of microorganisms like viruses and bacteria due to change of environmental survival conditions, have imposed a serious public threat to the stability and safety of many societies (Cuvillier Padilla, C. et al. 2022). Global warming, increasing level of air pollutants and wildfires are some of the risk factors that contribute to lung health worsening globally (Rom W.N. et al. 2021). Especially, traffic air pollution that produces perfectly subdivided atmospheric pollutants like dust, or gases (ozone, nitrogen oxides etc.), which are able to reach the most restricted regions of air tracks, the alveoli and initiate an inflammation signal cascade (Solanki, N.2022).

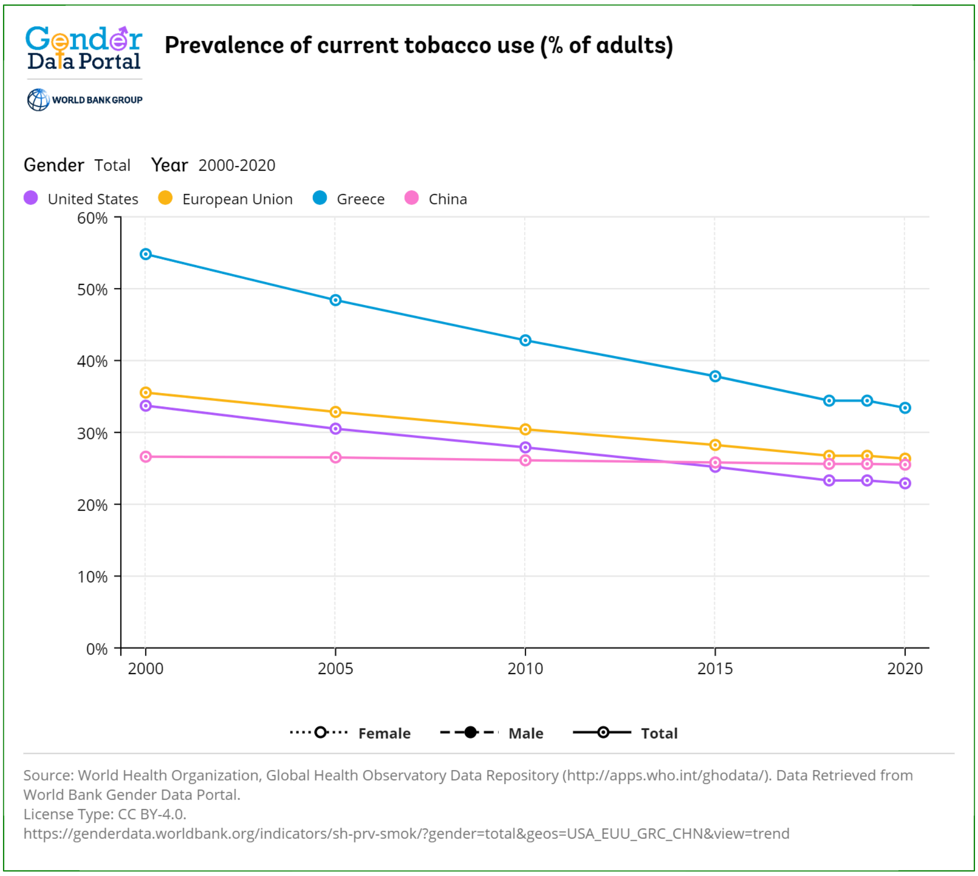
Figure 1.4 Incidence of Lower Respiratory Infections per 100,000 people, both sexes, 1990-2019, for Greece, European Region, the United States of America and China



Data from Global Burden of Disease, IHME (Accessed 13/11/2023)

Though people might have changed some of their lifestyle habits, the smoking of tobacco or non-tobacco products still forms a great concern for the health research community, despite the decrease of prevalence of total users (both sexes) in Greece, European Union, the United States of America and China (Figure 1.5). Vape products or electronic cigarettes may not pose the same danger to consumers' lung health like classic cigarettes but they seem to have a potential negative effect on people's addiction to nicotine and consequently the use of tobacco products (Schivo M. et al. 2014, Seiler-Ramadas R. et al. 2021).

Figure 1.5 Prevalence of current tobacco use (% of adults), 2000-2020, for Greece, U.S.A., European Union and China

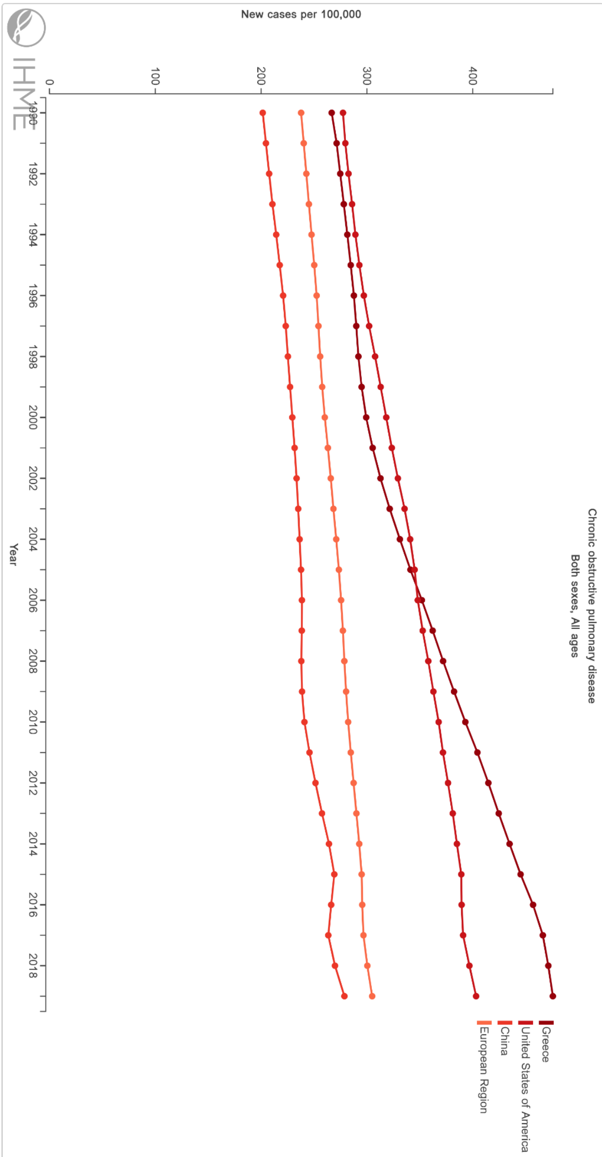


Among the chronic respiratory diseases in 2019, that have a great impact in people's health, COPD was the first, and only chronic pulmonary condition, in prevalence rate per 100,000, in Greece (6,360.71 cases) and China (3,175.37 cases), and second in United States of America (6,143.06 cases) and European Region (4,434.12 cases). Though chronic respiratory diseases remain low in the list of non-communicable diseases, it seems that there is an elevated tension over the last decades (Figure 1.6, 1.7).

The incidence and prevalence of chronic lower respiratory tract diseases vary among different regions, populations, ages and sexes. In idiopathic Pulmonary Fibrosis, studies show ambivalent results, where the incidence and prevalence were either greater or lower in Asian countries than in Europe (ranging from 0.09 to 1.30 and 0.30-4.50 per 10,000, respectively) and safe conclusions for the etiology of data differentiation, cannot be drawn (Maher TM et al. 2021, Hutchinson J et al. 2015).

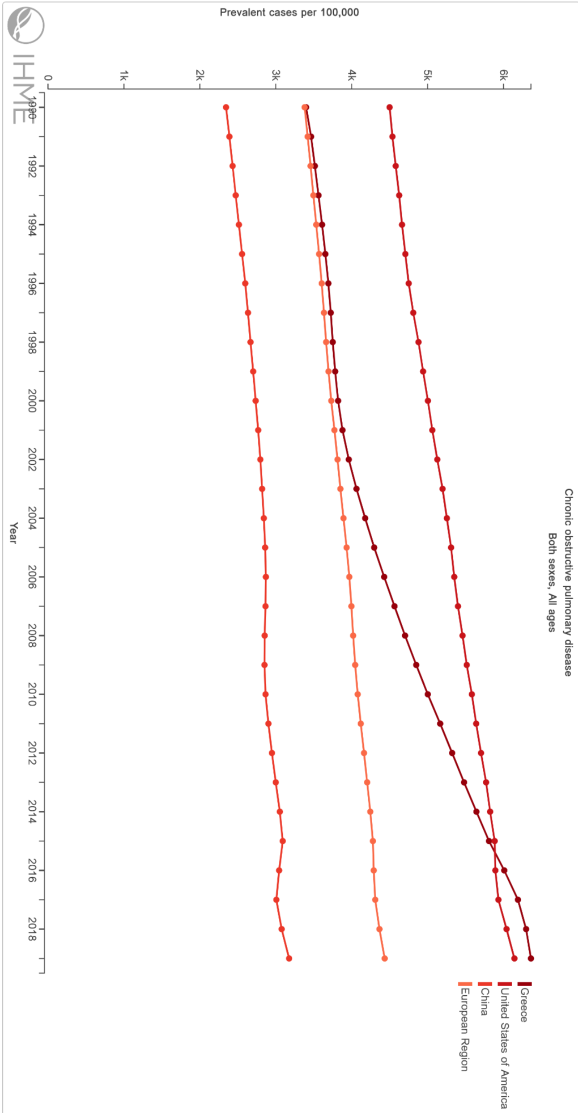
Apart from regional differences, it seems that age, sex and income characteristics play a significant role in the onset of a chronic pulmonary disease. In high-income countries, women populations and younger-aged people the prevalence of Chronic Obstructive Pulmonary Disease is far more decreased than in low-income countries, men populations and the elderly (Adeloye D et al. 2022). In 2019, in Southern Asian countries (Nepal, Bangladesh, India etc.), where the income of families is much lower than most of the Western countries, the prevalence of COPD was around 8.0-11.1% (Jarhyan P et al. 2022).

Figure 1.6 Incidence of Chronic obstructive pulmonary diseases, in Greece, U.S.A., China and European Region, for all ages, both sexes, 1990-2019



Global Burden of Disease, IHME, (Access: 12/11/2023)

Figure 1.7 Prevalence of Chronic obstructive pulmonary diseases, in Greece, U.S.A., China and European Region, for all ages, both sexes, 1990-2019



Global Burden of Disease, IHME, (Access: 12/11/2023)

Mortality rate

The evolution of chronic pulmonary diseases is directly affected by various factors like socioeconomic status, air pollution, or healthcare access. Research that was conducted in large urban centers of North America, Latin America, Europe, and China shows that even subtle elevations of air pollutants' levels in the atmosphere, like carbon monoxide (CO), ozone (O_3), particulate matter (large PM_{10}, and small $PM_{2.5}$), nitrogen oxides (NO_2, NO_X), and other particles, have a negative impact on the respiratory health of citizens and may contribute to a higher risk of mortality (Xu H. et al. 2022) from chronic lower respiratory tract diseases like COPD (Guo X. et al 2022, Bazyar J. et al 2019, Romieu I et al. 2012, Cortes TR et al. 2023).

Living with a chronic lung disease is very hard for patients due to the load of daily therapies in and out of hospital, as well as the burden of dealing with acute exacerbations. People who take in-hospital care for some time, they need to have a phase of rehabilitation in order to get back in their lives smoothly and restore their health to the former state. Rehabilitation might include 2 or 3 weekly sessions for a duration of some weeks or some months of breathing techniques like lip breathing, education about illness and medication management, psychological counseling, exercise training and nutritional counseling[3]. Rehabilitation practices that are implemented to people with chronic lung diseases have a great impact in the progress of the disease and mortality rate of patients. It seems that there is a doubtful decrease (pooled risk ratio 0.45 - 0.55) in relative risk for mortality for patients with COPD, who had been delivered rehabilitation (walking or cycling sessions, strength training, education) than those who had the standard care (follow-up by pulmonologist) (Puhan MA et al. 2005, Puhan MA et al. 2016, Ryrsø CK et al. 2018). On the contrary, patients with COPD who developed the frailty syndrome (age-related dysfunctions, dysregulations and deficiencies in several body systems like hormonal changes, insulin resistance, decrease of resting metabolic rate, strength and physical activity), had a raised mortality risk ratio of 4.21 than those who hadn't developed frailty syndrome (Verduri A et al. 2023, Xu J et al. 2023).

Chronic Obstructive Pulmonary Disease, Cystic Fibrosis, Sarcoidosis and other chronic lung diseases affect the organs of a patient in numerous ways. As a result of the different clinical manifestations, patients receive multiple symptom-relieving or curative medications and treatments that impede the progression of the disease. In research there is heterogeneity about the effect some drugs have on COPD-morbidity or all-cause mortality in COPD patients. There are ambiguous evidence that beta-blockers, which are given to heart conditions like atrial fibrillation, heart failure or angina, seem to have a protective effect on COPD mortality risk (0.69) (Etminan M et al. 2012, Gulea C et al. 2021). COPD exacerbations are characterized by intensive systemic inflammations that are related to short or

[3] National Heart, Lung and Blood Institute, Health Topic: Pulmonary Rehabilitation

long-term increased activation of platelets (Harrison MT et al. 2014). Antiplatelet therapy, especially aspirin, has seemingly decreased the mortality risk of patients with Ischemic Heart Disease comorbidity in COPD (Odds ratio OR 0.81; 95%CI 0.75-0.88) (Pavasini R et al. 2016).

Comorbidities, as mentioned before, play a significant role in the progression of chronic lung diseases. Cardiovascular diseases tend to coexist in patients with respiratory diseases. Anemia is a notable comorbidity in COPD, assumingly caused by the inhibition of erythropoiesis factors by inflammatory agents. Research demonstrated a significant correlation between the comorbidity of anemia and the in-hospital mortality of patients with COPD, compared to those without anemia (Rahimi-Rad MH et al. 2015, Xu Y et al. 2020).

Bronchiectasis is a disease that's usually manifested with similar or same clinical symptoms compared to patients with other chronic lung diseases like COPD or Cystic Fibrosis and that might lead clinicians to misdiagnosis. That's the reason why there is limited or unreliable evidence on the bronchiectasis-caused mortality rate in the population. Research shows an increased mortality hazard ratio in patients with bronchiectasis versus the patients without (adjusted Hazard ratio 1.20-3.40) (Henkle, E 2022), and it shows significant evidence that mortality risk is slightly increased in patients with Cystic Fibrosis-associated bronchiectasis compared to Non-CF associated bronchiectasis patients, when univariate (HR 0.565, 95%CI 0.424, 0.754, $p < 0.001$) and multivariate (HR 0.684, 95%CI 0.475, 0.985, $p = 0.041$) analysis were applied (Hayes D. et al, 2015). In Cystic Fibrosis, over the last decades the age-adjusted mortality risk has decreased to 1.10 per 1,000,000 from 1.9, and the median age shifted from 24 to 37 years old (Singh H. et al. 2023). Some of the major determinants of mortality are the decline rate of FEV1 (especially the predicted survival time for patients with FEV1<30 is 37 months), BMI under 19 kg/m2 and number of exacerbations (Silva, G.F. et al. 2020). The need for invasive ventilation and the yearly loss of FEV1 were directly and independently related to higher mortality in ICU-admitted CF patients, while ICU-mortality risk seems to be reduced (Texereau J. et al., 2006).

In the COVID-19 era, respiratory tract infections by sars-cov-2 have occupied the scientific community more than any other disease due to the severity of the disease, the widespread distribution of the virus (prevalence was 10,700 cases per million population by January 2021), the rise of ICU admissions, the elevated risk patients with comorbidities had (like cardiovascular diseases or cancer) (Saghazadeh A. et al, 2021), the mortality rate reached 4.4% by January 2021, and morbidity was around 2.1% of confirmed cases globally (Hanaei S. et al. 2021). Referring to chronic lung diseases, research shows that there is a heightened odds ratio for patients with COPD (Halpin DMG et al. 2022, Pardhan S et al. 2021) to ICU admission and mortality (age-adjusted OR 1.45-1.51) due to the Coronavirus Disease. Cystic Fibrosis patients are not severely affected by sars-cov-2 due to the genetic alterations and defective expression of some proteins (overproduction of ACE2 - Angiotensin-converting enzyme 2, reduced production of TMPRSS2 - Transmembrane protease, serine 2) of CF disease (Stanton BA et al. 2020, Mathew HR et al. 2021). However, transplant patients and patients with FEV1 less than 40% seem to be greatly affected by COVID (Terlizzi V et al. 2022) and have a greater admission or hospitalization or mortality rate than other lung transplant patients or Cystic Fibrosis patients (Carr SB et al. 2022).

Patients with chronic lung diseases are consistently affected by air particles, bacterial or viral or fungal infections, provoking serious inflammatory reactions that cause acute exacerbations and deterioration of their disease. Patients are frequently admitted to hospital care and are gradually, as they grow up, in need of more intensive and invasive treatments in order to get back to normal conditions, after rehabilitation. However, the aggregate result of exacerbations, readmissions and further exposure to unhealthy environments and habits, is an increased mortality risk and many lost years of life.

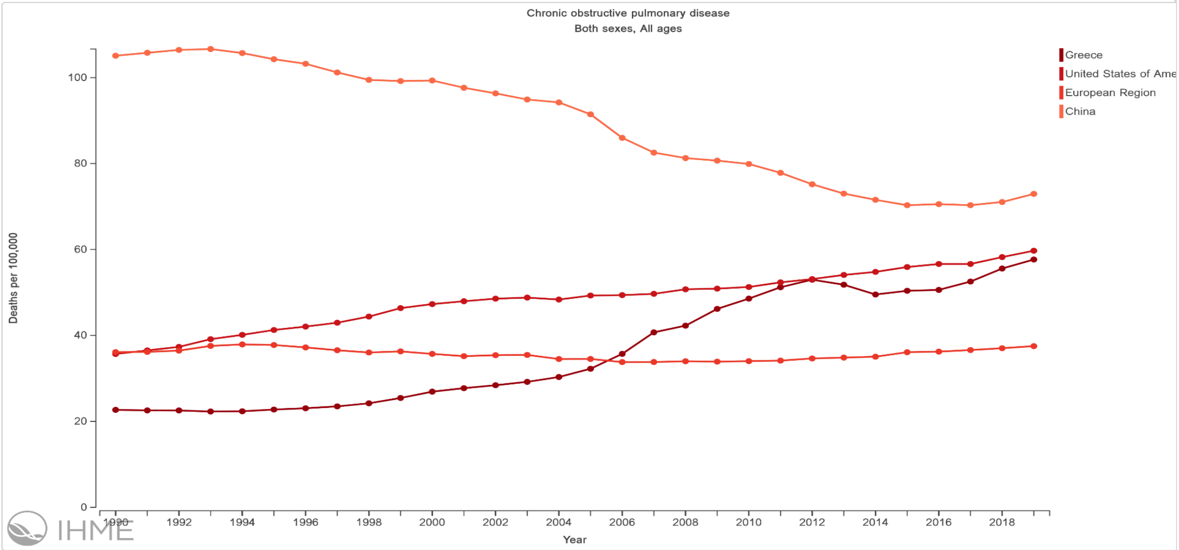
Table 1.3 Mortality Rate (per 1,000 citizens) for Chronic Lower Respiratory Diseases (J40-J47)* - standardized death rate by region, 2011-2020, both sexes and all ages

TIME	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
European Union - 27 countries (from 2020)	31.91	32.52	31.95	29.93	33	30.93	32.32	31.16	29.95	27.69
Germany	35.43	35.73	38.23	34.85	39.3	36.87	39.56	39.54	37.52	34.5
Greece	20.89	19.81	18.22	23.84	28.37	23.42	25.13	22.88	24.05	22.33

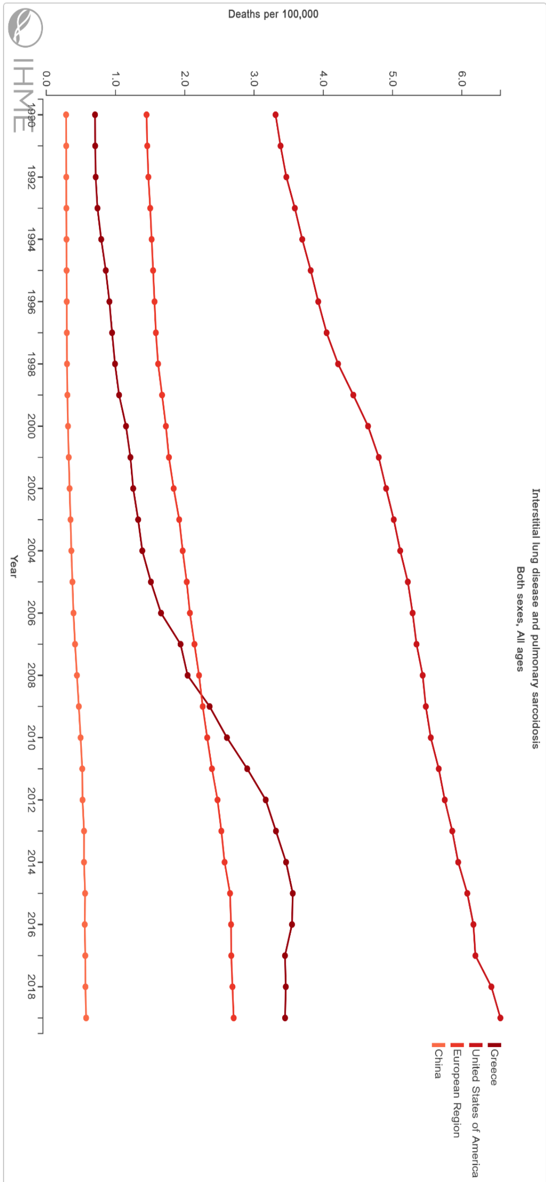
France	15.14	15.85	16.01	14.62	16.83	15.98	15.97	15.9	15.35	13.22
Netherlands	48.15	50.78	47.59	40.36	47.56	43.95	44.79	44.13	42.36	34.3
Eurostat Data Browser (Accessed 15/11/2023) *J40-J47: bronchitis, emphysema, COPD, asthma, bronchiectasis, chronic lung allograft dysfunction										

Figure 1.8 Mortality Rate of Chronic Respiratory Diseases, (A) COPD, and (B) Interstitial lung disease and pulmonary sarcoidosis, 1990-2019, both sexes, all ages, data for China, European Region, U.S.A. and Greece

A



B



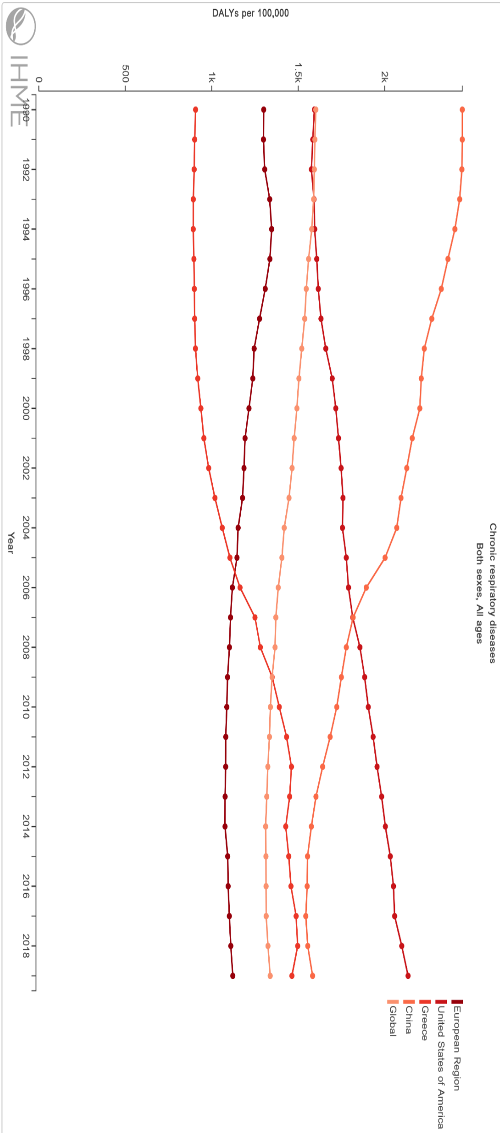
Data from Global Burden of Disease, IHME (Accessed 16/11/2023)

Quality of Life

From 1990 until 2017, globally, there was an increase in DALY's (85,701,654 - 103,533,107 DALY's) due to chronic lung diseases, which relies mostly on the rise of years of life lost (65,388,505 - 71,145,744 YLLs) by premature mortality. In contrast with the rate of global DALY's due to chronic respiratory diseases that was reduced to a small degree (1,601.95 - 1,338.08 DALY's per 100,000) (Figure 1.9). Especially in South Asia, it was noticed that the rate of years of life lost due to COPD were

1567 per 100,000 people compared to the years lived with a disability that were 640 per 100,000 (GBD Chronic Respiratory Disease Collaborators, 2020).

Figure 1.9 DALY's per 100,000 for Chronic Respiratory Diseases, both sexes, all ages, data for European Region, U.S.A. Greece, China and Global, 1990-2019



Data from Global Burden of Disease, IHME (Accessed 23/11/2023)

Evaluating the health-related quality of life in patients through metrics that measure the years lived with a particular disease or disability, or the years lost due to premature mortality resulting from a fatal disease, proves to be an approach whose representational accuracy is limited. Consequently, such assessments are often regarded as lacking in generalizability, as they may not comprehensively encapsulate the elaborate and multifaceted aspects in the overall well-being of individuals dealing with complex health conditions. There are many questionnaires or scores that are used by researchers, scientists and on-field clinicians to evaluate the quality of life of patients. Some of them, are:

- St. George's Respiratory Questionnaire (SGRQ), it's a 50-item tool for evaluation of obstructive airway diseases' symptoms, impact on patients' daily life and activity (Jones PW et al. 1992, Barr JT et al. 2000)
- COPD Assessment Test (CAT), it's a short 8-item questionnaire, that is specifically designed for the evaluation of HRQL of COPD patients and its use is opted out in hospital settings (Ayora AF et al. 2019)
- Chronic Respiratory Disease Questionnaire (CRQ), similarly this questionnaire was created for the assessment of HRQL in chronic respiratory diseases (Chauvin A et al. 2008)
- King's Brief Interstitial Lung Disease (KBILD) questionnaire, is intended to assess the HRQL of patients with Interstitial Disease and those with Idiopathic Pulmonary Fibrosis (Nolan CM et al. 2019)
- Leicester Cough Questionnaire (LCQ), is a tool used to assess the impact that chronic cough has on patients' social life, physical and mental health (Nguyen AM et al. 2022)
- Quality of Life-Bronchiectasis (QOL-B), is a self-reported assessment 37-item tool to evaluate the HRQL of patients with non-cystic fibrosis Bronchiectasis, that is suitable for clinical trials and daily medical practice (Quittner AL et al. 2015)
- Cystic Fibrosis Questionnaire-Revised (CFQ-R), it is a Cystic Fibrosis patients-specific evaluation tool for the measurement of HRQL (Quittner AL et al. 2009)

Health-Related Quality of Life (HRQoL) questionnaires and scoring systems have been employed by researchers and patients for diverse objectives. Scientists utilize them as predictive tools and indicators to measure the progression of diseases, contributing in the strategic allocation of resources. On the other hand, patients utilize these instruments as a means of expressing and explaining their preferences regarding the impact that various treatments, medications, and clinical interventions have on their lives, well-being, and engagement in social and economic activities. The utilization of self-administered questionnaires introduces a level of complexity, raising critical considerations about the subjectivity in responses and the perplexed interpretation of answers. Due to the diverse origins and profiles of the patient population, this complexity necessitates a more defined strategy in order to account for these individual differences in perception and experience (Mooney A. 2006). The optimal scope of these questionnaires is apparently to Identify the high and low-quality of life cases, in order to intervene medically, psychologically and socially, prevent the progression of the disease by detecting changes, or prioritize the distribution of resources and funds by classifying the needs of the population (Oga T et al. 2018).

As it was previously mentioned, many patients living with chronic respiratory diseases do not suffer only from one but more than one disease (either of the same organ or another, like the heart). Research shows that people from low-income communities and countries (low socio-economic status), who have poor health status or are elderly, are more likely to develop more than one disease (Laires P.A. et al. 2019). Over the last decades, the strategies and public health policies that the governments have implemented, were focused on overcoming an epidemic or a specific disease rather than dealing with comorbidities or multimorbidities. Multimorbid patients afflicted with chronic lung diseases often contend with an array of additional conditions, including ischemic heart disease, diabetes mellitus, dilated cardiomyopathy, as well as coexisting pulmonary conditions such as bronchiectasis, asthma, and interstitial lung disease. The intricate interplay of these concurrent health states not only amplifies the complexity of their medical condition but also stresses the perplexities inherent in diagnosing and implementing effective treatment strategies (Ekezie W et al. 2021). Multimorbidities have common risk factors like unhealthy eating habits, smoking tobacco, the use of alcohol, and physical inactivity and appear to have similar clinical manifestations, in contrast with comorbidities that are strictly distinguished (Afshar S. et al. 2017). The aggregate result of dealing with many severe health conditions, comorbidities, or multimorbidities, as well as many unhealthy environmental and personal habits, may lead to lower physical capacity like lung functioning (low levels of FEV1 or FVC) or mental disorders. As the disease(s) worsen over time, that will directly affect the quality of life of patients with chronic lung diseases, like COPD, and it will deteriorate the expression of symptoms and increase the effort patients need to put into their activities and rehabilitation (Adhikari TB et al. 2021).

Patients with Chronic Lung Diseases might continuously have a feeling of unease, anxiety and sadness due to the heavy load of dealing with a progressive disease, that is not getting better despite all the pressure, hard work and activities they might do. Everyday's daily routine of physical exercise, time-consuming treatments, side effects of medications (like hypertension or tachycardia caused by beta agonists-bronchodilators or hypotension and bronchoconstriction due to beta blockers that are given to multimorbid patients with heart conditions for tachycardia and hypertension (Farzam K et al. 2023, Sears MR 2002)), limitations in social activities and socializing due to fear of contracting viruses or bacteria that might cause acute respiratory infections, symptoms of disease like cough, dyspnoea, or sleep disorders, demand great amounts of energy for commitment and full engagement to therapy (Koslow, M. et al. 2021). Dyspnoea is one of the most annoying symptoms in COPD patients, causing them to refrain themselves from their activities (Farag T.S. et al. 2018). Exerting a significant amount of energy on routine tasks such as preparing for work or going to school or just for a walk, may prove excessively fatiguing for patients with chronic lung diseases, thereby inevitably compromising their overall quality of life.

Living with a chronic lung disease might be a heavy burden that permanently and deeply affects patients in a multifaceted way, since their young age. The persistent symptoms, long-term treatments and rehabilitation therapies impede them from having a “normal” and “easy” life. It might be difficult for patients to endeavor to manage their health condition, but it is not a generalizable conclusion. Research shows that patients dealing with severe diseases like Cystic Fibrosis demonstrate an unexpected capacity to confront their stressful and painful events that might have traumatized them (Niehammer U. et al 2023). Given the progressive deterioration of chronic lung diseases, the stigmatization of patients by society, and the constant and appalling contemplation of mortality might not be the only reasons affecting the health-related quality of life of patients, but have a substantial effect on their lives.

1.2 Transplantation

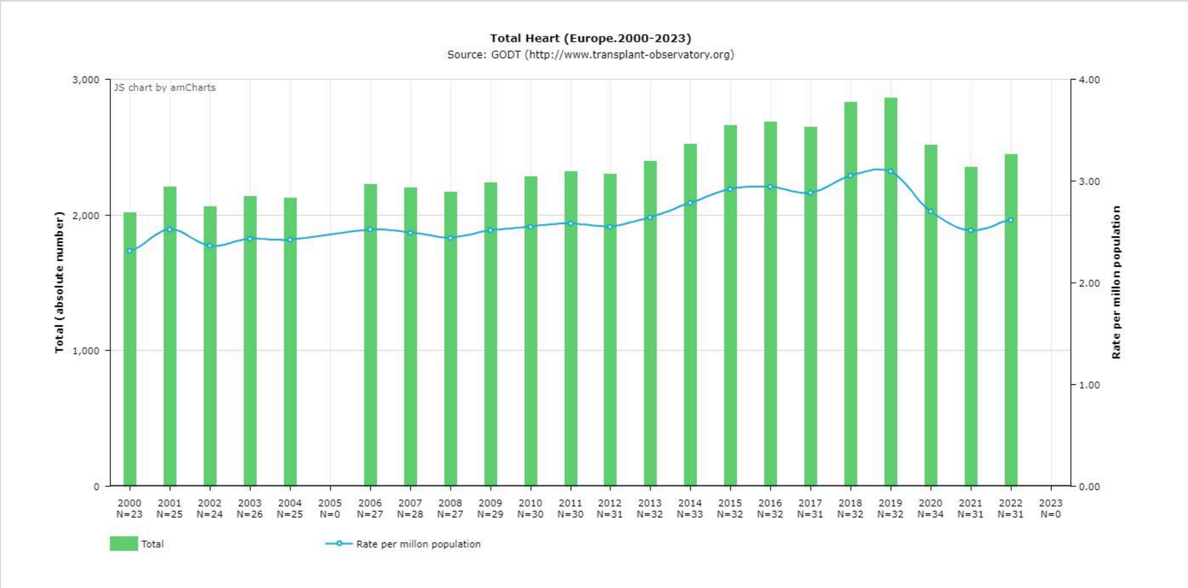
It's more than a gift, it's life that you give to people who lost it

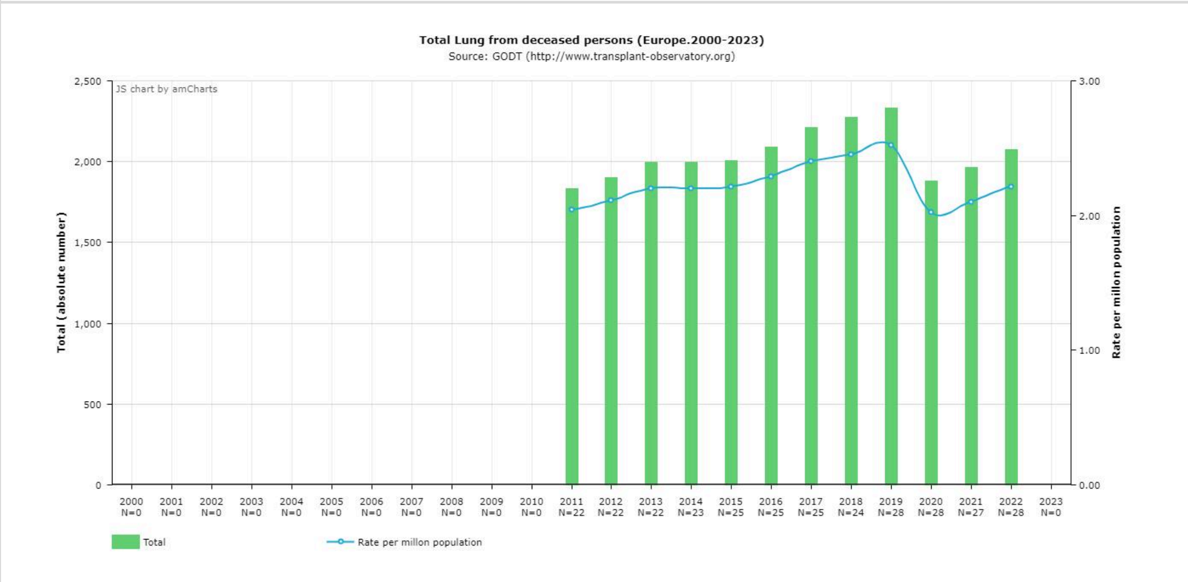
Originating from the Latin word “transplantare”, a conjugation of two words, trans-, that means across and -plantare, to plant somewhere. To plant somewhere else, to relocate something, first used for plants and since the 2nd millennium BC, through tradition and folklore stories and evidence, it has been used for humans too, especially and mainly for skin grafting. In the 1950s, after the industrial revolution and innovative use and exploitation of electric power and energy, the first solid organ transplants occurred, first transplanting kidneys for patients with renal failure, in 1954. Since 1960, other great successful (or not) transplant surgeries have taken place around the globe, like lung in Mississippi (Venuta F et al 2017), liver in Colorado (Starzl TE et al. 1982) and heart in Cape Town (Brink JG et al. 2009, Nordham KD et al 2021).

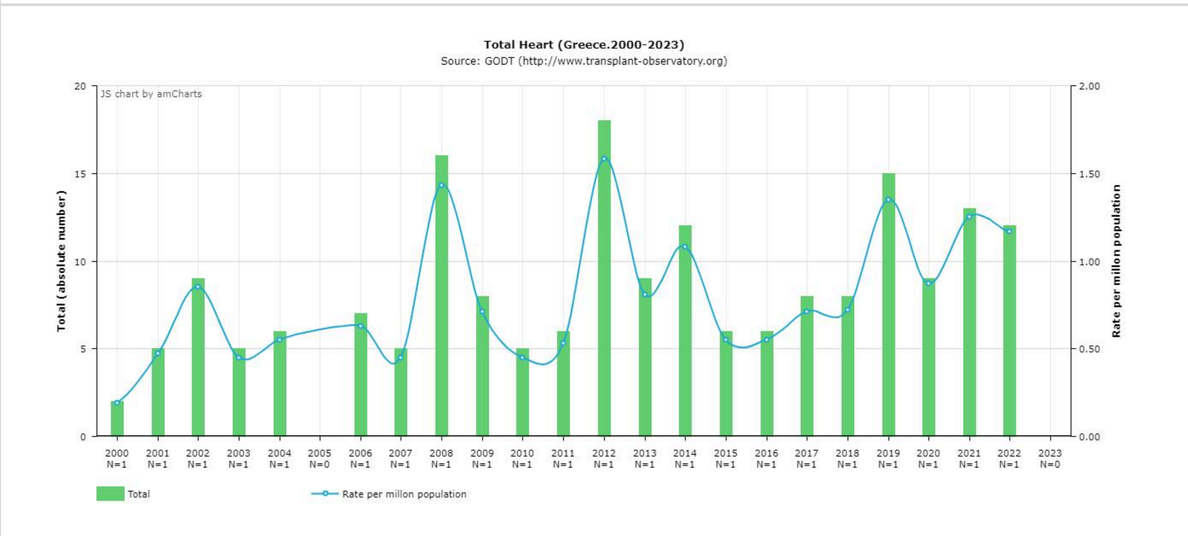
Over the last few decades, due to the radical transformation in the field of data and information mining, storing, editing, analyzing and transferring, there has been a significant increase in organ transplantations. In 2021, there were 144,302 solid organ transplants, yet this number represents just a fraction (around 10%) of the global demand. The United States of America and Spain emerged as the leading countries in organ donation by deceased brain donors or deceased donors by circulatory criteria (approximately 40 people per million population). Despite facing a significant decrease in contributions (~13%) during the year 2020, as a consequence of the widespread impact of COVID-19 pandemic (Nimmo A et al.2022), there was an 11% rebound in 2021. The age range exhibiting the highest amount of organ donations was 18–59, with an astonishing gradual rise during the past years in donations by the age group of over 59. In 2021, in the USA and Spain, kidney graft was the most transplanted organ (around 60% of total donations), followed by the liver (around 22%), the heart (around 7-10%) and the lung (around 5%)[4].

Figure 1.10 Heart and Lung Transplantations in Europe and Greece, 2000 - 2023 Data from Transplant Observatory

[4] Data from International Reports 2016-2021 on Organ Donation and Transplantation Activities, by Global Observatory on Organ Donation and Transplantation (GODT), produced by the WHO-ONT collaboration


Total Heart (Europe.2000-2023)
Source: GODT (http://www.transplant-observatory.org)
JS chart by amCharts
Total (absolute number)
Rate per millon population
2000 N=23
2001 N=25
2002 N=24
2003 N=26
2004 N=25
2005 N=0
2006 N=27
2007 N=28
2008 N=27
2009 N=29
2010 N=30
2011 N=30
2012 N=31
2013 N=32
2014 N=33
2015 N=32
2016 N=32
2017 N=31
2018 N=32
2019 N=32
2020 N=34
2021 N=31
2022 N=31
2023 N=0
Total
Rate per millon population


Total Lung from deceased persons (Europe.2000-2023)
Source: GODT (http://www.transplant-observatory.org)
JS chart by amCharts
Total (absolute number)
Rate per millon population
2000 N=0
2001 N=0
2002 N=0
2003 N=0
2004 N=0
2005 N=0
2006 N=0
2007 N=0
2008 N=0
2009 N=0
2010 N=0
2011 N=22
2012 N=22
2013 N=22
2014 N=23
2015 N=25
2016 N=25
2017 N=25
2018 N=24
2019 N=28
2020 N=28
2021 N=27
2022 N=28
2023 N=0
Total
Rate per millon population


Total Heart (Greece.2000-2023)
Source: GODT (http://www.transplant-observatory.org)
JS chart by amCharts
Total (absolute number)
Rate per millon population
2000 N=1
2001 N=1
2002 N=1
2003 N=1
2004 N=1
2005 N=0
2006 N=1
2007 N=1
2008 N=1
2009 N=1
2010 N=1
2011 N=1
2012 N=1
2013 N=1
2014 N=1
2015 N=1
2016 N=1
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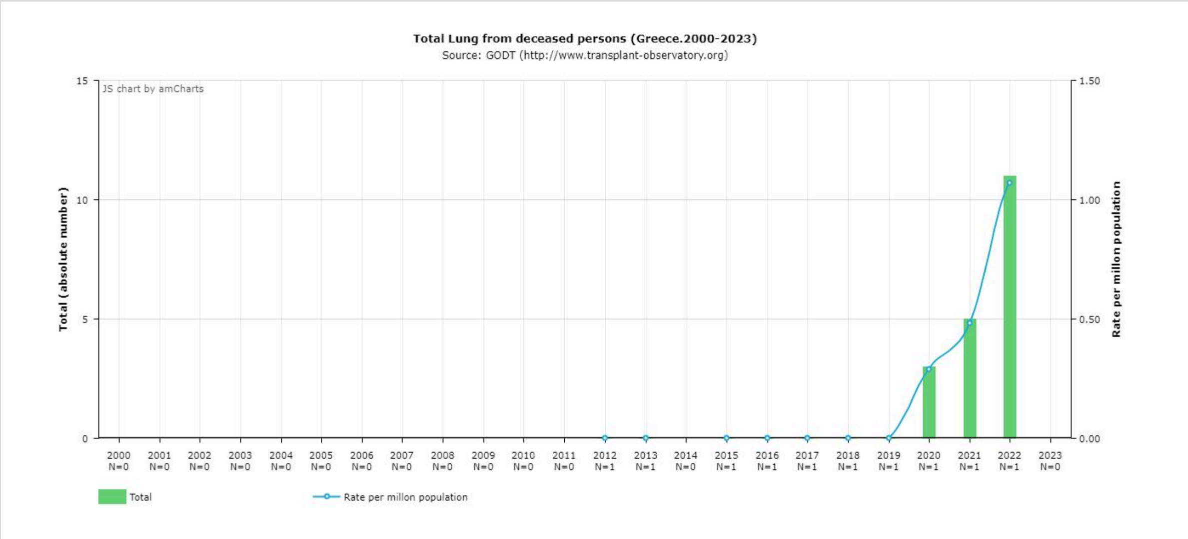
2018 N=1
2019 N=1
2020 N=1
2021 N=1
2022 N=1
2023 N=0
Total
Rate per millon population



1.2.1 Legal Acts and Guidelines in Greece, Europe and Internationally

Transplantation is a complicated procedure, requiring multidisciplinary knowledge and expertise, well-informed staff, including doctors, nurses, social workers, psychologists, and local transplant coordinators, advanced medical and technological equipment, infrastructure with sufficient properties, and obviously effectively promoting social awareness about organ donation and transplantation among the population. Since transplantation is a dual process involving both the donor and the recipient, many steps are required. It starts with the vital task of local, national and international boards to educate the public about organ donation, continues with the careful performance of operative procedures, and ends up with a comprehensive post-transplant patient follow-up care. To guarantee that everything goes well and produces successful outcomes, each of these stages must be done with caution, inside a strong legal framework, and subject to stringent safety audits.

Since 1980, there have been many efforts, globally, to harmonize the methods for the brain death determination. It's certain that the guidelines created by the American Academy of Neurology were a major influence for international scientific society (Citerio G et al. 2014). In Greece, by decision No. 9/20.03.1985 of the Hellenic Central Board of Health, the diagnosis of brain death or death by neurological criteria focuses on clinical examinations of brain stem functionality (brain stem reflexes testing) and apnea testing, in patients being in coma and having a severe brain damage, while laboratory testing like intracranial blood flow or electroencephalogram (EEG) is not considered a prerequisite or of any importance in the certification of brain death. Ancillary tests (such as electroencephalograms, angiography, etc.) are required in several nations, such as the Netherlands and Italy, to officially declare a person neurologically dead. The lack of technical skills and expertise by the operators and the increased frequency of false-positive and false-negative results are the main points of contention among scientists about the use of complementary testing for brain death certification (Robbins NM et al. 2018).

In Europe, there is a certain unevenness in regulations and guidelines concerning transplantation, donation of organs or determination of brain death. The Oviedo Convention on Human Rights and Biomedicine (ETS No 164) is the only internationally and legally recognized tool that protects and secures the rights and dignity of human beings in the biomedical field. Specifically, the Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin (ETS No. 186), that took effect in 2006, whose goal was the unification of laws regulating transplantation procedures, deceased or living donation, transport of organs, prohibition of financial gain, etc. across the members of European union (Lopp, L. 2013).

The establishment of the first National Transplantation Organization in Greece in 1999 (Law No 2737/1999), which was formed and recognized by the state, marked a significant change in the country's legal system's alignment with worldwide standards. Since 2011, Greece’s legal framework on organ and tissue transplantation was harmonized with the Directive 2010/53/EE of the European Parliament, which regulates the donation, preservation, transfer and transplantation of organs (neither auto transplantations, blood transfusions nor transfer of reproductive cells) (Law No 3984/2011). With the law 3984, two national registries in Greece were formed under the "opting in" system of organ donation: one for willing donors who consent to have their organs donated post mortem, and another for those who would like to be opted out of organ donation. In Law No 4512/2018 Article 260 it referred to the use of a “donor card”, that is an official proof of the person’s agreement with the NTO to donate their organs after death. The Regulation No. 5034/2023 is the most recent regulation that aims to harmonize the Greek legal framework with European laws concerning transplantations and organ donations.

In the USA, there are 56 Organ Procurement Organizations (OPO’s) that are fully responsible for the allocation, registration, information of people and organ donation of U.S. citizens. The federal Agency that audits the functions of OPO's are the Centers for Medicare & Medicaid Services (CMS). The United Network for Organ Sharing (UNOS) is another non-profit, "umbrella" organization, which aims to provide with the proper help, inquiries and expertise to facilitate the work of OPO's. Its main success was the establishment of a common network, the Organ Procurement and Transplantation Network (OPTN), a platform where OPO's connect with each other and share valuable information. In 1968, the first Uniform Anatomical Gift Act (UAGA) was enacted- the last update in 2006-, for the official banning on the sale of organs across States. In 1984, the Congress put into effect the National Organ Transplant Act (NOTA), which regulated the equal distribution of organs and in 1987 the Scientific Registry of Transplant Recipients (SRTR) was found, to keep in track with the organ recipients, the statistics concerning transplantations and follow-up metrics. A more broadly effective law about the protection of human beings in scientific experiments that has a definite impact on transplantations, is the Common Rule, that passed in 1991 and was updated in 2018 as the final rule (Federal policy for the protection of human subjects. Federal Register. 12. Vol. 82. 2017, pp. 7149–7274)[5] (Paganafanador, B 2017, Block, W.E. et al. 2019).

1.2.2 Organ Donation

Societies across the world deal with many serious problems like famine, water drainage, climate change, natural disasters, poverty, infectious and non-communicable diseases, criminality, and last but not least, a shortage of organ donors. Sometimes, transplantation constitutes the sole resolution to various critical health situations (as mentioned in subchapter 1.1), but clinicians and health authorities face an enormous hurdle: the limited number of organ donors (living or deceased) in contrast with the great demand.

When a person is taken to the ICU, after a severe crush or a heart attack, there are plenty of deterioration stages before being considered as a possible organ donor. It's not of any concern or ambiguity that healthcare professionals will do their best to keep the patient alive and ameliorate his/her health condition, through several evaluations and interventions in order to stabilize the vitals. When the signs indicate possible irreversible cardiac or brain death, then several tests and exams will be

[5] National Academies of Sciences, Engineering, and Medicine, *Legal, Regulatory, and Policy Frameworks for Organ Donation and Research Participation*, 2017

followed, to assess the patient's brain stem functions. If the clinicians certify the patient's brain or cardiac death (in the case of cardiac death, brain death will be expected in the next 72 hours, according to various national legal frameworks), then the patient's clinical history and physical integrity are examined in order to identify if the patient is a potential organ donor (Domínguez-Gil B 2021). Organ donation occurs when certain health criteria and legal prerequisites are met. Donors are classified as living or deceased donors. There are major differences among them that distinct the way health care professionals, transplant coordinators or even relatives behave. Deceased donation is further divided into donation after brain death (or death by neurological criteria) (DBD) and donation after determination of death by circulatory criteria (DCD). DCD is subdivided into four categories, according to Maastricht classification (Domínguez-Gil B 2021):

- Category I: found dead, uncontrolled, unexpected cardiac arrest, in or out of hospital
- Category II: witnessed, uncontrolled cardiac arrest, in or out of hospital
- Category III: controlled Withdrawal of Life-Sustaining Therapy (WLST)
- Category IV: controlled or uncontrolled cardiac arrest after brain death

Being a living or deceased organ donor constitutes a multifaceted and difficult decision that has to be made, whether by the living person or by the dead person's relatives and loved ones. Various cultural backgrounds, personal religious beliefs, political ideologies, or restrictions imposed by powerful, leading figures with societal influence and pressure are some of the numerous factors that play a significant role in the decision-making process of becoming an organ donor. Additionally, organ donation is highly related with the qualification and expertise of medical staff or transplantation coordinators, the presence of sufficient medical equipment or supplied infrastructures and the legal framework that regulates the donation of a local/national region. Health care professionals' attitude towards transplantation procedures has a great impact on people's belief on organ donation, because health care professionals participate in several intermediate processes like the pair matching, the approach of family to obtain consent, the recognition of a possible donor and the information of the public (Jawoniyi O et al. 2018). It's assumed that such a complicated system needs some measures in order to alleviate the shortage of donors and facilitate the procedures. These measures that might take the form of incentives, should be either addressed to the political and health system of a nation or to the society and every individual. There are three incentive models that prevail in the world (Fan, R. 2023):

- The *Liberal model*, a fully altruistic-centered model with no monetary or other beneficial motives, is run by most western countries.
- The *Compensationalist model* for living kidney donors, that is run by the Islamic Republic of Iran and the donor is reimbursed by the state and the recipient
- The *Familist model*, which was first introduced by Israel and then by China. It assigns a priority to the waiting list of potential recipients based on their relatives' registration in the organ donor registry, their own registration, or the past organ donation events of their relatives.

When a person makes the decision to be a willing donor, while still being alive, it’s fairly questioned if they truly recognise and acknowledge the meaning of transplantation and organ donation, before signing a “contract” or a consent form. In some countries and regions of the world, as it was mentioned in section 1.2.1, there are opt-out models, where the consent of the patient is presumed to be positive, while the opinion and consent of family and relatives is inquired. Over the last decades, there have been either far authoritarian theoretical models (routine salvaging (MacDonald H. 2015)) or far liberal models (encouraged voluntarism (Caplan A. 2014) in the USA since 1968) regarding organ donation (Fox, M.D et al. 2013).

Organ donation shouldn’t be characterized as a merely altruistic act due to its lack of self-gain or self-benefit. Altruism relies on the notions of caring about somebody else’s well-being and being completely indifferent about self-benefit or even self-sacrifice for others. In deceased organ donation, there is no benefit after all or self-gain after death, in contrast with living organ donation, where the person is clearly overwhelmed by a relentless feeling of giving life to others and benefiting them through sharing vital organs and self-sacrificing health stability. Therefore, it’s probably a feeling of solidarity rather than altruism that perfectly matches the act of

donation and should be treated and reinforced accordingly. Measures that should protect one's body autonomy and at the same time would help improve the organ shortage crisis, would definitely have a great impact on society (Aurenque D. 2016).
In literature and transplantation conferences, there is an issue promptly arising and broadly communicated, provoking the interest of the scientific, health, political, and societal worlds, and that is xenotransplantation. It can be briefly described as a process where animals are nurtured with the purpose of receiving their cells, tissues, or organs and allocating them to people in need, patients with organ failure, etc. Obviously, there are plenty of ethical considerations rising concerning the safety of xenografts, the spread of zoonotic diseases (additionally, transplant patients are in immunosuppression therapy), the exploitation of animals for the sole use of an organ, while livestock farming will increase, and the uncertainty of health outcomes and efficiency of a xenotransplantation compared to a human allograft transplantation that is based on many years of successful cases (Assadi G., et al. 2016, Reichardt JO. 2016).

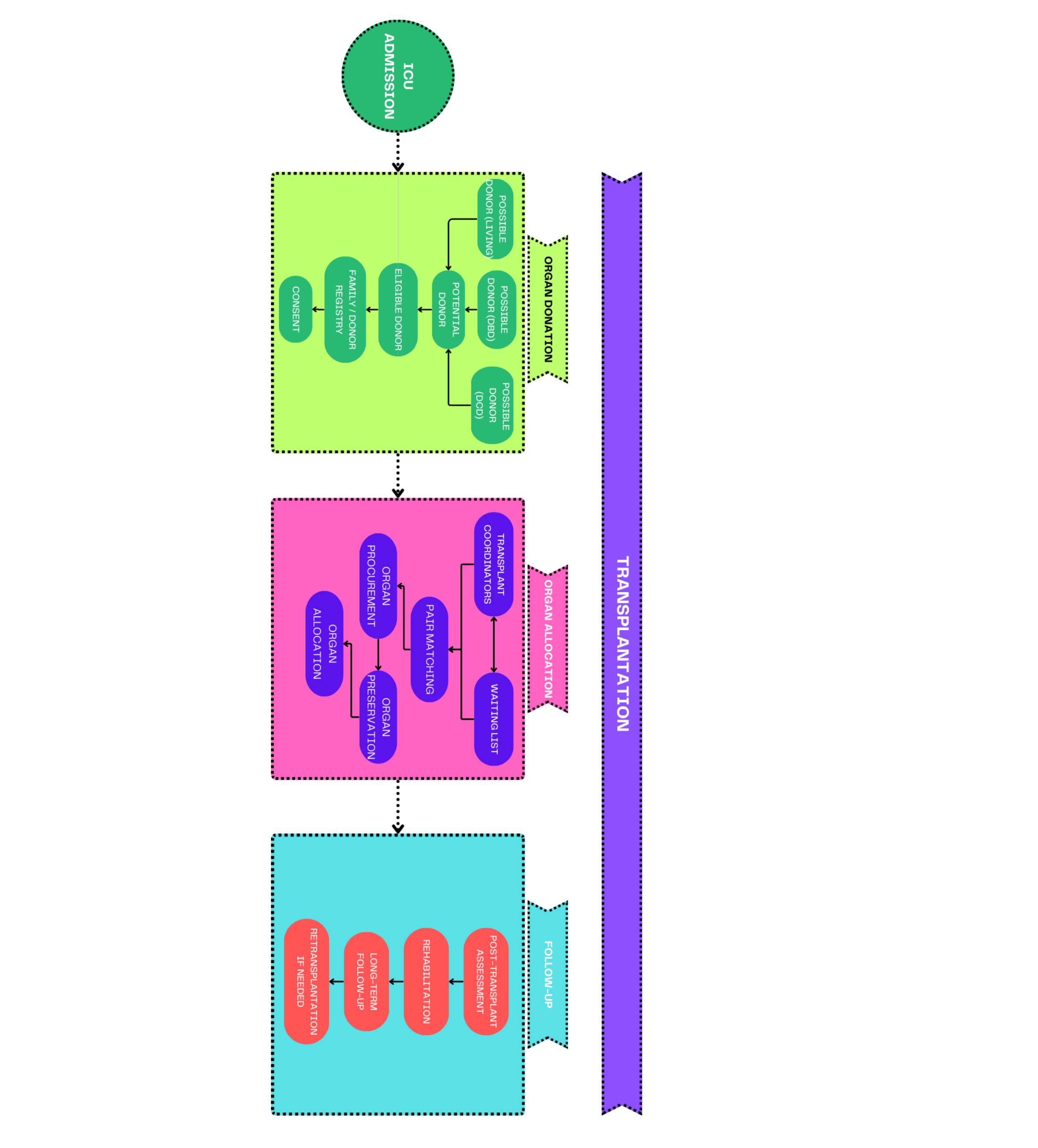
1.2.3 Transplant Procedure

According to Euro transplant Statistics Yearly overview of 2022, the most transplanted organ by deceased donors was kidney (n=2991) , followed by liver (n=1507), lungs (n=1176), heart (n=644) and pancreas (n=114). Transplanting an organ is not an easy procedure, given the variety of stages, the options to be chosen, the decision to be made, the cooperation of multidisciplinary healthcare professionals and administrative agents, and the interaction of different transplant centers, authorities, and people. Starting from the receiving of organs from moribund, deceased, or living patients, the allocation, and finally the post-transplant follow-up of the recipient, as indicated in the figure 1.11, there are several tasks to be completed. When a patient in a coma state is admitted to the ICU with a severe brain injury or un/controlled cardiac arrest (Glasgow Coma Scale score 3), he or she may be considered a possible donor after the clinical and neurological evaluation. When the main neurological brain reflexes are examined thoroughly and/or followed by ancillary tests and exams, the nurse or entatician in command of transplants will inform the local transplant coordinator to enact the transplantation process, including inquiring the family or searching the national donor registries to find the patient's agreement for donating his or her organs post-mortem (Moura LC et al. 2015).

Organ preservation

The preservation of organs, a crucial stage of transplantation process that is strictly adhered to, augments the survival of grafts, renders an effective transplantation, and so far various techniques have been followed according to the diversity of cases and causes of death. Though two kinds of preservation techniques are indicated, the static cold storage (SCS) and the machine perfusion (MP) in different temperatures. Normothermic machine perfusion, a mechanical flux of the perfusate solution, enriched with nutrients and oxygen (necessary in normothermic MP, in contrast with sub-normothermic MP) is a suitable technique for the preservation of organs for hours before and after their recovery from the donor (de Vries RJ et al. 2019). Warm Ischemic injuries and metabolic-energy deposits exhaustion in organs originated by circulatory associated deceased donors (DCD), are of paramount importance to monitor and eliminate, due to the great negative impact they have on survival of grafts.

Figure 1.11 Flowchart of Transplantation procedures



It seems that the implementation of machine perfusion and static cold storage (the leading technique in organ preservation and reconditioning (Bellini MI et al. 2023)) can essentially eliminate the detriment of transplants, while measuring biomarkers that can predict the viability of organs in advance. Such biomarkers are lactate concentrations in the heart graft perfusate and inflammatory mediators interleukins 1 or 8 in the lung perfusate or bronchoalveolar lavage (Resch T et al. 2020). Preserving organs seems that it ameliorates the outcome of transplantation long term, by reversing some of the injuries that the organs have suffered, decreasing the level of immunocytes and inflammatory agents in organs allocated from Extended

Criteria Donors (ECD), illustrating the significant impact of these techniques on transplants shortage crisis (Kvietkauskas M et al. 2020).

Selection of Recipient - Pair Matching

Waiting for a transplant might be a time-consuming and long-lasting procedure that tires patients, and consequently, their health deteriorates, resulting in a high rate of death (around 38–54% for lung-related diseases) (De Meester J et al. 2001). A patient with heart failure, may be disqualified from transplantation due to a number of health comorbidities, such as diabetes, liver or renal impairment, infectious infections, or anemia, because of the low post-transplant survival rate (Mantha A et al. 2022). Conversely, organ donors with less than ideal clinical histories—such as history of drug use, positive serology for hepatitis C, or left ventricular hypertrophy—may be selected for organ donation, as an alternative to the global organ shortage issue; these donors would then be paired with recipients who, despite the graft's state, are in dire need of a transplant because of a high prognosis of mortality due to the deterioration of their underlying disease (Resch T et al. 2020, table 4). Due to a small variance existing in the referral protocols and guidelines that are applied in the process of pre-selection and placement of patients on the waiting list, in each country, the prioritization of patients might be slightly different. However, there are some common criteria and key points:

For heart transplant referral,

- VO_2 max < 14 mL/min per kg
- the weak ejection fraction (<20%)
- NYHA class III to IV
- increasing requirement for diuretics due to enduring fluid overload
- low blood pressure

For lung transplant referral,

- the increased frequency of exacerbations
- the increased hospital visits
- the low forced expiratory volume (FEV1 < 30%)
- the high partial pressure of carbon dioxide (PaCO2 > 50 mmHg)

- the low partial pressure of oxygen (PaO2 < 55 mmHg)

which are strongly associated with the prognosis of mortality in patients with lung or heart diseases and who are therefore referred for transplantation (Verleden GM et al. 2017, de Jonge N et al. 2021).

Pair Matching

Relocating an organ requires a thorough investigation of the available recipient pool to find the appropriate and suitable matching profile. A perfect match suggests that the recipient will have a high survival rate in the years following the transplantation. However, sometimes, due to the urgency of a case, neither the list priority nor the criteria and guidelines are complied with. In heart and lung transplantations, the survival of recipients is contingent on certain donor-recipient features and variables, which are the sex, the age, the predicted total lung capacity, the predicted total heart mass, the cytomegalovirus serology, and the blood type. In lung transplantation, a gender or age mismatch seems to have a great impact on the recipient's survival due to the variance of predicted TLC values and the graft's condition. Lungs originating from women, thus the values of pTLC are lower than the median, and transplanted into men result in low late survival (5 or 10 years). Likewise, predicted total Heart Mass (pHM) is a strong prognosis factor, predicting the survival of a transplant patient depending on the size of the heart graft received by the donor. Conversely, a blood type identity mismatch but compatibility and CMV serology positivity seem to have not such a grave outcome.
Studies show that donor-recipient organ size matching is an essential factor for long-term patient post-transplant survival. In heart and lung transplantations, undersized grafts result in a raised probability of early (1-year) mortality. On the other hand, normal to oversized grafts, to a certain extent, lead to prolonged survival, fewer complications, and a decreased chance of graft dysfunction or graft failure. The differentiation of graft size between biologically different sexes relies on distinctive height and mass variances, as well as different levels of hormones, HLA increased sensitization, and therefore the matching between donor and recipient has to be performed very cautiously (Mangiameli G et al. 2022, Demir A et al. 2015, Eberlein M et al. 2016, Ayesta A et al. 2019).

The immune system of a human has the ability to recognize the body's cells and not attack them. On a cell's surface, there are certain proteins called Human Leukocyte Antigens (HLAs), which belong to the Major Histocompatibility Complex (MHC), and they bond with T-cells in order to help in the differentiation of human cells by foreign objects, cancer cells, bacteria, etc. During the transplantation procedure, it's crucial to maintain low HLA sensitization. Ideally, a perfect match results in fewer HLA mismatches, ensuring that the recipient's body does not react adversely to the donor's graft. Among the most known HLA locuses, HLA-DR locus mismatch plays a significant role in the progression of graft rejection and the prognosis of patients at 1 and 3 years (Ansari D et al. 2014).

1.2.4 Post-transplantation

Due to the severity of organ transplantation, patients need to be closely and consistently monitored during their stay in the hospital and out of the clinic afterwards. The first few days following surgery, an overload of feelings and sensory experiences, including pain and suffering in contrast to the excitement and enthusiasm that comes with the success of the process. Patients may feel as though their mentality has been revived, but it will take some time for their bodies to heal and regain a balanced state. During this stage, comprehensive support is essential and it requires direction from a multidisciplinary team, including psychologists, social workers, pharmacists, and other experts. Their combined knowledge and expertise is essential for creating an exact plan and schedule that consists of a disciplined training, a customized exercise program, self-care routine, and rigorous medication compliance. By working together, healthcare professionals, patients, and their relatives and friends, can ensure a thorough and all-encompassing rehabilitation process for the patients while also improving their quality of life and general well-being.

Follow-up

Post-transplant complications and deterioration of the patient's health is a very common phenomenon, imposing a necessary audit of the health condition on a regular basis. A short and a long-management program is implemented in order to eradicate the risk of graft rejection , that is the main and most serious complication (Al Mostafa, M. et al. 2022). There are plenty of examinations to evaluate the progress of a post-transplant heart or lung patient. Some of the indicated follow-up tests are (Laporta Hernández R et al. 2014):

- Forced expiratory volume (FEV1)/ Forced vital capacity (FVC), patients demonstrating decline (>10%) between two consecutive measurements, it's a sign of infection, rejection or dysfunction
- Exhaled Nitric Oxide (eNO), that is overproduced in bronchiolitis obliterans syndrome, after lung transplantation
- Bronchoscopy and Bronchoalveolar Lavage (BAL), which is used to detect immunocytes (CD4,8 T cells, neutrophilia) or cytokines (like interleukins) that suggest early symptoms of acute graft rejection.
- Imaging exams like chest x-ray or computed tomography
- Coronary flow reserve (CFR), coronary angiography (CA), dobutamine stress echocardiography (DSE) for the detection of cardiac allograft vasculopathy (CAV), an immune-induced or not damage of the endothelium of coronary vessels causing blocking and even rejection (Sade LE et al. 2014)
- Cardiopulmonary exercise testing (CPET), which includes a high-intensity interval training (HIIT) of 4 to 6 -minute high pace walk or run on a treadmill. During this test, the heart rate, oxygen consumption and muscle strength are measured (Choi HE et al. 2020).
- Endomyocardial biopsy from the right ventricular myocardium, several times in the first months and subsequently once every three months until the end on first year, which enables the early detection of cardiac rejection, before the occurrence of symptoms (Beckman EN et al. 2001)
- Gene expression profiling, used in heart transplant surveillance, a non-inferior, equally effective technique like biopsies, relying on the analysis of peripherally circulating mRNA, using the Polymerase Chain Reaction method (Pham MX et al. 2010)

Treatment and Complications Management

After a transplant, maintaining the patient's health is a complex procedure that can lead to many complications. Over the last decades, dealing with allograft rejection has been the epicenter of research, and there have been numerous efforts and studies to determine the pathophysiology of allograft dysfunction and rejection and to modify and adapt treatment regimens and protocols to transplant patients' needs. A previous donor-related disease, an injury during the procurement and allocation of the graft, an extended ischemic time period, as well as a not-perfect HLA mismatch, can cause the dysfunction or rejection of the allograft and many organ failure-like symptoms in the patient, augmenting the severity of the condition and hindering the therapy and management post-transplant (Ludhwani D et al. 2023).

The first few hours and days post transplant are a crucially important time that requires careful monitoring and immediate action in order to maintain the stability of the patient's health and to effectively address any unanticipated issues. The reason for this concern is that allografts have high susceptibility and there is a higher chance of adverse events involving hyperacute rejection and primary graft dysfunction (Sun H et al. 2022). Loss of graft function or a gradual decrease in lung capacity or blood volume pumped by the heart are signs of a profound complication.

It's a common phenomenon that complications are caused by infections of nosocomial or community-acquired bacteria (like Nocardia sp.), fungi (like Aspergillus sp.), or viruses (like Influenza) due to transplant patients' vulnerable immune systems (Joean O et al. 2022). There is a strong association between lung transplant infections and graft dysfunction, or bronchiolitis obliterans syndrome, a chronic condition of allograft rejection that happens to half of the long-lasting survivors (Valentine VG et al. 2009), emphasizing the contribution of exosomes, that means extracellular vesicles circulating in the body, which are mainly induced by pathogens like viruses, containing lung or heart cellular antigens and various substances like vimentin, highlighting it as a major cause of chronic allograft rejection (Gunasekaran M et al. 2020, Mohanakumar T et al. 2019, Sharma M et al. 2018). Infection-related outcomes have multiple causes, including multi-drug-resistant bacteria, BMI values above or below the median, and non-standard antibiotic prophylactic schemes, all of which have been linked to an increased risk of primary graft dysfunction (Paglicci L et al. 2021).

Besides constant testing of vital signs and symptoms, long-term follow-up and assessment strategies include several treatments that are administered to transplant patients to eliminate the possibility of graft rejection. The most significant class of drugs and standard therapy is immunosuppressive, which includes corticosteroids like prednisolone, calcineurin inhibitors like tacrolimus or cyclosporine, nucleotide synthesis inhibitors like azathioprine or mycophenolate mofetil, and monoclonal antibodies like rituximab (Hussain Y et al. 2022). These drugs induce immunosuppression to such a level that patients are at great risk of infection by any potentially virulent microorganism, and certain preventive measures like vaccination have not had the same effect on transplant patients as on pre transplant patients or healthy individuals (van Kessel DA et al. 2017). Immunosuppression can cause a variety of issues for transplant patients, with infections being a common outcome, despite the widespread availability and distribution of modern antibiotics and antivirals.

In addition to immunosuppressive drugs, there are other drugs administered according to the organ allocated, the health condition and the patient. Some of these classes of drugs are the following:

- Antibiotics, that are usually given in a preventive way, like beta-lactams (cefazolin, ceftazidime, piperacillin/tazobactam, carbapenem, all affecting gram-negative bacteria like *Staphylococ*cus aureus, Enterococci, Pseudomonas aeruginosa or Burkholderia cepacia, or vancomycin for resistant strains (Anesi JA et al. 2018, Coiffard, B. et al. 2020, Pióro A et al. 2022)
- Antifungals (systemic voriconazole and inhaled amphotericin B for several weeks after lung transplantation for the prevention of infection by the invasive *Aspergillus* sp., or oral itraconazole for 4-6 months for Aspergillus sp. positive specimen, trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii*, echinocandins like caspofungin for invasive aspergillosis too (Uribe LG et al. 2014, Nina Singh 2000, De Mol W et al. 2021)
- Antivirals (antivirals are administered either prophylactically or at the onset of an infection in order to minimize the clinical impact of the virus. For instance, acyclovir, valaciclovir, famciclovir are given for *Varicella zoster virus* (VZV) or chickenpox infection, remdesivir for sars-cov-2, oseltamivir or baloxavir for influenza A or B, maribavir for cytomegalovirus (CMV) (Munting A et al. 2021). There are certain modifications in vaccine regimens, that might be an earlier

dose administration before the transplantation or non recommendation of live, attenuated vaccines like measles (Duchini A et al. 2003)

- Painkillers
- Gastroprotective drugs
- Inotropes
- Antihypertensive drugs
- Diuretics
- Coagulation modifiers

Rehabilitation

The extended time of inclination and motionlessness during the hospital stay, which may last several days, weeks, or even months depending on the patient's pre-transplant health condition, can lead to a noticeable loss in physical strength and muscle flexibility. Recognizing the significance of this, patients are strongly encouraged, according to International and European guidelines, to actively engage in an extensive rehabilitation program.

A range of interventions should be included in the program, aimed at meeting the patients' specific and individual needs, that would either minimize the emotional and sentimental overload or improve the physical capabilities. First and foremost, engaging in physical activity, involving 6-min walk sessions on treadmill, specialized breath-diaphragm exercises, aerobics (Abidi Y et al. 2023), is essential for whole-body recovery and a smooth reintegration into life after transplantation. It seems that exercise regardless of intensity (high or medium pace 60-90% of VO_2 in peak exercise) has a great and positive impact on transplant patient's body and mentality, as it increases muscle stamina, and ameliorates the health-related quality of life by reducing the anxiety, the depression and the probability of experiencing any complications (Yardley M et al. 2018).However, in order to maintain their high volume of oxygen consumption (VO2 peak), muscle capacity, and reduced anxiety levels, heart transplant patients need to continue the high-intensity interval training (HIIT) during their long-term daily routine (Yardley M et al. 2017) in an optimized way, balancing and aligning hard workouts to both self-care and self-engagement.

Receiving the proper amount of nutrients (proteins, lipids, carbohydrates), micronutrients (calcium, zinc, vitamins, etc.), and supplying the body with sufficient amounts of calories and energy that are required to rebuild and regenerate the fully-damaged and injured organs before (due to inflammation, dysfunction, and underregulation of the body provoked by an underlying disease) and after a transplantation (because of the overproduction of oxidative radicals, the ischemia that affected the allograft, and the high demand for energy storage needed for the operation) is a crucial part of rehabilitation. Transplant patients need to adapt to a strict dietary regimen, including low-sodium meals to avoid oedema, low-sugar or low-lipid foods to avoid the development of diabetes or dyslipidemia, calcium and vitamin D to avoid osteoporosis due to immunosuppressive drugs adverse effects on bones, and many other nutritional daily interventions, following dieticians consultation and being closely monitored in order to prevent complications related to nutrient deficiencies or overconsumption (Zeltzer SM et al. 2015, Jomphe V et al. 2018).

Furthermore, another critical component of the transplant procedure that needs to be carefully considered concerns the psychiatric evaluation of the recipient before and after the allograft allocation, equally with the donor’s. Transplantation impacts a patient's life in a peculiar and perplexing way, economically, vocationally, and psychosocially. Acknowledging the health situation, the benefits and consequences that it brings about, the restrictions and lifestyle modifications that need to be made, as well as the risk that invokes such an interventional and invasive operation on the body, have to be communicated in a specialized and individualized way by an expert psychiatrist. The health professional, included in the multidisciplinary team, has to be aware of the current health, physical, and mental health of the patient, any past psychiatric disorders, the treatments that are or were administered, and the patient’s close relationships, occupational, or social features. In addition, psychosocial evaluation does not have only the form of an interview, questioning solely about the medical history of a patient, but represents an utterly utile medium for valuable and elaborate consultation of the post-transplant patient on matters of medication adherence, adverse events or side effects of treatments, rehabilitation, self-control, and self-exclusion from harmful substance consumption like alcohol or tobacco, as well as long-term guidance on the psychological effects that transplantation stimulates in patients and the need for casual expert assessment (Sarkar S et al. 2022, Kalra G et al. 2011, Schulz K et al. 2015).

Quality of Life

Evaluating a patient’s life and progression of health comprises more than one significant part, like physical integrity, mental state, social interactions or relationships, occupation, education, etc. Achieving the goal of surviving through the organ(s) of another person and having a “second chance to life" seems to bring about various, ambivalent overall results for transplant patients over time beyond the operation. Even though an operation of such severity and substantial influence on the body may bring pain, discomfort, and many alterations to the lifestyle of the patient, studies show that there is an increment brought about in well-being and a great amelioration of the patient’s pre-transplant disease-related symptoms like dyspnea, coughing, fatigue, or multiple infections, in the first three to five years after the transplantation (Bleisch B et al. 2019, Tropea, I et al. 2022).

It’s usual that patients self-monitor their conditions and subsequently refer them to their clinicians for further examination. For that reason there have been created plenty of patient self-reporting questionnaires for out-of-hospital use, during rehabilitation or for long-term self-assessment, or in-hospital instruments utilized in cooperation with a health professional, some of which are the *Medical Outcomes Health Survey Short-Form 36-item* (SF-36), utilized the most in Health Related Quality of Life (HRQoL) investigating studies, *EuroQol-5 Dimension* (EQ5D), *Beck Depression Inventory* (BDI) or the *Hospital Anxiety and Depression Scale* (HADS), and other disease-specific forms (concerning the diseases that led to the transplantation) like *Cystic Fibrosis Quality of Life Questionnaire* (CFQoL), the *Kansas City Cardiomyopathy Questionnaire-12,* the *Somatic Disease Severity Score* (SDSS), and the *Saint George Respiratory Questionnaire* (SGRQ), or more general health care questionnaires like the *General Health Questionnaire* (GHQ) and the *World Health Organization Quality of Life Test–BREF* (WHOQOL-BREF). In the previously-mentioned questionnaires, it’s getting clear that besides the pathophysiological determinants (decreased forced expiratory volume, shortness of breath, hypertension, or development of cardiac allograft vasculopathy) in a patient's well-being, there is a strong correlation between emotions and feelings (like anger, distress, anxiety, fear, overwhelm etc.), as well as psychiatric disorders or personality traits (like depression or impatience and irresponsibility, etc.) with the health-related quality of life of a transplant patient (Seiler A et al. 2016).

Based on the available data, there are several variables influencing the overall health-related quality of life of patients since the completion of the allocation process. The older age, the female sex, the infections or other complications, the employment insecurity and the social isolation are associated with attenuated quality of life. On the other hand higher values of FEV_1%, fewer daily limitations due to disease's symptoms like fatigue or cough, increased energy, and better prognosis are some of the profound factors that elevate the quality of life of transplant patients in comparison with patients having the disease that leads to transplantation (Raguragavan A et al. 2023, Stącel T et al. 2020, Carvalho WDN et al. 2021 Oct, Carvalho WDN et al. 2021 Jan). Constant hospital readmissions, ranging from 1 to 5 admissions per year, and prolonged hospital length of stay, with a median of 16 days, proving infections and septic episodes as the leading causes of re-hospitalizations, contribute to the overall physical, psychological, and social quality of life deterioration of the recipients (Jalowiec A et al. 2008, Pothuru S et al. 2022). Moreover, pre-transplant mechanical circulatory support seems to have a negative effect on the quality of life of post-transplant patients soon after the operation, with a great risk for a stroke event (the odds ratios vary significantly depending on the mechanical support system) (Bickel TJ et al. 2021), while patients not eligible for transplantation, receiving mechanically support, have a better quality than those who don't receive (Grady KL et al. 2022).

After the operation, the patient may not be able to achieve every goal, fulfill every desire, or accomplish any assigned task due to the limitations experienced from the transplantation. There is certainly some sort of *impairment*, the medical approach, or *disability*, the social and psychological approach, and profoundly, the stigma around abilities and discriminations hampers the acceptance and inclusion of the person in society. Complications, including diabetes, chronic rejections or allograft dysfunction, infections caused by antimicrobial-resistant pathogens, and progressive inflammatory reactions, worsen the health condition of a patient since an early stage post-transplant, thereby rising in an exponential manner the years lived with a disability (YLD) and consequently the health-related quality of life being minimized. In lung transplants, after 60 months of constant follow-up, disability incidence has risen almost 15%, resulting majorly from the onset of chronic allograft dysfunction, different infections or inflammatory syndromes (ex. Bronchiolitis obliterans) (Diel R et al. 2023, Todd JL et al. 2019). Significant decline in daily tasks management or self-care is notified soon after the first 5 years in heart transplant patients with comorbidities like skeletal-muscle-related illnesses or of female sex, making prominent the need for rehabilitation, further modifications in lifestyle, nutrition, social interactions etc., and specialized interventions in order to stabilize or ameliorate the quality of life of patients (Grady KL et al. 2005).

So far, studies show that the survival of patients decreases rapidly after 5–10 years from transplantation, despite the up-to-date results that demonstrated a better outcome compared to the past, derived from the extensive engagement of scientists and health organizations on the subject of transplantation as well as the efforts of clinicians to improve the lives of their patients. It is undoubtedly a measure that certifies the necessity of further researching novel therapies, treatments, and strategies that will contribute to the elaborate coping and resolution of challenging complications patients face after transplantation and to the enhancement of the long-term survival and increase of the health-related quality of life of lung or heart recipients in the modern world (Suarez-Pierre A et al. 2021, Wilhelm MJ 2015).

Chapter 2
Artificial Intelligence in Heart and Lung Transplantations

2.1 Introduction to Artificial Intelligence

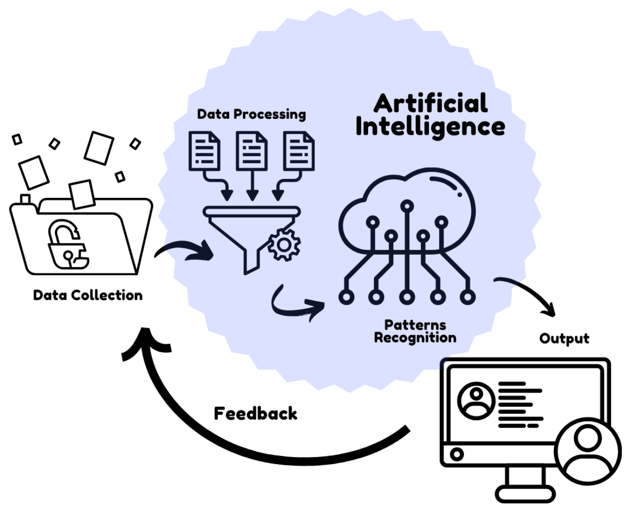
With artificial intelligence, people have had the ability to understand and imitate human genius, natural intelligence, and the remarkable concept of logical thinking. AI emerged in the 1950s, during a period of unprecedented and catastrophic war. It was first introduced by John McCarthy, a computer scientist at MIT who established the term AI in science, signaling the onset of a new era for computers and technology (Kaul V et al. 2020). Humans have always had the insatiable need to discover the mechanisms of action of natural processes, like the movement of flocks of birds in the air, the cooperation of thousands of ants when searching for food, or the pathfinding of *Physarum polycephalum*, a single-cell slime mold, in the environment. Behind those processes, there are different mathematical explanations, biological reasonings, and numerous data points composing a matrix of individuals, forces, and interactions that bring about the results that we, the humans, can comprehend and receive through our senses.

Parallelly, decision-making in human nature is a well-structured form of classified options that are interconnected in an undisclosed manner, relying on the reception and editing of a large set of external data while mixing them with personal beliefs and ideological values. In an effort to copy this process, humans have crafted AI algorithms and machines, starting with robots that could play chess and win a championship (IBM's Deep Blue versus Garry Kasparov[6]) to machines that can detect subtle alterations and cancer cells in tissue biopsies (Pantanowitz L et al. 2020).

2.1.1 But what is Artificial Intelligence?

Artificial Intelligence is computational algorithmic models that were created to be able to think, behave or act like people in a rational way. Partly or fully independent AI algorithms also have the ability to recognize patterns in complex and multidimensional data sets, sequences that people do not understand their structure and utility, thus they invented the term "black box" to cover and describe the lack of comprehension· while being supervised or not by humans, AI models learn from the output-feedback they produced in each loop and evolve in time, certain priorities that not all the AI algorithms have (Monte-Serrat et al. 2021, Stine et al. 2023, Sweta Modak et al. 2022).

Image 2.1 Stages in Data processing by AI

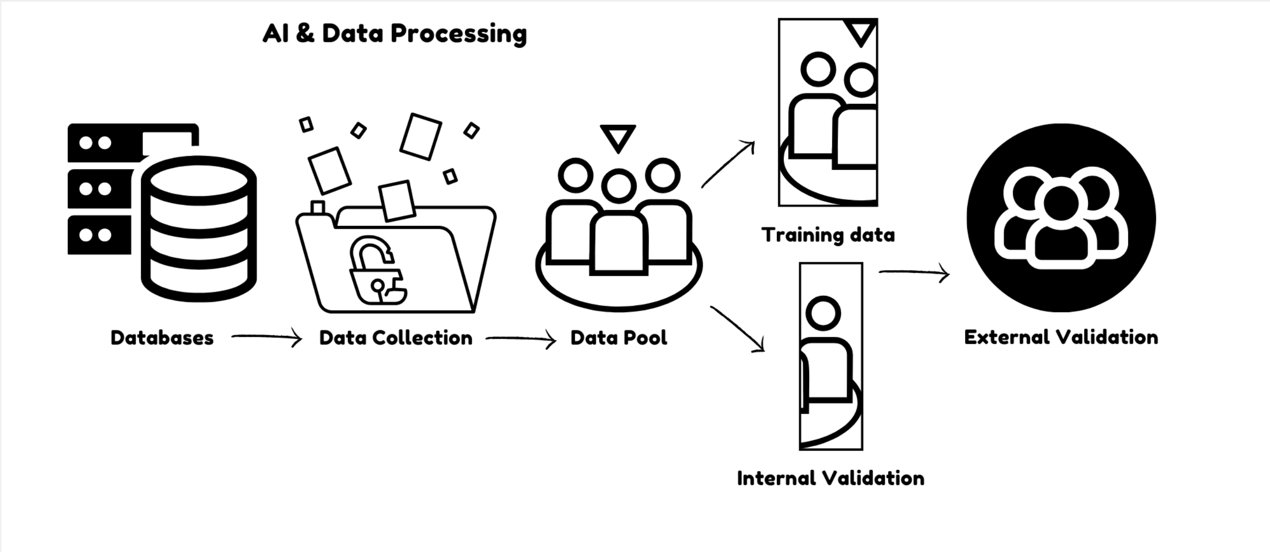


AI wouldn't be capable of working without the use of its "raw material", which is data, characterized by a great diversity in quality features and properties. They are observations of the environment or measurements that may have a structure or not (images, voice recordings, videos, etc.) that "AI agents" (Zinchenko, O. 2023) have collected, and information originated from electronic databases or registries. The

[6] Kasparov Proves No Match for Computer, By Rajiv Chandrasekaran, 1997

preprocessing of data is required in order to be suitably and efficiently analyzed, including transforming information from the raw resource to an easily manageable dataset, conforming to the prerequisites of the AI algorithm design, rearranging or labeling them (ex. classifying images into different groups), and fixing the errors or dealing with the missing values by using techniques like data imputation (Diogo Telmo Neves et al. 2022). When the AI algorithm is provided with the necessary data pool, as a first step, it is designed to be trained accordingly to labeled data and either function on the rules and guidance of people or find patterns that associate data with labels and produce on its own the demanded output, which is further reused as feedback for modifications to the model. Moreover, the AI model is utilized in non-familiar data from the same dataset that it was trained on for internal validation before being used in a totally unknown dataset for external validation (Chinesta F, et al 2022). For example, in the Churpek et al. 2020 study about acute kidney injury, a machine learning AKI predictive score model was trained and internally validated on a dataset of patients (60% of the data for training and 40% for validation) admitted to the University of Chicago hospital between 2008 to 2016 (Koyner JL et al. 2018), and it was externally validated or tested on patient datasets from Loyola University Medical Center (LUMC) and Northshore University Health System (NUS) from 2007 to 2017 and 2006 to 2016, respectively.

Image 2.2 AI & Data Processing, Segmentation of data in training group, internal validation group and external validation group



Examining the function of the model in populations with distinguished properties like different underlying diseases or socioeconomic characteristics supports the generalizability of the AI model, which means the capacity to detect and predict a situation in populations that vary from the training population (external validity). At the same time, it's of the same importance to elaborately assess the AI model internally in populations with the same properties as the training sample in order to attest to the accuracy and reproducibility of the artificial intelligence (internal validation) (Ramspek CL et al 2020).

Artificial Intelligence may be called an "umbrella"- collective term involving all the types of intelligent machines which have been manufactured for several and specific reasons, each one forming a subset of AI algorithms. There might exist countless types of AI because of their continuously evolvement, but there are certain subsets, some of which are (Qureshi Amad et al. 2021):

- Machine Learning (ML) algorithms have the ability to analyze the input data and recognize patterns connecting the parameters that are undisclosed to humans. Therefore, the ML models do not need specific rules or guidance to function, besides classification of data in groups (supervised/ unsupervised learning), thus labeling is certainly a vital part of the process that cannot be missed(Marcele O.K. et al. 2024, Peter Wittek 2014).
- Deep Learning (DL) is a subset of Machine Learning models that are based on *artificial neural network (ANN)* computation technology. ANN are multi-layer domains, composed of many smaller parts, the layers that are

called neurons, which reproduce natural neurons performance, thus each part collecting and processing data in a sequence. DL algorithms outweigh ML in applications with complex and vast feature datasets due to their ability to analyze and correlate properties in a great amount of data (Sarker, I.H. 2021).

- Natural Language Processing (NLP) is a subset of AI models that comprise all the human speech or text imitating machines that are equipped to recognize and detect phrases, words, semantic content, the emotions of the human, and patterns in vocal or written texts. They are capable of processing those data and analyzing the content in order to respond to commands and give suitable and immediate resolutions (Paaß, G. et al. 2023, Chowdhary, K.R. 2020).
- Swarm intelligence is a computing technology that mimics the intelligence, the interactions, and the communication in natural swarms of birds or insects that contain independent and self-determined components, each of which is influenced by its surroundings and the neighboring parts in the process of decision-making (what’s the next move or destination that they follow, etc.), according to environmental parameters or conditions prevailing (Abhishek Kumar et al. 2022, Andrés Iglesias et al. 2020, Abhishek Banerjee et al. 2022).

2.1.2 Can AI be associated with Health?

Since the beginning of the 4th Industrial Revolution, humanity has witnessed a tremendous development in novel technologies and their many applications in daily activities like the food product chain, the transport sector, or the management of businesses, as well as their major influence in political or economic decisions. Over the last decades, people have been in great need of quick and efficient storage and analysis of vast amounts of health data that have been collected constantly at hospital infrastructure, out-of-hospital clinics, or even patients' houses. Moreover, there was an augmented workload for clinicians and medical care staff, and patients’ needs increased at an exponential rate, leading to medical burnout and the incapacity of healthcare facilities to provide better health services to meet the patients’ needs. Additionally, a major hamper to healthcare professionals is bureaucracy, a factor that becomes more complex by the years. Filling out forms or waiting patiently for papers to be assessed and approved in order for a treatment to begin has a great impact on time spent with patients and effectively dealing with the cure (Penberthy, J.K et al. 2020). It's true that in many cases, the delayed approval of a treatment or the delayed admission to a specified unit of a clinic is not due to the lack of expert systems like artificial intelligence voice agents; but the issue is found in the constraints that public or private insurance companies impose upon their clients, as Dr. Chavi Karkowsky indicates in an article in the New York Times (Karkowsky, C. 2023).

However, facing prominent and equally significant issues or limitations to better well-being, like poor adherence of patients to treatment or using precision medicine by individualizing medical interventions according to a patient's special needs, requires analyzing a lot of data and devoting huge amounts of resources (money, equipment, etc.), time, and workforce than in the past (Davenport T et al. 2019). Therefore, through thorough investigation, it was firmly concluded that an alternative to the resolution of these issues, apart from implementing different health policies and strategies, was to apply new technological, virtual, and artificially intelligent machines in the healthcare system, a step towards the effective improvement of the complicated situation (Sargiotis, G.-C. 2023).

2.2. Applications of AI in Heart and Lung Transplantations

Artificial Intelligence applications in healthcare system have integrated new capacities in imaging, disease differentiation, medication adherence, patient monitoring or medical history recording, through the improved and more effective analysis of health data derived by registries or clinical settings in real time or retrospectively (Vivek Kaul et al. 2020). Additionally, to address the elevated need for management and proper allocation of resources in the healthcare system, along with the mitigation of disproportionate expenditure, AI machines have been introduced to improve the cost-effectiveness of health systems (Ramezani, M et al. 2023). Nowadays, healthcare providers have shifted attention to patient-centered health policies, due to the advancement of patients progressive participation in decision-making. Moreover, patients need to have a more complete audit of their health status at a daily pace, like controlling their medication scheduling or assessing any severe alterations in their health, for example extreme variations in glucose levels, and instantly intervening to reduce the deterioration of any acute medical condition (Adam Bohr et al. 2020)

Lung and heart transplantations like any other clinical procedure or medical intervention are associated with critical medical errors that have severely impacted the effectiveness of the transplantation procedure like the unnecessary delays of patients in waiting lists, extended warm ischemia time or serious organ injuries in the organ preservation stage, or poor donor-recipient pair matches compatibility, as well as many other omissions or mistakes that have leaded to unsuccessful organ donations, early allograft dysfunction or failure events or short post-transplant survival (Ison MG et al. 2012). Safety issues in the transplantation process remain a crucial factor in a patient's survival and well-being. Relevant studies demonstrate the inability of healthcare stakeholders to communicate promptly and sufficiently about health issues arising after the analysis of data like exams or the inability to make essential decisions over the detection or prediction of potentially catastrophic situations for patients (Stewart DE et al. 2015). In addition, it's important to refer to another vital parameter to the minimized transplantation effectiveness that is the shortage of organs available for allocation, a subtle issue raising awareness over the scientific community. The current state in organ supply across the planet has alerted nations and there was a widespread demand for carrying out immediate measures to determine the scale of the problem and address it competently (Spanish Ministry of Health, N.T.O. 2023).

2.2.1 AI applications in Solid Organ Transplantations

Artificial intelligence algorithms have gradually been inserted in healthcare systems around the world, in an attempt to positively affect and restrain the progression of health crises that afflict patients, medical staff and organizations, with enormous consequences. In the field of solid organ transplantations, there have been plenty of AI applications during the past years that have facilitated the procedures and have helped improve the waitlist mortality, pair-matching between donors-recipients or post-transplant outcomes. In an article published in "Financial Times" magazine, Sarah, a chronic patient with cystic fibrosis and alpha-1 antitrypsin deficiency shared her story of waiting in a transplant list for almost 26 months until an AI model opted her in for receiving her new liver (Madhumita, M. 2023).

Several studies referring to Artificial intelligence and its applications on solid organ transplantations have strongly supported its contribution to different parts of the process like the prognosis of survival of patients with a chronic disease which leads to transplantation, an amendment that can help clinicians in the recipient selection process, according to the severity of cases (Xu C et al. 2023, Weiss J et al. 2023). Moreover, it's the estimation of waiting time and patient-survival in a pretransplant list, indicating particular features that are associated with better or worse outcomes (Sapiertein Silva JF et al. 2021). AI models have been used for the determination of effectiveness of therapies and medications administered for the life support of end-stage patients until their pre-selection for transplantation (Lee H et al. 2023, Shou BL et al. 2022), or they have served for the assessment of organ quality pre- and post-transplant through the analysis of biopsies obtained from allografts to assist to the better allocation of organs (Yoo, D. et al. 2024) or the assessment of preservation techniques (estimation of the long-term effect of cold or warm ischemia time) and protocols followed in each country and medical centers that play a significant role in prognosis, organ function or failure (Jadlowiec CC et al. 2024). There have been also studies that the performance of AI models was examined for the prediction of cancer development in allografts (Amir Zadeh et al. 2024), or the constant short-term or long-term management and evaluation of post-transplant complications (Fodor M et al. 2024), like graft failure or graft dysfunction (Yi Z et al. 2024, Michelson AP et al. 2023), and patient-survival or mortality after a definite number of days (30-day survival) (Linse B et al. 2023), months (1-month, 3-month survival) or years (1-, 3-, 5-, 10-year survival) (Tian D et al. 2023). Finally, in post-transplant monitoring of patients, AI machines have demonstrated validated efficiency for working as follow-up agents by collecting data, analyzing them, detecting risk factors (like onset of diabetes (Al-Imam A et al. 2022, Bhat V et al. 2018), inflammation, infection (Kherabi Y et al. 2022), sepsis (Kamaleswaran R et al. 2021), etc.), or monitoring the patients' engagement in treatments (Rosenberger EM et al. 2017). Furthermore, AI models have the capacity to trace individualized patterns and sequences in each patient's data profile, thus recommending personalized resolutions and alternatives to complications after transplantation or a priori, considering their strength in performing and counting the probabilities of several outcomes and events (Basuli D et al. 2023).

Due to the capability of AI, especially machine learning or deep learning models, to compile and evaluate immense quantities of data in contrast with traditional statistical models, they’re highly accurate, precise and sensitive to predict and distinguish certain risk factors among a great variety of demographic, clinical, or therapeutic variables that have a (linear or nonlinear) correlation with health outcomes like mortality, morbidity, sepsis, graft dysfunction or failure, etc., according to univariate or multivariate analysis of information originated from questionnaires, registries, or cohort retrospective studies. The prediction of these factors will improve and facilitate decision-making for clinicians and transplant coordinators by providing essential insights and expanding their knowledge of the procedures (Gholamzadeh, M et al. 2022).

According to data, Artificial intelligence models have been used widely in transplantations in order to eliminate several disproportionate hurdles that would face patients either pre- or post-transplant. Their novel technology opened up new horizons in medicine, exposing humanity to different points of view and establishing new approaches for comprehensive actions on the issues and problems besetting the patients and healthcare systems. Their applications have brought about many benefits but a great amount of risks too. For instance, Sarah Meredith described in her story that the waiting time for patients of her age (25-40) has considerably increased compared to past years and to other age classes of patients (over 60 years old), after the implementation of AI models, which ultimately changed the waitlist prioritization (Madhumita, M. 2023).

Despite the advances in technology and the promising applications of AI in medicine, it’s unfair to presume that machines operate in a just and indiscriminate manner, without technical or moral limitations. It’s far from utopian to believe in an unbiased and free-from-error world of AI, which unstoppably serves the human kind as if everything were in control. Due to the fact that medicine and, even worse, transplantation are inextricably connected with the continuum of life, a misinterpretation of results or input data from the models could jeopardize the well-being and lives of patients, making the legal and moral implications extremely serious (Boris Babic et al. 2020)

Chapter 3
Systematic review analysis

3.1 Introduction

3.1.1 Rationale

Since medical centers around the world have been using AI for some years now, it seems logical to query the overall AI models' utility and benefits or risks in healthcare systems and patients’ lives. Especially in heart and lung transplantations, there hasn’t been much research, but recently, due to the lack of knowledge of clinical staff and the uncertainty raised by the perplexed and opaque functions of machines, which were contrary to the principles of medicine and the legal restraints being implemented by past regulations on experimentation on critically ill patients. Thanks to the progress in artificial intelligence computing and analytical systems, a legitimate interest was demonstrated by health-related corporations and scientists, which significantly accelerated the introduction of AI health models in routine clinical medicine and, furthermore, in transplantation over the old fashioned but tediously and stably well- performed traditional interventional methods. However, it is of paramount importance to acknowledge the fact that in health, every machine’s or therapeutic approach's outcomes or performance need to be evaluated for their effectiveness, accuracy, discrimination, sensitivity, and generalizability.

3.1.2 Research Aim

After thorough research on AI applications in heart or lung transplantations in literature and databases, it was noticed that there are quite a few studies that focus on AI and heart or lung transplantations, but almost none that systematically collects, analyzes and reviews the existing data on patients' outcomes and AI models' performance. That's why, *the purpose of the present research was the presentation of data concerning the performance of AI models that were applied in heart or lung transplantations and their association with the patients' health outcomes.*

3.1.3 Objectives

The objectives of this systematic research are the following:

- To examine the performance of Artificial Intelligence models that were applied in heart or lung transplantations
- To analyze the impact that AI models have had on patients' health outcomes (like mortality, graft rejections, sepsis, etc.)
- To explore the factors that make AI a potentially effective method for solid organ transplantation
- To present the problems and obstacles that arise (technical difficulties, legal restrictions, risks) from the application of AI in heart and lung transplantation
- To highlight the ethical dilemmas that arise from the use of AI in heart and lung transplantation
- To examine the prerequisites for the proper implementation of AI in solid organ transplantation

3.2 Methods

3.2.1 Scientific Protocol

A scientific protocol was prepared prior to the main research in order to pose the relative hypothesis.

3.2.2 Eligibility Criteria

For the selection of the scientific studies used in the present qualitative systematic research, certain eligibility criteria were implemented, the PICOTS (Moons KG et al. 2014, Debray TP et al. 2017) and Study design:

Table 3.1: P.I.C.O.T.S.S. (representing the eligibility criteria of studies selected from literature for analysis)

Population	The research was focused on post- transplant patients who had had or were going to have a lung or heart transplantation, and were above 18 years old, with a sample size of more than 100 subjects
Index	Index encompasses every artificial intelligence model that was applied in research (machine learning, deep learning, artificial neural networks, convolutional networks, logistic regression, etc.)
Comparators	there were no comparators due to the diverse nature of artificial intelligence performance metrics
Outcome	post- transplant (30-day, 1-month, 1-, 3-, 5- year) mortality, survival, graft dysfunction, graft failure and main AI model performance outcome: AUC or AUROC (area under the curve)
Timing	the time point at which the prediction model under review is used is during or post- transplant phase
Setting	The intended clinical setting is the transplantation setting, the clinics and ICU departments, the clinicians involved and the out-of-hospital follow-up. The intended uses of AI models are prediction of health outcomes in patients who have had or are going to have a transplantation
Study design	cohort retrospective studies, from 2000 until 2023

3.2.3 Information sources

The online libraries that were used for the thorough investigation and selection of studies were 3, which are:

- Scopus (http://www.scopus.com/home.url)(10 October 2023 - 24 October 2023)
- PubMed (https://pubmed.ncbi.nlm.nih.gov/)(10 October 2023 - 24 October 2023)
- ScienceDirect (https://www.sciencedirect.com/)(10 October 2023 - 24 October 2023)

3.2.4 Search

For an elaborate search in the scientific databases, certain keywords and terms were used in a sequence

Table 3.2 Literature research algorithms consist of key terms that are used for the identification of related studies	
Scopus	TITLE((("artificial intelligence") OR ("machine learning") OR ("deep learning") OR ("neural networks")) AND (("transplantation") OR ("transplant")) AND (("heart") OR ("lung") OR ("lungs")))
Pubmed	(((artificial intelligence[Title]) OR (machine learning[Title]) OR (deep learning[Title]) OR (neural networks[Title])) AND ((transplantation[Title]) OR (transplant[Title])) AND ((heart[Title]) OR (lung[Title]) OR (lungs[Title])))
Science Direct	((("artificial intelligence") OR ("machine learning") OR ("deep learning") OR ("neural networks")) AND (("transplantation") OR ("transplant")) AND (("heart") OR ("lung") OR ("lungs")))

The filters and limitations that were applied in the database research were,

- the language or articles to be solely the English
- the publication date was from 2000 to 2023
- access to the full text of the studies was open for academic use.
- the document type to be “research articles”, excluding reviews, systematic reviews, case reports, conference papers or abstracts, books or chapters,

news, or other (specifically for the databases ScienceDirect and Scopus researches were limited to “Research Articles”)

3.2.5 Study selection

In the initial part of research sampling, after the implementation of keywords, the results were extracted, and the titles and abstracts of studies were estimated if they met the eligibility criteria. In the second phase, every piece of research and the detailed analysis of every important point were examined exhaustively and opted for systematic analysis. The research analysis was conducted by only one researcher.

3.2.6 Data collection process

If the study met the eligibility criteria, then the data selection process followed, starting with the creation of a table, which contained all the desired information that originated from the enrolled studies. The process ran in an independent manner, following a general-to-specific pattern where the more general data were selected first and the more specific data were selected in the end. For instance, the title of the study and the publication data were recorded in the beginning, and then the performance metrics of AI models and conclusions for main health outcomes were recorded in the end. The data selected were documented in a table and validated multiple times.

3.2.7 Data items

The variables that were collected from the individual studies are the following:

- Publication date of the study
- Type of study
- Databases/registries
- Sample size (recipients and donors group)
- Sample age (recipients and donors group)
- Sample ethnicity groups (recipients and donors group)
- Sample sexes (recipients and donors group)
- Location
- Transplant Organ (heart or lung(s))
- AI Algorithm type

- Main Performance Metric
- Secondary Performance Metrics
- Study aim
- Mainly examined health outcome(s)
- Results about performance metrics (internal validation)
- Results about performance metrics (external validation)
- Results about examined health outcome(s)
- Limitations of studies

3.2.8 Risk of bias in individual studies

In the analysis of the included studies from the literature, an additional process that had to be done was the risk of bias assessment. Biases are such an important component of research that they need to be thoroughly investigated in order to avoid false conclusions. Specifically, in this study, the evaluation of biases focused on systematic biases, which are due to sampling, selection of candidate variables, handling of missing values, presentation of outcomes, or analysis of data. For this reason, the tool that was used for the risk of bias assessment in the included individual studies, was the PROBAST tool (**P**rediction model **R**isk **O**f **B**ias **A**ssessment **T**ool), which has application on studies referring to prognostic models (and diagnostic that they're not included in the present study) (Wolff RF et al. 2019). A more specialized version of PROBAST for Artificial Intelligence is meant to be released in 2024 (Collins GS et al. 2021).

The domains of the PROBAST tool that were analyzed in this present study were the following:

1. Participants

    - 1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?
    - 1.2 Were all inclusions and exclusions of participants appropriate?
    - Applicability concerning participants, settings and dates

2. Predictors

- 2.1 Were predictors defined and assessed in a similar way for all participants?
- 2.2 Were predictor assessments made without knowledge of outcome data?
- 2.3 Are all predictors available at the time the model is intended to be used?
- Applicability concerning the definition, assessment or timing of predictors in the model

3. Outcome

- 3.1 Was the outcome determined appropriately?
- 3.2 Was a pre-specified or standard outcome definition used?
- 3.3 Were predictors excluded from the outcome definition?
- 3.4 Was the outcome defined and determined in a similar way for all participants?
- 3.5 Was the outcome determined without knowledge of predictor information?
- 3.6 Was the time interval between predictor assessment and outcome determination appropriate?
- Applicability concerning the outcome, its definition, timing or determination

4. Analysis

- 4.1 Were there a reasonable number of participants with the outcome?
- 4.2 Were continuous and categorical predictors handled appropriately?
- 4.3 Were all enrolled participants included in the analysis?
- 4.4 Were participants with missing data handled appropriately?
- 4.5 Was selection of predictors based on univariable analysis avoided?
- 4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of controls) accounted for appropriately?
- 4.7 Were relevant model performance measures evaluated appropriately?

- 4.8 Were model overfitting and optimism in model performance accounted for?
- 4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?

An overall assessment of the risk of bias and the general applicability of studies was made in order to summarize the effect of biases on each study's impact on research. The aim was to judge in total the systematic errors that scientists have made in their research in order to make certain assumptions and suggestions on the conduct of studies relating to AI and transplantations in the future. The assessment was conducted by one researcher, which is certainly a grave limitation and systematic error of the present study.

3.3 Results

3.3.1 Rationale of Systematic Research

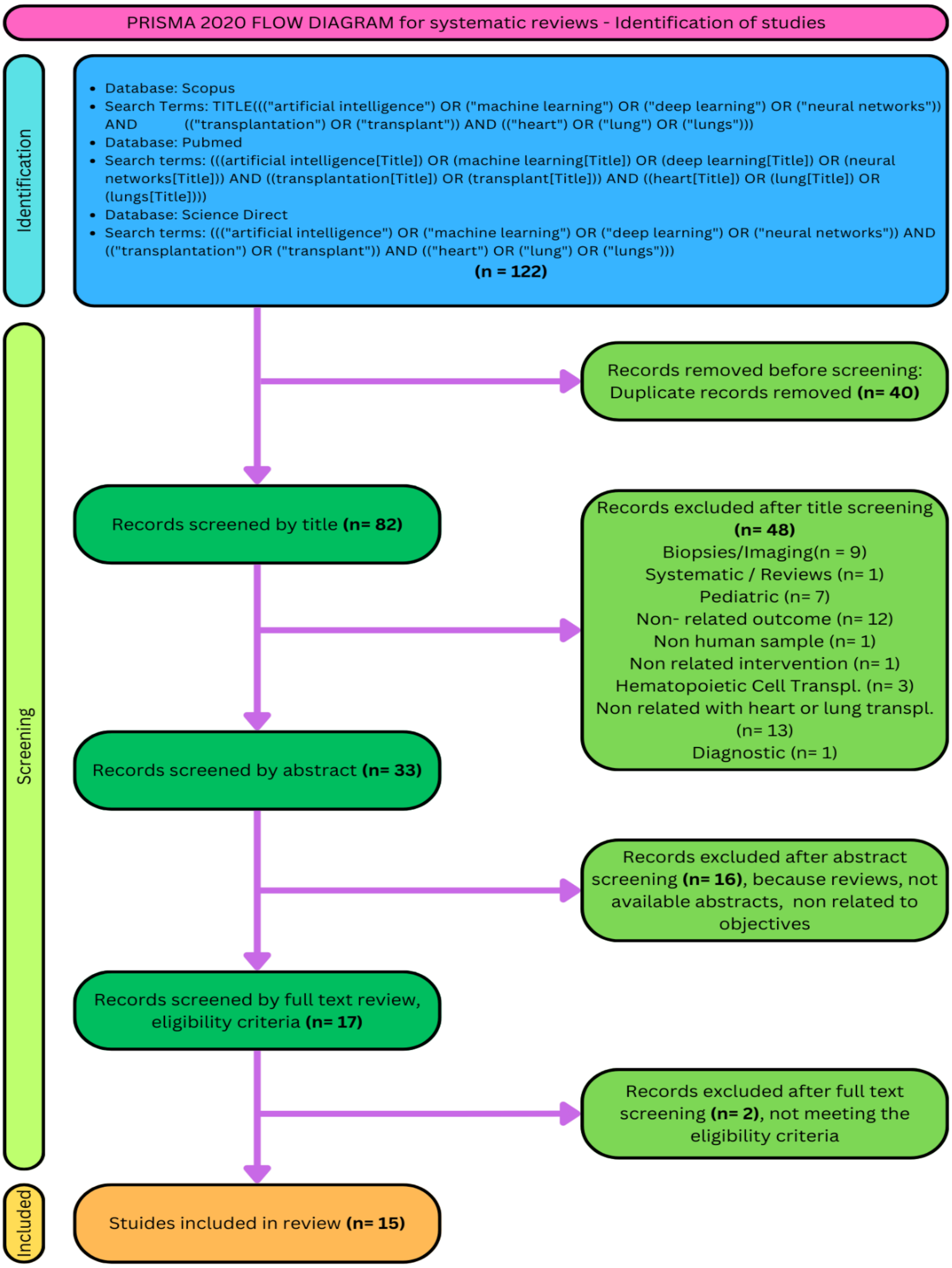


Figure 3.1: PRISMA flow chart of systematic Research

In the identification of studies phase, there were certain steps that had to be followed, in order to conclude with a representative number of eligible studies for analysis. The PRISMA 2020 flow chart (Figure 3.1), presents the steps in the research process and the reasons/ some of the inclusion and exclusion eligibility criteria that were implemented in the literature.

In the first step, after the literature research in scientific databases (Scopus, Pubmed and ScienceDirect) with terms and filters, the number of resulting studies were 122. By removing the duplicates, systematic reviews, conference papers, book chapters, and those not related to criteria studies, and by screening the title and abstract, the remaining number was 17. After fully reviewing the studies, 2 were removed for not meeting the criteria (not having access to assess them, (1) *Michelson AP et al., Developing machine learning models to predict primary graft dysfunction after lung transplantation. Am J Transplant. 2023*, (2) *Medved D et al., Predicting the outcome for patients in a heart transplantation queue using deep learning.2017*) and the concluded number of studies for analysis was eventually 15.

3.3.2 Presentation of results

The studies selected for further analysis are the following:

Table 3.3 Studies selected for systematic review and analysis after literature research				
#	Study	Authors	Transplant organ	Publish date
1	Temporal shift and predictive performance of machine learning for heart transplant outcomes	Robert J H Miller et al.	heart	July 2022
2	Enhanced survival prediction using explainable artificial intelligence in heart transplantation	Paulo J. G. Lisboa et al.	heart	November 2022
3	Using machine learning to improve survival prediction after heart transplantation	Ayers et al.	heart	July 2021
4	Pre-operative Machine Learning for Heart Transplant Patients Bridged with Temporary Mechanical Circulatory Support	Shou et al.	heart	September 2022
5	Machine learning helps predict long-term mortality and graft failure in patients undergoing heart transplant	Agasthi et al.	heart	May 2020

6	State-of-the-art machine learning algorithms for the prediction of outcomes after contemporary heart transplantation: Results from the UNOS database	Kampaktsis et al.	heart	June 2021
7	Prediction of 1-year mortality after heart transplantation using machine learning approaches: A single-center study from China	Zhou et al.	heart	July 2021
8	Machine learning-based prediction of mortality after heart transplantation in adults with congenital heart disease: A UNOS database analysis	Kampaktsis et al.	heart	October 2022
9	A machine learning model for prediction of 30-day primary graft failure after heart transplantation	Linse et al.	heart	March 2023
10	Improving prediction of heart transplantation outcome using deep learning techniques	Medved et al.	heart	February 2018
11	Predicting heart transplantation outcomes through data analytics	Dag et al.	heart	2017
12	A two-stage machine learning framework to predict heart transplantation survival probabilities over time with a monotonic probability constraint	Hamidreza Ahady Dolatsara et al.	Heart	October 2020
13	Machine Learning–Based Prognostic Model for Patients After Lung Transplantation	Tian et al.	lungs	May 2023
14	The Lung Allocation Score and Other Available Models Lack Predictive Accuracy for Post-Lung Transplant Survival	Jay M. Brahmbhatt et al.	lungs	May 2022
15	An explanatory analytics model for identifying factors indicative of long- versus short-term survival after lung transplantation	Mostafa Amini et al.	lungs	June 2022

All the investigated studies had a retrospective collection of data that derived from either large or small cohort studies, patient registries, or transplant databases like UNOS (United Organisation for Organ Sharing) in different time periods within the timeframe (1987–2021). In our systematic review, there were 12 studies referring to heart transplantations (385,060 total number of heart transplant patients) and 3 referring to lung transplantations (57,984 total number of lung transplant patients). The demographic characteristics of the samples are demonstrated in Table 3.4. The patient sample size ranges from 381 to 103750 observations, while in the majority of studies, a patient registry or database was used in order to train and validate the AI models. Only one study was found to include data from the external validation procedure of the training model (Lisboa et al. 2022), while the rest 14 studies didn’t include in their methodology an external validation method. The United Network for Organ Sharing was the main data resource except for studies (Agasthi et al. 2020, Zhou et al. 2021, Linse et al. 2023, Tian et al. 2023), including data from donors and recipients since 1987. As a result, the United States of America was the major region (12 studies referring to data originated from USA multicenters) among the selected studies where transplantations have taken place. For most of the studies, it was possible to extract information about transplant recipients' and donors' demographics, like age, ethnicity, or sex. Few are the studies that provided no information about the target population (Miller et al. 2022, Ayers et al. 2021, Agasthi et al. 2020, Linse et al. 2023, Dag et al. 2017, Dolatsara et al. 2020, Tian et al. 2023, Amini et al. 2022). Among the studies that provided data about the transplantations, the mean age of recipients was 50.72 and the mean age of donors was 32.83 (excluding studies that reported age by range or median, with no information about the mean (Miller et al. 2022, Shou et al. 2022, Linse et al. 2023, Dag et al. 2017, Dolatsara et al. 2020, Amini et al. 2022). The most transplanted races of people in the investigated studies were white (64–83.2%), followed by black/African American (8.5-23.4%), Hispanic (5.9–8%), and Asian (1.5–3.4%). Details about the ethnicity of donors are given only in one research study (Kampaktsis et al. 2021), indicating that in the period 2010–2018, in the USA, almost 64% of 18,625 transplantations that were carried out were related to white donors, followed by black people (16.3%), Hispanic people (16%), and Asian people (1.8%). The most frequently recorded feature in the analyzed studies was the recipients' and donors' sex. There are a few studies that indicate only one sex of the sample, which might have been either male or female, and there are no references about intersex people or other genders. Among the recipients, 71.4% were males and 28.6% were females, while 79.8% of overall donors were males and 30% were females.

Table 3.4 Demographic Characteristic of the eligible for analysis studies (including data resource, sample size, age, ethnicity and sex of recipients, donors and subgroups, and region(s) of data

#	Data resource	Sample size	Age	Ethnicity	Sex	Region
1	UNOS database, (1994-2016)	59590	recipients: 55 (median) (IQR 46-61), donors: 29 (median)	NR	recipients: male (44692), female	USA

			(IQR 21-40)		(14898), donors: male (41731), female (17859)	
2	UNOS and SRTR database (1997-2016)	42185	Cohort1: recipients: 52 (mean) (± 12 SD), donors 32 ± 12, and Cohort 2: recipients: 54 ± 13, and donors: 33 ± 11	recipients: Asian (1100), Black (7624), Hispanic (3067), white (29949)	recipients: female (10229), male (31956), donors: female (12485), male (29700)	USA
3	UNOS database (2000-2019)	33657	recipients: 52.8 (mean) ± 12.5 (SD) years, donors: 31.8 ± 11.9	NR	recipients: female (8389) , male (25268), donors: female (9816), male (23841)	USA
4	UNOS database (2009 - 2017)	1584	recipients:45-64 (range). donors: 23-45	recipients: white (1014), black (371), hispanic (125), other (74)	recipients : male (1169), female (415), donors: male (1066), female (518)	USA
5	ISHLT registry (2005-2009)	15236	Recipients: 50.955 (mean),±12.389 (SD), 18-77 (range), Donors: 36.554 (mean), ±12.550 (SD), 18-77 (range)	NR	Recipients: Female (3375) (22.2%), Male (11861) (77.8%), Donors: Female (4673) (30.7%), Male (10563) (69.3%)	18 countries, including the United States of America, Australia, France, etc.
6	UNOS database (2010 - 2018)	18625	Recipients: 53 (mean), Donors: 33 (mean)	recipients : white (12330), black (3934), hispanic (1497), Asian (638), donors: white (11976), black (3036),	recipients: female (4981), male (13644), donors: female (4656), male (13969)	USA

				hispanic (2983), Asian (336)		
7	Huazhong University of Science and Technology (2015-2018)	381	recipients: 43.783 (mean), 16.453 (SD), donors: 32.527 (mean), 12.7 (SD)	Chinese	recipients: male (249), female (132), donor: male (281), female (100)	China
8	UNOS database (2000-2020)	1033	recipients: VAL: 35.9 (mean) (±13.3 SD), TR: 34.6 (12.9), donors: VAL: 28.3 (11.3), TR: 27.9 (10.9)	recipients: White VAL: (608) (84%), TR: (240) (77%), Black VAL: (52) (7%), TR: (32) (10%), Other VAL: (62) (9%), TR: (38) (13%)	recipients: Female (402), male (631), donors: female (380), male (653)	USA
9	ISHLT registry, (1994-2013)	65759	Recipients: Control: 51.4 ± 11.9, (median 54, range 18–79 years), PGFwithin30days: 52.1 ± 11.6, Donors: Control 34.1 ± 12.7, PGFwithin30days 38.3 ± 12.8	NR	Recipients: Control: Female (13,607) (21.5%), male (51357) PGFwithin30 days: female (536) (21.7%), male (1929)	world
10	UNOS database (1997-2011)	27860	recipients: 51 (mean) ± 13 (SD) years, range 18 -78 years, donors: 32 ± 12 years	Recipients: African American (4427)	recipients: male (21151), female (6709), donors: female (8191), male (19669)	USA
11	UNOS database (1987-2012)	15580	NR	NR	NR	USA
12	UNOS database (1987-2016)	103570	NR	NR	NR	USA
13	Wuxi People’s Hospital (2017-2019)	504	recipients: 55.56 (mean), 12.27 (SD) years	NR	recipients: male (334) (66.3%), female (170)	China

14	UNOS (2005-2017)	19900	Alive without re-transplant after 1 year (n=16964): 55.1 (mean), 13.1 (SD) Death or re-transplant within 1 year (n=2936): 56.5 (mean), 13.1 (SD)	recipients: white (16555), black (1736), asian (302), pacific islander (17), american indian (62), hispanic (1174), mulit-racial (63)	recipients: female (8109), male (11791)	USA
15	UNOS (1987 - 2021)	37580	NR	NR	NR	USA
NR: No reference, SD: standard deviation, IQR: Interquartile range, VAL: validation set, TR: training set, PGF: primary graft failure, USA: United States of America						

In most of the studies, the research aim was the estimation of accuracy, specificity and sensitivity of Artificial Intelligence Algorithmic Models in the prediction of health outcome(s). In Table 3.5, there are presented data about the research aim of the studies, the algorithms used in each study, and their types, as well as the purpose of utilization of these algorithms (e.g. classification, regression, survival analysis, feature selection). As it was previously mentioned there was only one study that included an external validation method of the interpretable model(s) (Lisboa et al. 2022). Moreover, the majority of studies had as target outcomes, the 1-year post-transplant survival (Miller et al. 2022, Ayers et al. 2021, Kampaktsis et al. 2022, Dolatsara et al. 2020, Brahmbhatt et al. 2022, Amini et al. 2022), mortality (Lisboa et al. 2022, Shou et al. 2022, Kampaktsis et al. 2021, Zhou et al. 2021, Medved et al. 2018), graft survival (Dag et al. 2017), 3-year post-transplant survival (Kampaktsis et al. 2022, Dolatsara et al. 2020), mortality (Kampaktsis et al. 2021), 5-year post-transplant survival (Dolatsara et al. 2020), mortality (Agasthi et al. 2020, Kampaktsis et al. 2021), graft survival (11) and failure (5), 1-month or 30-day survival (15,13), graft failure (9), 9-year graft survival (11), 90-day survival (1,15) and multiple time periods post-transplant survival (15,12). The most used AI algorithm was the Logistic Regression (1, 3, 6, 7, 9, 10, 11, 12, 15), followed by Random Forest (1, 3, 7, 12, 14, 15), Support Vector Machines (6, 7, 11, 12, 15), Extreme Gradient Boosting (1, 4, 7, 12), Decision Trees (6, 11, 12, 15), AdaBoost (3, 6, 7), Gradient

Boosting Machine (5, 7, 15), Artificial Neural Network (7, 12, 15), LASSO (2, 12, 14), Cox Regression (1, 13), Deep Neural Network (3, 10), K-nearest Neighbor (6, 15), Multi-Layer Perceptron (9, 11), Random Survival Analysis (1), Survival Gradient Boosting (1), Partial Response Network (2), IHTSA (2), IMPACT (2), EBM (2) , Gradient Boosted Trees (15), SVM-FuzCoC (6), CatBoost (8), Linear discriminant analysis (12), Random Survival Forest (13), Houston Methodist model by Chan et al. 2019 (14), “Clinician” model (14) and SHAP (15) (Table 3.5).

Table 3.5 Data about the aim and objectives of the studies included in the review

#	Research Aim	Health Outcome(s)	Artificial Intelligence Method	External Validation
1	To evaluate the performance of machine learning and statistical algorithms to predict post-transplant mortality after heart transplantation, using data from the UNOS database	1-year post-transplant all-cause mortality	Random Forest (ens. learn., class.,, regr.), Logistic Regression (Stat.model /ML, class.), XGBoost (ens. learn, class. and regr.), Random Survival Analysis (ens. learn, surv. an.), Survival Gradient Boosting (ens. learn., surv. an.), Cox regression (surv. an.)	No
2	To evaluate two AI models by using two external cohorts: transplant data from a regional database in Scandinavia, and UNOS database	1-year post-transplant mortality	Partial Response Network-Lasso (LM, feature selection and signal processing), IHTSA (stat. model/ML), IMPACT (stat. model/ML), EBM (ens.learn., regr. and class.)	Yes
3	To apply modern machine learning methods in order to enhance survival prediction following orthotopic heart transplantation	1-year post transplant survival	Deep Neural Network (DL), Logistic Regression (stat. model/ML), AdaBoost (ens.learn., class.), Random Forest (ens. learn., class.)	No
4	To research for specific elements in pre-operative risk assessment for populations where the risk scores are poorly validated	1-year post-transplant mortality	XGBoost (ens. learn., class. and regr.)	No
5	To create a machine learning-based risk prediction model to predict survival and graft failure (GF) five years following orthotopic heart transplantation	5-year post-transplant all cause mortality and graft failure	Gradient Boosted Machine Algorithm (ens. learn., class. and regr.)	No
6	To create and validate machine learning models in	1-year, 3-year and	SVM-FuzCoC (ML, class.), Adaboost (ens. learn., class.), SVM (ML, regr. and	No

	order to improve the predictive accuracy of mortality after heart transplantation	5-year post-transplant survival	class.), Decision Tree (ML, regr. and class.), KNN (instance-based learn., class. and regr.), and Logistic Regression (stat. model/ML)	
7	To evaluate the performance of machine learning techniques to predict overall 1-year mortality in post heart transplant patients in China	1-year post-transplant mortality	Logistic Regression (stat. model/ML), SVM (ML, regr. and class.), RF (ens. learn., class. and regr.), XGBoost (ens. learn., class. and regr.), AdaBoost (ens. learn., class.), GBM (ens. learn., class. and regr.), ANN (DL class., regr., feature selection)	No
8	To develop and evaluate a machine learning model using data from ACHD patients that had a HT in the USA, in order to predict survival.	1-year and 3-year post-transplant survival	CatBoost (gradient boosting algorithm, ens. learn, class. and regr.)	No
9	To develop a neural network model for prediction of the within 30-day PGF risk of heart transplant patients	30-day post-transplant primary graft failure defined as death	Multi-layer Perceptron (ANN/DL, class., regr. and pattern recognition), Logistic Regression (Stat.model /ML, class.)	No
10	To compare the predictive accuracy and performance of two risk models, International Heart Transplantation Survival Algorithm (IHTSA) and Index for Mortality Prediction After Cardiac Transplantation (IMPACT)	1-year post-transplant mortality	Deep Neural Networks (DL, class., regr., pattern recognition), Logistic Regression (Stat.model /ML, class.)	No
11	To create a data-driven method for predicting post-heart transplant patients' outcomes after one, five, and nine years and to comprehend how the significance of the predictors varies over these three time periods	1-,5-,9-year post-transplant graft survival	SVM (ML, regr., class.), Multi Layer Perceptron (ANN/DL,class., regr. and pattern recognition) , Decision Trees (ML, class., regr.) and Logistic Regression (Stat.model /ML, class.)	No
12	To create and explain a modeling framework that may be applied to generate data-driven, individualized, and monotonically constrained probability curves.	1-year post-transplant survival, multiple time periods post-transplant survival (1-10 year)	Logistic Regression (Stat.model /ML, class.), Linear discriminant analysis (SL, class.), ANN (DL, class., regr., pattern recognition), Decision Trees (ML/SL, class., regr.), SVM (ML/SL, regr. and class.), XGBoost (ens. learn., class. and regr.), LASSO (ML/LM, feature selection), and RF (ens. learn., class. and feature selection)	No

13	To create and validate a prognostic model employing random survival forests to predict patients' overall survival following LTx	1-month, 1-year, post-transplant overall survival	RSF (ens. learn., class. regr., survival analysis), Cox regression (surv. an. and regr.)	No
14	To determine the predictive performance of all the models by taking into account the 3-year post-transplant outcomes, including donor variables, and to assess the accuracy of the LAS and other models for predicting 1-year post-transplant mortality.	1-,3-year post-transplant mortality	Houston Methodist model by Chan et al. 2019 (ML, surv. an.), LASSO (ML/LM, feature selection), RF (ens. learn., class. and feature selection), Clinician model (expert rule-based model)	No
15	To identify the critical elements that contribute to a lung post-transplant patient's survival, using AI methods and prediction models	short (1-year) and long term (10-year) post-transplant survival	Decision Tree (ML, class. and regr.), Gradient Boosted trees (ML, ens. learn., class. and regr.), RF(ML, ens. learn., class. and regr.) , KNN (instance based learning, class. and regr.), ANN (DL, class., regr. and pattern recognition), SVM (SL, class. and regr.), Logistic Regression (Stat.model /ML, class.), SHAP algorithm (variable selection and interpretation)	No
Ens. Learn. = ensemble learning, class. = classification, regr. = regression, surv. an. = survival analysis, XGBoost = extreme gradient boosting algorithm, Lasso= Least Absolute Shrinkage and Selection Operator, PRN = partial response network, IHTSA = International Heart Transplant Survival Algorithm, IMPACT = index for mortality prediction after cardiac transplantation, EBM= explainable boosting machines, LM = linear model, DL= deep learning, Stat. model = statistical model, ML = machine learning, KNN = k-nearest neighbor, RF= random forest, AdaBoost = Adaptive Boosting, GBM = gradient boosting machine, ANN = artirficial neural network, SVM = support vector machines, SL = supervised learning, RSF = random survival forests, SHAP = SHapley Additive exPlanations, SVM-FuzCoC= Support Vector Machine with Fuzzy-Complement Output Coding				

Following, in order to evaluate the predictive performance of the AI models, the results of performance metrics from internal validation processes have been presented, indicating the model's accuracy in predicting health outcome(s) (like mortality or graft failure) based on patients' data (Table 3.6). The metrics that have been used to evaluate the predictive performance of AI models, for discrimination were AUROC (Area Under the Receiver Operating Characteristic curve), Precision Recall curve (4,11,9) , Sensitivity (7,8,14,15,13,6,12) (n=7), Specificity (7,8,14,15,13,11,6,12) (n=8), Positive Predictive Value (PPV) (8,14,6) (n=3), Negative Predictive Value (NPV) (8,14,6), Harrell's C-index or Concordance Index or

C-statistic (10), G-mean (12), integrated AUC (iAUC)/time-dependent AUC (tAUC) (13), Net Reclassification Index (NRI) (3), Decision Curve Analysis (DCA) (3). Regarding calibration, the used metrics were calibration plots (1,14,3,12,2), Hosmer Lemeshow test (2, 10), integrated Brier score (iBS)/predictive error (PE) (13). Model accuracy was used for either the discrimination or calibration evaluation of the model(s) (7,8,14,21). Model accuracy was used for either the discrimination or calibration evaluation of the model(s). The most commonly used metric was the AUROC or AUC.

Table 3.6 Results of Performance Metrics for Internal Validation of AI models			
#	Performance Metrics	Results	
		Discrimination	Calibration
1	AUROC, Brier Score, calibration plots	For 1-year survival Shuffled 10-fold cross validation (CV): Random Forest (0.893, 95% CI: 0.889-0.897), XGBoost (0.820, 95% CI: 0.814-0.826), LR (0.661, 95%, 0.654-0.668), Cox Regression (0.638, 95%, 0.632-0.645), Rolling CV: XGBoost (AUC 0.657, 95% CI: 0.647- 0.667), LR (0.641, 95% 0.631-0.651), RF (0.634, 95%, 0.624-0.644), Cox Regression (0.615, 95%, 0.606-0.625), For time-to-event information, SGB (0.621; 95%CI: 0.611-0.630), RSF (0.619, 95%, 0.610-0.629) For 90-day survival Rolling CV LR (0.674; 95%, 0.662-0.686), XGBoost (0.669, 95%, 0.657-0.681), RSF (0.647, 95% 0.636-0.659), RF (0.645, 95%, 0.633-0.657), SGB (0.631; 95%, 0.620-0.643), Cox regression (0.625; 95%, 0.613-0.637)	For 1-year survival Shuffled 10-fold cross validation Brier Score: RF 0.060, XGBoost 0.072, L2 Logistic Regression 0.225, Cox Regression 0.106 Rolling cross-validation XGBoost 0.202, L2 LR 0.202, RF 0.129, Cox Regression 0.096 Calibration Plots: RF (intercept -0.061, slope 0.586), XGBoost (-0.090, 0.462), L2 LR (-0.039, 0.352), Cox Regression (0.003, 0.902), RSF (0.008, 0.752), SGB (-0.080, 1.500) For 90-day survival Rolling cross validation Brier Score: L2 LR 0.177, XGB 0.179, RF 0.082, Cox Regression 0.059
2	AUROC, Hosmer–Lemeshow chi-square (HL)	PRN - LASSO 0.653 (95% CI 0.643–0.662) in Development Phase and 0.605 (95% CI 0.582–0.628) in Training Phase For discrimination: PRN-LASSO 0.628 (CI 95%: 0.602–0.654), IHTSA 0.635 (CI 95%: 0.609–0.662) p = 0.488, IHTSA recalibrated 0.643 (CI 95%: 0.617–0.669), p= 0.197,	Hosmer–Lemeshow (HL) chi-square was 15.01 for the PRN model (p = 0.135) calibration for IHTSA and IMPACT models was poor (p < 0.001)

		IMPACT 0.602 (0.575–0.628), p= 0.094, EBM 0.634 (0.607–0.660), p= 0.173. External Validation: PRN-LASSO full data set imputed 0.626 (CI 95%: 0.588–0.665)	External validation: Calibration plot for PRN-LASSO for full data set imputed intercept = 0.976 slope: 1.141
3	AUROC, Net Reclassification Index (NRI), Decision Curve Analysis (DCA), calibration plots	Full Ensemble ML method 0.764 (95% CI, 0.745–0.782) (p < 0.0001), Neural Network Ensemble 0.691 (95% CI 0.671- 0.712), p <0.0001, LR ensemble 0.691 (0.671-0.712), p <0.0001, Adaboost Ensemble 0.653 (0.632-0.674), p < 0.0001, Random Forest Ensemble 0.691 (0.671-0.711), p<0.0001, Logistic Regression (singular) 0.649 (0.628-0.670), p<0.0001 Ensemble method NRI 72.9% ± 3.8% (p < .001) improvement compared to LR, p<0.001. DCA: the full ensemble method improved risk prediction compared to all other models	Calibration Plots Full Ensemble Method, well calibrated, intercept -> 0, slope -> 1
4	AUROC, Precision Recall curve	AUROC : XG Boost 0.71 (95% CI: 0.62–0.78), Precision Recall Curve: AUCPR = 0.357 for the XGBoost model	NR
5	AUROC	Prediction of mortality and graft failure at 5 years of GBMachine 0.717 (95% CI 0.696–0.737) and 0.716 (95% CI 0.696–0.736) respectively	NR
6	AUROC, Sensitivity, specificity	1-year mortality Adaboost 0.689 (95% CI 0.665–0.715), IMPACT 0.57, SVM 0.637, KNN 0.526, DT 0.650, LR 0.642, Sensitivity: Adaboost 63%, SVM 63.4%, KNN 42.6%, DT 57.5%, LR 61.1%, Specificity: Adaboost 68.5%, SVM 55.6%, KNN 62.4%, DT 67.9%, LR 59.2%, PPV Adaboost 21.6%, SVM 16.5%, KNN 13.5%, DT 19.9%, LR 17.1%, NPV Adaboost 93.6%, SVM 91.7%, KNN 88.7%, DT 92.1%, LR 91.7% 3- and 5- year mortality AUC Adaboost 0.605 and 0.628, respectively. 3-year mortality Sensitivity 62.07%, specificity 54.73% 5-year survival Sensitivity 61.44%, Specificity 59.56%	NR
7	AUROC, Accuracy,	For discrimination: RF 0.801(95% CI: 0.697–0.891), Adaboost 0.641 (0.479-0.788),	NR

	Sensitivity, Specificity	LR 0.688 (0.549-0.816), SVM 0.714 (0.574-0.834), XGBoost 0.769 (0.662- 0.869), GBM 0.786 (0.661–0.896), ANN 0.755 (0.639- 0.851), Naïve 0.500 (0.500-0.500) Accuracy, Sensitivity, Specificity : RF 0.828 (0.747–0.899), 0.268 (0.059–0.529), 0.927 (0.866–0.976), Adaboost 0.798 (0.717–0.869), 0.260 (0.059–0.500), 0.894 (0.821–0.954), LR 0.807 (0.727–0.879), 0.201 (0.000–0.429), 0.917 (0.851–0.966), SVM 0.849 (0.778–0.919), 0.000 (0.000–0.000), 1.000 (1.000–1.000), XGBoost 0.828 (0.747–0.899), 0.138 (0.000–0.353), 0.953 (0.902–0.989), GBM 0.819 (0.737–0.889), 0.271 (0.077–0.533), 0.916 (0.845–0.966), ANN 0.849 (0.778–0.919), 0.066 (0.000–0.214), 0.988 (0.962–1.000), Naïve 0.848 (0.778–0.909), 0.000 (0.000–0.000), 1.000 (1.000–1.000), respectively	
8	AUROC, Predictive accuracy, sensitivity, specificity, PPV and NPV	1-year survival: CatBoost 0.800 (95%CI: 0.687, 0.811), predictive accuracy of 75.2%, a sensitivity of 75%, a specificity of 75%, a PPV of 42%, and a NPV of 93%, 3-year survival: CatBoost 0.690, predictive accuracy of 74.2%, a sensitivity of 51%, a specificity of 85%, a PPV of 63%, and a NPV of 78%	NR
9	AUROC, precision recall curve	For random imputation, one hidden layer network AUROC 0.690 (95% CI 0.67 - 0.69), precision recall curve 0.082. LR AUROC 0.67 (CI 0.66, 0.68), p-value = 0.002, area under precision-recall curve 0.076	NR
10	AUROC, Harrell's C-index, Hosmer-Lemeshow test	For 1-year mortality, discrimination: AUROC (95% CI) time era: 1997–2008: IMPACT 0.61 (0.59–0.62), IHTSA calibrated 0.69 (0.68–0.70), p= 0.001, time era: 2009–2011: IMPACT 0.61 (0.58–0.63), IHTSA calibrated 0.65 (0.63–0.68), p= 0.001 // Harrell's C-index (95% CI) time era: 1997–2008: IMPACT 0.56 (0.56–0.56), IHTSA calibrated 0.62 (0.61–0.62), p = 0.001, time era: 2009–2011: IMPACT 0.58 (0.56– 0.61), IHTSA calibrated 0.63 (0.61–0.65), p = 0.001	The Hosmer-Lemeshow (HL) for one-year, using ten groups, was of 40 in the IHTSA model and 101 for the IMPACT model, both with a P-value less than 0.05 IHTSA better calibration
11	AUC, Accuracy, specificity,	1-year graft survival: LR.NO AUC (standard deviation) 0.630 (0.027), Accuracy 0.881	NR

	precision recall curve	(0.012), Recall 0.128 (0.083), Specificity 0.988 (0.016) 5-year graft survival : LR.NO AUC 0.677 (0.024), Accuracy 0.679 (0.010), Recall 0.354 (0.018), Specificity 0.861 (0.019) 9-year graft survival: LR.NO AUC 0.840 (0.027), Accuracy 0.748 (0.027), Recall 0.820 (0.024), Specificity 0.593 (0.052)	
12	G-mean, AUROC, Specificity, Sensitivity, Accuracy, calibration plots	(Algorithm, G-Mean, AUC, Specificity, Sensitivity, Accuracy): LR: 0.610 (0.599, 0.621), 0.655 (0.645, 0.664), 0.593 (0.575, 0.611), 0.629 (0.618, 0.639), 0.624 (0.614, 0.633) UP-LASSO-logistic regression (Month 1, Year 1, Year 2, Year 3, Year 4, Year 5, Year 6, Year 7, Year 8, Year 9, Year 10): AUC 0.608, 0.581 ,0.571 ,0.594 ,0.619 ,0.631 ,0.654 , 0.671 ,0.698 ,0.703 ,0.702	Calibration Plots: UP-LASSO-logistic regression survival probabilities underestimate the observed averages for the first 5 years. For the later years, the predicted probabilities are relatively close to the observed ones.
13	iAUC, tAUC Integrated Brier Score (iBS) and predictive error (PE), sensitivity, specificity, accuracy	Model, time of prediction, iAUC/tAUC (95% CI) (p value), 1 to 48 mo: RSF 0.879 (0.832-0.921), Cox 0.658 (0.572-0.747) <.001, 1 mo RSF 0.858 (0.792-0.917), Cox 0.624 (0.523-0.728) <.001, 1 y RSF 0.921 (0.877-0.957), Cox 0.717 (0.633-0.800) (<0.001) 1-month survival prediction: RSF sensitivity 86.1%,specificity 68.7%, accuracy 72.9%. 1-year survival prediction RSF sensitivity 88.7%, specificity 79.6%, accuracy 82.8%	iBS (95% CI) (p value) 1 to 48 mo: RSF 0.130 (0.106-0.154), Cox 0.205 (0.176-0.233) (<0.001), 1 mo: RSF 0.123 (0.096-0.153), Cox model: 0.181 (0.100-0.219), (<0.001), 1 y: RSF 0.115 (0.095-0.139), Cox model: 0.195 (0.098-0.225) (<0.001)
14	AUC, Specificity, Sensitivity, PPV, NPV, calibration plots	1-year survival: Model, Specificity, Sensitivity, PPV, NPV, AUC Clinician 0.67 (0.65-0.68), 0.52 (0.48-0.57), 0.22 (0.19-0.24), 0.89 (0.87-0.90), 0.61 (0.58-0.64), LASSO, 0.75 (0.73-0.77), 0.41 (0.37-0.46), .22 (0.20-0.26), 0.90 (0.88-0.91), 0.61 (0.58-0.64), Random Forest, 0.76 (0.74-0.77), 0.44 (0.39-0.48), 0.24 (0.21-0.27), 0.89 (0.87-0.90), 0.62 (0.59-0.65), Chan et al. 2019, 0.68 (0.66-0.70), 0.48 (0.43-0.52), 0.21 (0.18-0.23), 0.88 (0.86-0.89), 0.59 (0.56-0.61), LAS, 0.66 (0.64-0.67), 0.44 (0.39-0.49), 0.18 (0.16-0.21), 0.87 (0.85-0.88), 0.55 (0.52-0.68)	Calibration slope LASSO model (1.45, 95% CI [1.10, 1.80]), clinician (0.85, 95% CI [0.67, 1.10]) Random Forest models (0.96, 95% CI [0.76, 1.16])
15	AUC, Accuracy,	For both short-term and long-term survival prediction, Model, Accuracy, Sensitivity,	NR

	Sensitivity, Specificity	Specificity, AUC: DT, 60.78%, 61.60%, 59.97%, 61% GBT, 71.75%, 67.14%, 76.25%, 74% RF, 77.92%, 76.26%, 79.58%, 79% KNN, 61.01%, 51.73%, 70.07%, 65% ANN, 66.67%, 57.89%, 75.25%, 70% SVM, 65.20%, 51.73%, 78.35%, 65% LR, 69.47%, 64.45%, 74.38%, 75%	

According to the results, the AI models showed very good discriminatory performance in predicting post-transplant health outcomes, and the predicted values were well aligned with the observed values for long term outcomes (12). The AI models with the best performance, based on AUROC metrics, for the prediction of 1-year post-transplant mortality, were the XGBoost 0.71 (4), and the Random Forest 0.801 (7). For the 1-year post transplant survival outcome, the models that showed the highest performance, based to AUROC metrics, were the shuffled 10-fold cross validation Random Forest 0.893 (1), Random Forest 0.790 (15), Random Survival Forest 0.921 (13), CatBoost 0.800 (8), and an Ensemble ML method 0.764 (3). For the 3-year survival, the highest discriminatory performance was shown by the CatBoost 0.690 (8), with an accuracy of 74.2%. For the prediction of graft failure and survival, the most effective model is Logistic Regression 0.840 for 9-year survival (11) ,a MultiLayer Perceptron with only one hidden layer 0.690 for 30-day survival (9), and Gradient Boosting Machine 0.716 for 5-year graft failure (5) . For predicting 1-year survival, higher sensitivity and specificity were demonstrated by RSF (88.7% (13) and 79.6% (13)). In addition RSF showed the best accuracy 82.8% (13), the CatBoost model showed the best PPV 42% (8) and NPV 93% (8). For 1-year mortality, SVM and Naive models showed the highest accuracy (84.9%) (7), and GBM showed the highest specificity 91.6% (7), while Catboost showed the highest sensitivity 75% (8). Regarding calibration of AI models, RF, XGBoost and Cox Regression showed good calibration based on their Brier Scores (0.060, 0.072, 0.096, respectively) (1), for 1-year survival. Likewise, based on the calibration plots, for 1-year survival, Cox Regression (intercept: 0.003, slope: 0.902) (1), and RSF (intercept: 0.008, slope: 0.752) (1), showed the best alignment of predicted probabilities to the observed ones. Based on Hosmer-Lemeshow test, the Partial Response Network-LASSO showed the best calibration (15.01, $p = 0.135$) (2), in comparison with IHTSA (40, $p<0.05$) and IMPACT (101, $p< 0.05$) (10), for the prediction of 1-year mortality.

In each study, there were limitations that affected the accuracy of the models and caused biased assumptions about results and outcomes. The most common limitation that scientists confronted in their research was the retrospective analysis of data from cohort or registry data, which encompasses the inability to review time-to-event data firsthand, handle properly missing data, or collect further information about different variables and features. Missing values is the next most significant limitation in the development of AI models, impacting the generalizability of models, their accuracy, and their discriminative strength. Other factors that contribute to restriction of the AI models' functionality are data quality and variability, that are often in dispute, absence in some databases of donor variables, variables concerning pre-transplant or waiting list phase, the lack of standardization associated with multi-center studies (non standardized classification of cases, lack of uniform terms), the changes that have been implemented in allocation systems throughout the years, clinical management of substantially ill patients, or the management of post-transplant patients, the absence of external validation in most of the studies except of study number (2), class imbalance between groups presenting or not the health outcome(s), small and insufficient population sample and under-representativeness of minority classes, causing poor sensitivity, lack of transparency and explainability of Machine Learning models as well as lack of comparisons between other artificially intelligent models, that could help to the assessment of non-inferiority.

3.3.3 Risk of Bias Assessment

To draw safe conclusions about the results that have been collected, it is crucial to make a risk of bias assessment, a procedure that will determine the effect of different biases (e.g. selection, performance, etc.) in the validity and accuracy of the findings of this systematic review. In the following table 3.7, there are demonstrated the results of the assessment process. The analyzed studies were divided into two categories, one about heart transplantations and the other about lung transplantations. In the PROBAST tool, biases concerning participants, predictors (variables), outcome(s) and their analysis, are evaluated, as well as the applicability of studies' methodology to the review question(s). From the assessment, it was concluded that most of the studies appeared to be profoundly biased either due to the exclusion of certain groups of patients during the selection of a representative sample for the research (1,4,7,8,14,15,13,3,11,9,5,6,12,2), or due to the inclusion of variables in the development dataset that may not be available during the application of the predictive machine (4,8,13,3,5,6,2), or due to the use of small, unstandardized patient registries or cohorts (7,13), or due to the low number of patients with the relative outcome (4,7,15,13,12), or due to the absence of calibration metric methods (4,7,8,15,11,9,5,6). The examined studies seem to be overall applicable to the review question and objectives, compared to the overall risk of bias, which is explained by the determination of more general inclusion criteria to this present review.

Table 3.7 Assessment of risk of bias with the use of PROBAST (Prediction model Risk Of Bias ASsessment Tool)

HEART									
	Risk of Bias (ROB)				Applicability			Overall	
#	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability
1	+	✗	✗	+	+	✗	✗	+	✗
2	+	+	✗	+	+	✗	✗	+	✗
3	+	✗	✗	+	✗	✗	✗	+	✗
4	+	+	✗	+	✗	✗	✗	+	✗
5	+	+	+	+	+	+	✗	+	+
6	+	+	✗	+	✗	✗	✗	+	✗
7	+	✗	+	+	✗	✗	✗	+	✗
8	+	+	✗	+	✗	✗	✗	+	✗
9	+	✗	✗	+	✗	✗	✗	+	✗
10	✗	✗	✗	+	+	✗	✗	+	+
11	+	✗	✗	+	+	✗	+	+	+
12	+	✗	✗	+	+	✗	+	+	+
LUNG									
	Risk of Bias (ROB)				Applicability			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability

13	➕	➕	➕	➕	❌	❌	➕	➕	➕
14	➕	❌	❌	❌	❌	❌	❌	❌	❌
15	➕	❌	❌	➕	❌	➕	❌	➕	➕
❌: low risk of bias, ➕: high risk of bias									

Chapter 4
Discussion

4.1 Comments on Results

Transplantation of heart or lung organs seems to be a complex medical procedure demanding high-quality health services offered by expert staff, the prognostic and diagnostic infallibility of technical equipment, as well as specially developed infrastructure that meets the unique requirements of this very sensitive and accurate procedure. In the present research, the scope was to assess the overall efficacy and implications of AI models in health, especially in the context of heart and lung transplantations, given the extensive use of AI in medical settings across the globe. Although AI applications in heart or lung transplantations have been studied in the past, a thorough examination of the relationship between AI models and patient health outcomes is lacking. The objectives of this study were to evaluate artificial intelligence's impact on lung or heart transplant procedures by presenting performance metrics, to examine the AI models' effect on patient health outcomes, and to address the biases and bioethical concerns that arise from their use.

From the 15 studies that were included in the analysis of this present research, some conclusions were drawn regarding the performance of AI models and their impact on patients' health outcomes. Machine learning, deep learning algorithms depend on the input dataset's size in order to develop accurate and efficient models and benefit from large datasets (Lina Zhou et al. 2017, Alexandre Bailly et al. 2022). Most of the included studies used large datasets, ranging from 381 to 103,570 participants, with a mean value of approximately 29,536 participants and a median of 19,900. Large population datasets can provide more data points for investigation, capture more patterns that could be interpreted by AI and lead to more reliable conclusions. In systematic reviews of Gholamzadeh et al. 2022 and Naruka et al. 2022 dataset sizes ranged from 30 to 310,773 records, while the most used database for data extraction was the UNOS database, as in the present research. Over the last few years, there has been a strong interest in the use of small scale samples to develop and train AI models because of their capacity to generate high quality output relying on more specific groups, in order to reduce overconsumption of resources and energy. In addition, novel AI technologies have the capacity to generate high quality artificial samples using different techniques, like transfer learning, which involves training existing models on smaller and more specific groups, or hyperparameter tuning (Douzas G et al. 2022, Bose S et al. 2021, Dahmen J et al. 2019). In the studies included in the present review, there were no artificially sampled augmentation techniques implemented, but another technique called "hyperparameter optimization" was applied in order to attain better performance of the model by optimizing the parameters of the algorithm prior to the development of the AI model (Lisboa et al. 2022, Shou et al. 2022, Agasthi et al. 2020, Kampaktsis et al. 2021, Linse et al. 2023, Tian et al. 2023).

Diversity and inclusion of minority groups in research have become very important issues over the last few years. Discriminations in research, especially research relating to health, wouldn't be missing, as most of the studies that were analyzed present a remarkable disparity between men and women who had already had a transplant and between white people and black, Asian, or Hispanic people. This great inequality in transplant procedures isn't solely a consequence of AI applications; it originates from structural discrimination. It may affect the development of biased and non-inclusive AI models and, subsequently, the decision-making for organ allocation, donor-recipient pair-matching, or post-transplant prognosis. In the present review, results about the demographic characteristics of the study populations suggest that there's structural discrimination against female and non-white organ recipients, as their numbers do not approximate the number of male and white recipients. The same suggestion applies to the diversity of donors. In both groups, male and white subjects outweigh non-white and female subjects. In contrast with the present systematic review, other researchers like Naruka et al. 2022, Palmieri et al. 2023, Gholamzadeh et al. 2022, Rahman et al. 2023, have included studies with pediatric population samples in their reviews. There are no mentions made about religious or socio-economic backgrounds; that is a common ground for the present research and other reviews. Most of the studies included in this review used data extracted from the UNOS database, an American transplant database that collects, edits, analyzes, and stores information about donors, recipients, and procedures derived from the United States of America. Despite the representation of many American ethnic groups, small population groups like American Indians are excluded from research, marking the great disparities that people experience and the major impact they may have on public health policies regarding American citizens (Korngiebel DM et al. 2015). Moreover, a significant remark is that there are only two studies that were conducted in China, and the other two studies contain data from international registries. It seems that researchers from around the world prefer the UNOS database as a reliable and accurate resource to extract data for the development of their models. However, that might pose serious restrictions on the generalizability and performance of AI models when they are applied to different and distinct populations, compared to the development dataset.

It's notable that one of the main purposes of artificial intelligence applications in health is the prognosis or prediction of a health outcome or a disease. Specifically, in the present review, the main purpose of AI applications was the evaluation of the performance of AI models in the prediction of post-transplant survival, mortality, graft dysfunction, or graft failure in patients with an underlying heart or lung disease. Naruka et al. extracted data from studies that covered similar purposes and had similar objectives as the present review, differing in that in the present review there were no pediatric-related studies included. The optional timeframe for data selection and analysis, starts from the very first moment after the completion of transplantation surgery and will last for as long as the follow-up procedure goes on. That time period is divided into three parts, the short-term (0-3 months), the mid-term (3-12 months) and the long-term (over 1 year). In transplantation research, long-term post-transplant follow-up and clinical evaluation get more complicated and difficult due to patient withdrawal and, subsequently, the loss of essential input data. That's a core reason that the prediction of 1-year health outcome(s) is primarily selected as a targeted outcome. Additionally, a 1-year outcome is often regarded as a more stable and trustworthy timeframe where most complications are likely to manifest, patients are expected to be mostly adapted to the new organ(s) and proper treatment is expected to have a greater possibility of success (Gibbons A et al. 2021, Ruck JM et al. 2024, S. Rabbani et al. 2021). In the present systematic review, it was observed that the prediction of 1-year health outcome was the most frequently studied outcome, with mortality or patient survival being the main outcomes. There were also results about 30-day, 90-day, 1-month, 3-year, 5-year, 9-year and long term outcomes. In Palmieri et al. and Naruka et al. reviews, there are likewise presented studies predicting 3-month, 1-year, 3-year, 5-year or more health outcomes for post-transplant patients.

The variety of AI model types that have been used in the reviewed studies is wide, encompassing different kinds of algorithmic classes like linear models (Logistic Regression) (Miller et al. 2022, Zhou et al. 2021, Amini et al. 2022, Ayers et al. 2021, Dag et al. 2017, Linse et al. 2023, Kampaktsis et al. 2021, Dolatsara et al. 2020, Medved et al. 2018), decision tree-based models (Decision Trees, Random Forest) (Miller et al 2022, Zhou et al 2021, Brahmbhatt et al 2022, Amini et al 2022, Ayers et al 2021, Dag et al 2017, Kampaktsis et al 2021, Dolatsara et al 2020), support vector machines (Amini et al 2022, Dag et al 2017, Kampaktsis et al 2021, Dolatsara et al 2020) or neural network models (Zhou et al 2021, Amini et al 2022, Ayers et al 2021, Dag et al 2017, Dolatsara et al 2020, Medved et al 2018). Most of the models are classified into the supervised, semi-supervised learning group of algorithms due to their potential for classifying and regressing observed and independent values, relying on labeled data, highlighting the widespread application and significant impact of ML algorithms on healthcare due to their profound efficacy, interpretability, and transparent feature engineering. None of the algorithms used in the reviewed studies of the present research are classified as unsupervised learning algorithms.

A model may perform exceptionally well in the development population but in a poor manner in an external sample since the prediction algorithm is customized based on the development data. In the evaluation process, external validation plays an essential role since it offers a third-party assessment of the model's performance on untrained data and constitutes a tool for the corroboration of credibility. In most of the studies, different techniques were applied for the assessment of overfitting (the remarkably good performance of a model when applied to training data), like cross-validation (Miller et al 2022, Zhou et al 2021, Amini et al 2022, Ayers et al 2021, Dag et al 2017, Linse et al 2023, Agasthi et al 2020, Dolatsara et al 2020, Lisboa et al 2022, Medved et al 2018), bootstrapping (Shou et al 2022, Zhou et al 2021, Tian et al 2023), instead of implementing external validation (Lisboa et al 2022). By introducing these techniques into the validation process, biases regarding randomness, sampling, and selection are mitigated, but there’s a strong concern about the size and representativeness of the dataset. In the present study, there was only one study (Lisboa et al. 2022) in which external validation of the AI model, which was first trained on the UNOS dataset (which contains data from transplantations performed in the USA), was implemented on a differentiated patient dataset (the Scandinavian Thoracic Transplantation Database), which contains data about thoracic transplantations performed in Norway, Denmark, Sweden, Finland, and Estonia. External validation processes can be divided into three types: the first type concerns validation on the same or similar population and setting, matching the development dataset; the second type concerns multiple datasets matching the target population and setting; and the third type concerns totally different datasets (Sperrin M. et al. 2022). In the study of Lisboa et al. 2022, the external validation concerned a matching population and setting, differentiating by demographic characteristics and specifically geographically (geographic validation), that was not performed in a separate study, raising concerns about experimenter, confirmation, or publication biases introduced by the development scientific team, as well as questioning the integrity of the evaluation process (Chava L Ramspek et al. 2021).

For the evaluation of models’ performance, the process involves two significant components: the calculation of discrimination and calibration. Calibration determines the alignment of predicted and observed risks. The ability of a model to distinguish patients who have and do not have a specific feature or health outcome is determined by discrimination. In the present review, certain performance metrics have been included in the analysis. In Agasthi et al. 2020 study, AUROC or AUC is considered the best discrimination metric among others. It can take values from 0 to 1, showing exceptional discriminative strength when it is close to 1, and poor discrimination when it's closer to 0.5. Acceptable prices are above 0.6 that show a good model's efficiency in predicting higher risk for subjects with the outcome compared to subjects without the outcome (White N. et al. 2023). In the present review, the performance metric values of AI models varied according to the outcomes, the time periods, and the implemented internal validation techniques. According to the results of the present systematic review , 10-fold cross validation Random Forest (AUROC 0.893) (Miller et al 2022), Random Forest (AUROC 0.801) (Zhou et al 2021), and CatBoost (AUROC 0.800) (Kampaktsis et al 2023), exhibited excellent discrimination, and good calibration in predicting 1-year mortality. For the 1-year post transplant survival, RF (AUROC 0.790) (Amini et al 2022), RSF (AUROC 0.921) (Tian et al 2023), and Ensemble ML method (AUROC 0.764) (Ayers et al 2021) seem to have shown the highest AUC values. Likewise, sensitivity and specificity values pointed out the elevated accuracy of Forest AI models in the prediction and classification of binary outcomes like mortality or survival. In the Clement et al. review 2021, a key point that needs to be elaborately examined and emphasized is that the most commonly used AI models are Random Forest and Artificial Neural Networks in the research of AI applications in solid organ transplantations. This finding can be substantiated by Nursetyo et al. study 2019, where Decision Trees and Artificial Neural Networks showed very good discrimination (around AUC 0.700-0.800) and accuracy that was over 0.750 for both models, while Random Forest showed very good discrimination (AUC 0.800-0.850) in the prediction of graft rejection after kidney transplantation too. Moreover, in the Senanayake S. et al. study 2019, AI models have been used to predict kidney graft survival after transplantation at different time points, like some days or even years after the procedure. The models showed very good discriminative strength, with AUC ranging from 0.65 to 0.88, including Artificial Neural Networks and Random Forest, which outperformed other techniques - traditional linear methods like logistic regression or cox regression - a point that was similarly highlighted in the present systematic review. It's remarkable that few studies include time-to-event data using survival models. In contrast with the previously mentioned studies, the present research included studies that used time-to-event data (survival analysis techniques) in the development datasets. Survival observations like the time of diagnosis or onset of a disease, the time of death, the end of follow-up, or the time of censoring seem to have a profound impact on the predictive performance of AI models on real-world health outcomes, and subsequently, they could affect primarily clinicians' decision-making (Dey T et al. 2022,Jennifer Le-Rademacher et al. 2021).

4.2 Bioethical Considerations

Speaking of AI models in solid organ transplantations, there come up great questions about the ethical concerns that arise from the procedures. First of all, in order to address these concerns, it would be wise to point out certain essential facts about AI applications in transplantations. Consider the fact that AI models are basically machines, which are created, developed and programmed by humans to collect, analyze, decode, edit, and produce information according to the demands of their creators. They are able to manage large amounts of data at a tremendously fast pace and detect patterns and connections between data points that humans are not capable of. Some of their functions are still incomprehensible to humans due to lack of transparency and complex algorithmic models. Over the last few decades, novel AI applications have taken over in different healthcare settings, like transplant settings, for decision-making, detection of complications, or prediction of health outcomes. By analyzing those facts, certain ethical considerations emerge and need to be addressed, which relate to the liability and accountability of AI models, the biases and discriminations that output isr subject to, the opacity of AI processes, and the safety, privacy, and misuse of patients' data by AI models and their developers.

4.2.1 Liability and Accountability

In AI model development, different parties are included, such as software developers, healthcare organizations, regulatory agencies, and healthcare providers, that are in charge of creating, applying and monitoring AI technology in solid organ transplantations. However, there are critical concerns about the duty of care that healthcare professionals owe to patients, while software developers have no such duty, and the responsibilities that need to be assigned when patients are harmed or negligence occurs in the design or implementation of AI models. Standard guidelines and legal frameworks are currently lacking in solutions and measurements for

AI-provoked harm to patients (Mittelstadt B 2021, p. 13-19). Clinicians may be unable to evaluate the AI recommendations, thus drawing false conclusions and making wrong decisions in a clinical setting, or even worse, some fully autonomous machine learning models are perfectly capable of performing in an unsupervised manner, figuring out the hidden patterns that connect data and processing them in ways that people have no control over (Maliha G et al. 2021). That results in complicated procedures (namely the “AI black box”), making it difficult to figure out who’s responsible and for what (Sullivan HR et al 2019). Making a decision relying on opaque methods raises a concern about the accountability of clinicians and whether they should be morally responsible when AI reaches conclusions in ways that neither the clinicians nor software developers may know, thus not being fully responsible for any harm that may be caused by, for example, the continuation or cessation of a treatment (Habli I et al. 2020). In the case of transplantations, it’s far more complicated because the false interpretation of a patient's clinical records could lead to a false decision by the clinicians, about whether to have or not have a transplant, subsequently leading to the loss of a second chance at life.

4.2.2 Biases and Discrimination

Biases can be found literally in every single phase of artificial intelligence model development and procedure, as they’re naturally inherent in social values, structures, laws, and behaviors that their human creators unintentionally integrate into datasets, algorithms, or output interpretation methods. However, biases also originate from datasets and the analysis of output by clinicians (Ueda D. et al. 2024). In the present review, there was a separate risk of bias assessment performed in order to assess how biased the conclusions that scientists have drawn in their studies are, and to figure out the sources of bias in research on AI applications in heart or lung transplantations. From the analysis that was conducted, it’s apparent that the most biased parts of studies concern the representation of populations in research, the inclusion and exclusion criteria, the occurrence of missing values and their mishandling, as well as the absence of calibration estimates that indicate high or poor reliability on predicted outcomes. Speaking of selection and sampling bias, it is noticed that the studies’ samples comprised mostly of white and north american men, with little representativeness of women or different nationalities groups, as

Mittelstadt et al. mention on their report too (Mittelstadt et al. 2021, p.49). Those minority biases that are introduced by the under-representativeness of minority groups increase systemic discrimination, lead to false results (for example, female subjects’ metrics may be incorrectly analyzed) and lead to poor performance of AI models (poor predictive performance of health outcomes, detection of variances in biometric values, acute graft dysfunction symptoms) when applied into the general population (overfitting phenomenon) (Ueda et al. 2024). The studies that have been analyzed in this review used and extracted data retrospectively from cohorts or patient registries, which have been standardized, preprocessed, missing values been handled and got ready for analysis compared to real-world data that AI models may encounter in real-life clinical settings for the stratification, labeling of cases or production of output for decision-making (Abràmoff MD et al. 2023). Through the present systematic review, specific biases have been addressed, but there are certainly more disparities that many groups experience in healthcare, like impaired people or LGBTQI+ people, and specifically in the the AI - transplant field, that need to be pointed out (Sargiotis G.-C. 2023).

4.2.3 Opacity and Transparency

Machine learning models, and especially deep learning methods, have three basic layers (input, hidden, and output). The hidden ones may have such a complex structure that their connections may not be interpretable, so transparency of procedures may be impossible and comprehension of the reasoning behind the production of output and results may greatly affect the critical thinking and decision-making of clinicians. Lack of tangible and intelligible evidence affects the explainability and fairness of AI in healthcare. Concerning explainability, it should be mentioned here that according to traditional statistical methods, predictors that seem to have an important impact on health outcome prediction have totally different effects when analyzed by AI models. The interpretation of predictor importance may be related to the linearity of traditional statistical methods compared to the multi-dimensional approach of machine learning models to the data. For example, in the present review, there is little reference to HBV infection, and HBsAg positivity seems to have a slight importance in the prediction of mortality, graft failure, or other complications that are instigated, unlike what the literature claims (Avelino-Silva VI et al. 2010, Thongprayoon C et al. 2018). The opacity of procedures affects healthcare in different ways, like hindering clinicians from fully trusting the machines and affecting the validation and evaluation procedures (Amann J et al. 2020). Lack of transparent AI algorithms makes the need for a relative legal framework and development of guidelines imperative, as more and more applications of AI in heart or lung transplantations will occur in the future. It’s crucial that novel AI or ML approaches in healthcare be fully comprehensible, interpretable, and understandable by clinicians and staff (who are not software experts) (Elendu C et al. 2023).

4.2.4 Safety, Privacy and Consent

Advancements in AI and solid organ transplantations are accompanied by significant concerns about privacy, consent, and safety of patients. Artificial intelligence applications in transplantations require vast amounts of private health data in order to process them. To perform a transplantation, each participant's legal consent must be acquired. It is crucial for the smooth operation of procedures that the models work properly and methods be to a sufficient extent intelligible to patients in order to create a safe place for them. The transplant patients must be fully informed, which raises some concerns about the capacity of patients to comprehend the functions of AI, given that neither clinicians nor other staff members have been so far educated or familiar with the inner functions of the algorithmic models, which carry out complex procedures and involve multiple hidden levels (Elendu et al. 2023). Patients often have no clue on the purpose of collecting, processing and using their private data by AI models. It is also quite natural that patients lack digital health knowledge (digital health illiteracy) due to age, cultural, or educational disparities (Kotsenas et al. 2021). A significant concern is whether the staff’s experience on AI-related procedures should be disclosed to patients or not, as some advocate that this information could affect patient’s decisions and their safety. In addition, due to work overload and information overload, errors seem to increase, thus hospitals or clinics are in great need of personnel recruitment or other alternatives should be found, like the application of novel technology that would resolve bureaucracy issues, facilitate operational procedures, and improve the decision-making of clinicians (Nijor S et al. 2022). However, there are critical and ethical considerations about the safety of patients regarding the implementation of AI models in procedures. So far, humans have been actively performing in an efficient manner, questioning the abilities of machines and the potential risks that lurk behind the benefits of them (Cohen, I. Glenn 2020).Therefore, it is imperative that legal, ethical and regulatory issues be resolved and legal frameworks define the significance of informed consent in each phase of transplantation procedure (Elisa J. Gordon et al. 2020).

4.3 Conclusions

The present systematic review was developed in an effort to fill the gaps that existed in the literature concerning the impact of AI applications in heart and lung transplant patients' health outcomes, the predictive performance of AI models, and the biases and bioethical considerations raised by the use of machines in transplantations and generally in healthcare. Heart and lung transplantations require high-quality health services involving fully capable and experienced staff, advanced technical equipment, and specialized infrastructure to ensure better health outcomes. The performance of AI models depends on dataset size and variability, with a growing interest in using smaller and more specific samples. However, it's important to state that the use of size-restricted samples may introduce structural discriminations and biases, particularly affecting minority groups relating to transplantations, like female and non-white recipients, which may influence AI model development and decision-making processes. In this review, most of the analyzed studies extracted and utilized data from the UNOS database, a strictly North American-population registry for transplant patients, limiting profoundly the generalizability to diverse populations and geographic regions. Among the AI models that were used in studies, their predictive performance metrics varied greatly, underlying ensemble Ensemble Methods like Random Forest and XGBoost as the most promising and credible models for satisfying results. Supervised learning algorithms were the predominant type of AI model, while unsupervised learning approaches were less common. External validation was a challenge that most scientists chose not to undertake that risky challenge, probably affecting dataset representativeness and integrity and raising concerns about model performance in real-world and real-time clinical settings. In order to evaluate model performance, calibration and discrimination metrics were included in the analysis, pointing out Logistic Regression and Gradient Boosting Machine models as the most efficient in predicting long-term outcomes. It is evident that AI models, especially Machine learning models, outperform traditional statistical models in detecting the non-linearity of data and the hidden patterns that connect data points and lead to certain outputs. Though there is evidence that machine learning methods perform fairly well, exhibiting good discrimination, accuracy, sensitivity, specificity, and calibration (Ravindhran B et al. 2023), there are inconsistencies about the efficiency and performance of AI models in heart or lung transplantations, a finding that indicates the necessity of further thorough research on the applications of machine learning models in heart or lung transplantations.

4.4 Recommendations for future research

Over the last few years, there has been a great interest in AI applications and the benefits people can have from their use in healthcare. In this systematic review, the main scope was to present those facts about the utilization of AI models in transplantations and how they impact patients, that were obtained through a qualitative analysis of related studies. However, it would be more efficient for future research to conduct a meta-analysis study, as both the qualitative and quantitative composition of data would be analyzed, resulting in more thorough knowledge on artificial intelligence predictive performance, the dimensionality of variables, as well as the restrictions and concerns about the biases and limitations of studies. In addition, in the present review, it was considered significant that the analysis be focused on the predictive performance of machines and studies referring to diagnostic performance be excluded. Thereby, considering the evolution of artificial intelligence in the transplantation field, a future research approach on diagnostic capacities of AI models on transplantations, and the use of real-time data in clinical settings for the detection and diagnosis of complications, would substantially benefit decision-making processes and subsequently improve the lifespan and quality of life of transplant patients. Moreover, it would be wise in future reviews that pediatric and adult populations be both included in the analysis, as it would definitely increase the representativeness and generalizability of the findings and results. It seems that AI applications in the heart and lung transplantation fields haven’t been adequately investigated so far, and it’s deemed necessary that further research be conducted in the future in order to have a more intelligible insight into AI capabilities and possible risks from its use in healthcare.

4.5 Limitations

In order to draw safe conclusions, it is crucial to make a mention of the limitations and biases of the present systematic review, which require careful consideration when interpreting the findings. Firstly, the eligibility criteria applied were relatively broad, resulting in the inclusion of studies with considerable heterogeneity in terms of the AI methods utilized, the health outcomes, and the evaluation metrics employed. This variability may have introduced biases and affected the generalizability. Additionally, pediatric populations were excluded from the analysis, potentially limiting the applicability of the findings to non-adult patients and certainly introducing selection and sampling bias. Furthermore, the disproportionately greater number of heart-related studies included in the review compared to lung-related studies may have reoriented the conclusions towards heart transplantations, which could result in leaving out important insights about lung transplant patients' outcomes and feature estimates. Another significant limitation pertains to the lack of a quality assessment procedure that hinders the ability to evaluate the overall quality of the reviewed studies and may negatively impact the reliability of the findings. During the risk of bias assessment, certain biases were deemed to pose a high risk due to inadequate information regarding the research conduct or analysis, raising concerns about the validity of the results. Moreover, it was considered helpful to limit the research only to studies that were published exclusively in English, leading to the exclusion of studies published in other languages, therefore omitting essential information from the analysis. Lastly, both the risk of bias assessment and systematic review analysis of data were conducted by a single analyst, which may have introduced publication, interpretation, or methodological bias. Despite these limitations, it's important that the findings of this review provide valuable insights into the current situation of AI applications in heart or lung transplantations, laying the groundwork for further investigation and enhancement of AI-based approaches in this critical healthcare field.

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