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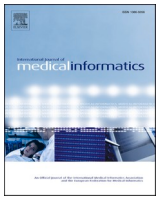

Review article

Artificial intelligence, big data and heart transplantation: Actualities

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ABSTRACT

Background: As diagnostic and prognostic models developed by traditional statistics perform poorly in real-world, artificial intelligence (AI) and Big Data (BD) may improve the supply chain of heart transplantation (HTx), allocation opportunities, correct treatments, and finally optimize HTx outcome. We explored available studies, and discussed opportunities and limits of medical application of AI to the field of HTx.

Method: A systematic overview of studies published up to December 31st, 2022, in English on peer-revied journals, have been identified through PUBMED-MEDLINE-WEB of Science, referring to HTx, AI, BD. Studies were grouped in 4 domains based on main studies' objectives and results: etiology, diagnosis, prognosis, treatment. A systematic attempt was made to evaluate studies by the Prediction model Risk Of Bias ASsessment Tool (PROBAST) and the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD).

Results: Among the 27 publications selected, none used AI applied to BD. Of the selected studies, 4 fell in the domain of etiology, 6 in the domain of diagnosis, 3 in the domain of treatment, and 17 in that of prognosis, as AI was most frequently used for algorithmic prediction and discrimination of survival, but in retrospective cohorts and registries. AI-based algorithms appeared superior to probabilistic functions to predict patterns, but external validation was rarely employed. Indeed, based on PROBAST, selected studies showed, to some extent, significant risk of bias (especially in the domain of predictors and analysis). In addition, as example of applicability in the real-world, a free-use prediction algorithm developed through AI failed to predict 1-year mortality post-HTx in cases from our center.

Conclusions: While AI-based prognostic and diagnostic functions performed better than those developed by traditional statistics, risk of bias, lack of external validation, and relatively poor applicability, may affect AI-based tools. More unbiased research with high quality BD meant for AI, transparency and external validations, are needed to have medical AI as a systematic aid to clinical decision making in HTx.

1. Introduction

In selected patients with advanced heart failure (HF), heart transplantation (HTx) may improve the quality of life, and life expectation [1]. Yet, death rate is higher in subjects who received HTx than in unselected standardized reference populations [2]. As advanced HF most likely worsen over time [3,4], HTx may be triggered by worsening in functional capacity, recurrent hospitalizations, need for circulatory mechanical support [5–7]; however, those conditions predict worse prognosis both pre- and post-HTx [8–10]. Epigenetics may contribute further to estimate prognosis in HF, and therefore candidacy or exclusion to HTx [11–14]. Mandatory requirements [15] to avoid immediate

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post-HTx rejection [16,17], along with the paucity of hearts for HTx, impacts waitlist time, and selects characteristics of the patients persisting on waitlists [18], which in turn may raises concerns on potentially increasing receiver- and donor-related risks of early graft failure [15,19–25]. Therefore, accurate patients profiling for events while on waitlist, and efficient mechanisms of allocation, are growing needs to maximize post-HTx survival [24]. Nevertheless, the waitlist time, and urgency defined by hemodynamics and progressive multi-organ failure, still represent dominant factors for allocation mechanisms in HTx. Algorithms able to measure risk of untoward events before and after HTx, and optimize efficacy of HTx, starting with optimal allocation, are desired targets and unmet needs in the real-world [16,19,26,27]. Ideally, a personalized medicine may be built through deductive and inductive processes of network medicine [28], taking benefits from applications of Artificial Intelligence (AI) to high-quality and medical oriented data, including big data (BD). With this regard, high-quality and medical oriented BD may fuel AI-based processes to develop aids for decision-making may be significantly less affected by biases (Fig. 1), as compared to knowledge built on probabilistic statistics applied to small databases with significant risk of bias [29]. The present review investigated the extent to which AI and BD are used to optimize HTx chain supply and outcome, from HF etiology definition to prognosis pot-HTx.

2. Methods

The present systematic review was conducted following the Preferred Reporting Items for Systematic review and Meta-Analyses guidelines [30], and aimed at reporting scientific papers of the potential role of AI and BD in HTx supply chain, and applicability to the real world. Literature scrutiny targeted the following main issues (Fig. 2): 1) which patient may benefit most from HTx, and when, during the clinical history of advanced HF (i.e., indication, timing, risk while in list); 2) which level of approximation we may tolerate when predicting condition in which HTx is unlikely to improve the patient's specific prognosis, so that alternative surgical treatments should be considered (i.e., appropriateness and futility of the procedure, change in risk–benefit of different surgical procedures over time, weighting and managing error of estimations impacting decisions); 3) how should be estimated the probability of mid-term and long-term survival using current knowledge on factors profiling post-HTx patients in surveillance programs, and improve duration and quality of life after HTx (i.e., predicting outcomes before and after transplantation, define and set minimal therapeutic targets before indications to HTx is issued, monitoring for allograft rejection [31], optimize immunosuppressant therapy; ethical implications raised by patients' clinical status impacting decisions). Thus, full-papers published in English language up to December 31, 2022, were searched in PubMed, OVID-Medline, Web of Science, and Cochrane library. On-line libraries were inquired using standard keywords according to the following hierarchy: "transplantation" and "heart" and "artificial intelligence" and ("big data" or "heath information technology" or "deep learning" or "machine learning" or "algorithm" or "rejection"). Furthermore, selected studies were grouped in the following 4 domains based on objectives and results: Etiology; Diagnosis; Prognosis; Treatment. A systematic attempt was made (collegially by VP, MTV and AM) to give a nonanalytic metric of the quality of the studies according to proposed standards [32], including the Prediction model Risk Of Bias ASsessment Tool (PROBAST)[33] and the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD)[34]. Risk of bias according to PROBAST [33] was scored as the number of items fulfilled among the four pre-defined domains (Participants selection, Predictors selection, Outcome definition, Analysis), and empirically defined as LOW to studies in which at least 66% of the items were traced, whereas it was defined high for studies with less than 33% of the items were traced; those with % of the items traced between 33% and 66% were classified at intermediate risk of bias. Overall quality of reporting was scored empirically as % of the items traced among the 30 indicated by Cabitza F. and Campagner A.[32], all equally weighted. However, external validation was reported separately as potential nonanalytic indicator of quality of reports.

In a specific and original section, as a test of validity, generalizability, and applicability in the real-world of AI-based prognostic functions, an open-access AI-based algorithm to predict post-HTx mortality [24] was applied to a cohort of persons (n = 84 HTx with age above 18 years, urgent cases 39% defined cardiogenic shock or complicated left

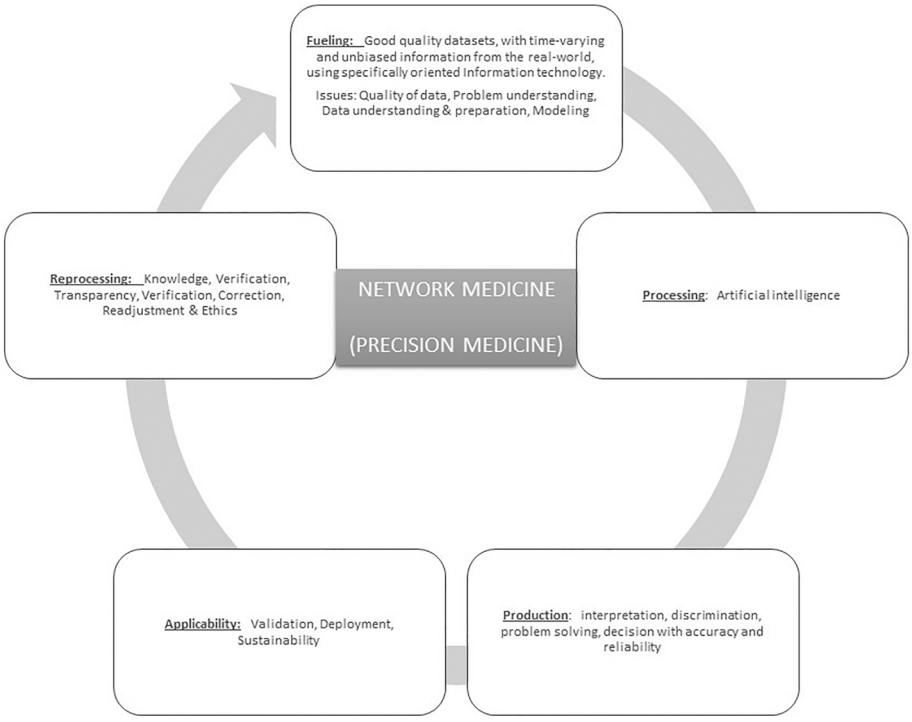

Fig. 1. The process of knowledge-building byartificial intelligence (AI) applied to good-quality datasets from real-world, including Big Data (BD). AI-based of "try-error-feedback-adjust" method of learning mimics human intelligence. Varying and auto-adjusting algorithms, or a network of algorithms, generate predictions, discriminate and make decisions, further providing data and functions for clinical research and applications. Issues related to quality and transparency of reporting on diagnostic and prognostic functions (risk of bias, problem understanding, data understanding and preparation, modeling, validation, deployment and sustainability, see references #32–34) need to be accounted for in order to have well performing, reliable functions yielding reproducible and generalizable outputs.

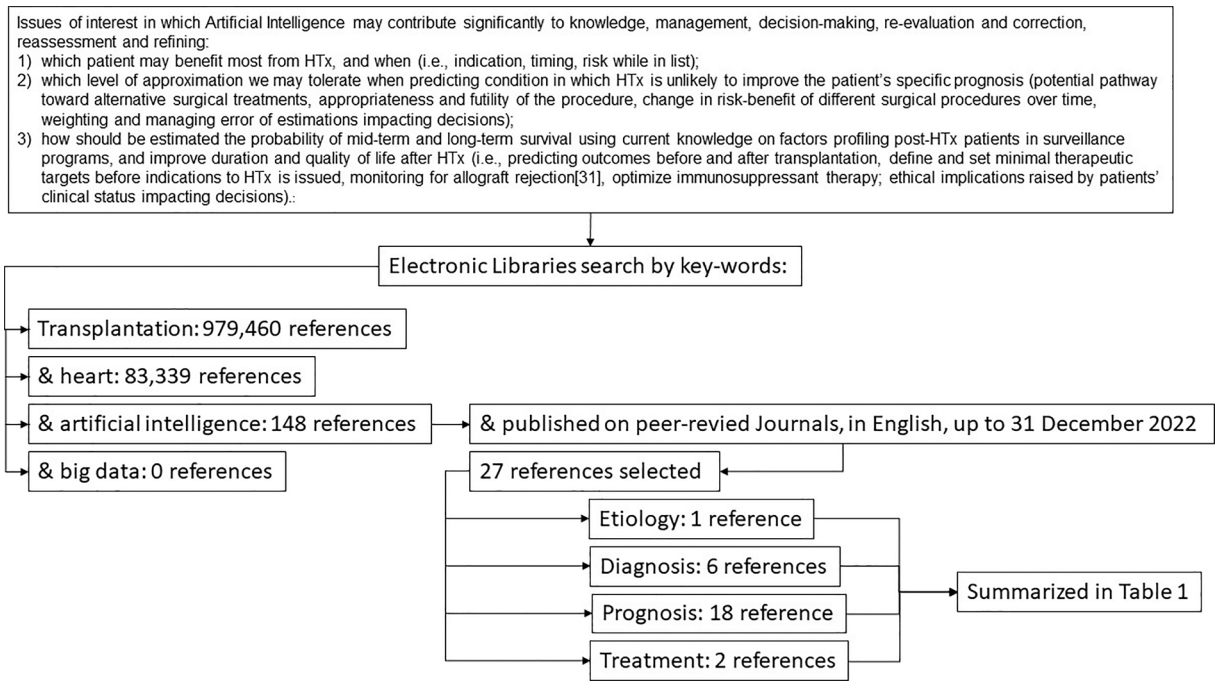

Fig. 2. The flow-chart illustrates the scope, the process of the scrutiny of the electronic libraries to identify appropriate publications, and the results of the selection criteria applied.

ventricular assist devise, or frequent arrhythmias with syncope and effective internal automated cardiac defibrillator shock) selected and transplanted at the Heart Transplantation Unit of the "Azienda Ospedaliera dei Colli Monaldi-Cotugno-CTO". The number of cases was limited to a narrow observation window (2019–2021) to minimize biases by changes in clinical and procedures occurring overtime.

3. Results

Overall, from initial 979,460 papers identified by the term "transplantation", 83,339 referred (nonexclusively) to "heart" (9%), among which 148 (0.2%, 0.02% of the total initial number) referred to "artificial intelligence". Twenty-seven studies were further selected as published in English on peer-reviewed studies, none of which formally used BD (Fig. 2). Table 1 summarizes the selected studies grouped according to the pre-specified domains, and a specific column reporting on risk of bias, eventual external validation of the diagnostic or prediction models proposed, and the extent of information on quality of reporting available on each report. With regard to overall quality of reporting, and empirical index was based on the 30 items grouped in 7 domains identified elsewhere [32]. With regard to the selected studies, information on patients and predictors were in general provided with sufficient details, whereas the more frequently recognized potential bias referred to lack of details on how predictors were identified and examined, details on handling of and reporting on missing data and outliers, clear description of errors, details on model-building strategy. The majority of the models were based on retrospective cohort studies without external validation, aspects related to applicability, and deployment and sustainability of the models [32].

Etiology: Garcia-Canadilla P et al. in 2022 [35] demonstrated that machine learning (ML) may refine the accuracy of identification of a familial/genetic pattern in DCM, and of prognosis, in pediatric candidates to HTx or transplanted. Diagnosis: in experimental animal models, Kienzl et al. in 2009[36] identified 95 protein spots over more than 1,500, associated with 1.5-fold higher likelihood of early acute HTx rejection compared to controls, and generated a novel pathophysiologic and diagnostic models of acute allograft rejection. Others reported that deep learning (DL), supervised by external human aid for decision, may allow automated and standardized identification of tissue characteristics of allograft rejection [37,38]. Castellani C. et al. in 2020[39] used ML to refine diagnostic tools for diagnosis of allograft rejection using plasma derived extracellular vesicles surface protein profiling. Peyster et al.[40] used a system called 'Computer-Assisted Cardiac Histologic Evaluation (CACHE)-Grader' pipeline in 2,472 endomyocardial biopsy slides for an automatic evaluation of density and orientation of lymphocytes, myocytes, and stroma, to be classified in a reproducible 4-grade clinical standard for cellular rejection diagnosis. CACHE-grader was initially trained with the aid of human intervention, the DL-based mechanism for automated interpretation showed 61% agreement [95% confidence interval (CI): 55.2–66.0%] with the reference grade records from human operators, and subsequently showed superior sensitivity for high-grade rejection in validation samples (74.4% vs. 39.5%, $P < 0.001$) compared to reference. Wei et al. [41] applied ML to urinary proteomic for searching and define signature of possible allograft rejection, which could be used for a relatively automatic self-administrated surveillance of cardiac allograft vasculopathy. Overall, those pilot studies remain without large consensus, external validation and application on a large scale. Prognosis post HTx: Oztekin A. et al. [42] used neural networks to manage more than 200 variables in more than 16,000 cases to predict survival in heart–lung transplantation with an accuracy that ranged between 79% and 86%, slightly better than that estimated by common logistic methodology in the validation sample. The AI-based model revealed novel interactions among variables collected pre-transplantation, which were not initially considered in conventional models as predictors of events. Delen D et al. [43] used a ML to identify prognosis in thoracic organs transplantations, overcoming the limitations of the traditional statistical methods based on small pre-defined sets of variables. In 2015 Nilsson J et al.[24] compared three existing scoring models (donor risk index, risk-stratification score, and index for mortality prediction after cardiac transplantation) with a novel AI-based algorithm, and found that the accuracy of the novel model was excellent (C-index 0.600 [95% CI: 0.595–0.604]) with predicted events at 1-year, 5-year and 10-year versus actual up to 84% versus 83%, 71%-71%, and 55%-54% in the derivation cohort; 84% versus 83%, 72%-711%, and

Table 1
Artificial intelligence in heart transplant: *overview of the studies selected.*

Author	*Year of Pub*	*Reference #*	*Type of Study, N*	*Objective*	*Results*	*Risk of bias, External validation, Quality of reporting by % of the Items traced*
Domain: Etiology						
Garcia-Canadilla P et al.	2022	35	Cohort study for model validation, n = 72	Machine learning, unsupervised, has been used to Investigate left ventricular remodeling and mechanics in combination with clinical characteristics and heart-failure treatment and death or heart-transplant in pediatric idiopathic, genetic or familial dilated cardiomyopathy.	Machine learning identified echocardiographic features and clusters associated with high-risk of death or transplantation.	Low, NO, 70%
Domain: Diagnosis						
Kienzl K et al.	2009	36	Experimental animal research, N = 24 murine heart transplantation (N = 1541 protein spots)	Hearts transplantation in mice. Major histocompatibility donor-recipient mismatch. Large-scale proteome analysis to identify specific biomarkers for acute cardiac allograft rejection.	Of the protein spots, 95 were identified by and automated gel analysis system (DeCyder 2D ver. 6.5, GE Healthcare) as relevant by narrowing filter settings so that differences in the spot volume between proteins from various sample were >=1.5-fold between cases with acute rejection and those observed in syngeneic grafts,	Intermediate, NO, 40%
Tong L et al.	2017	37	Cohort study for model validation	Classify the patients with or without allograft rejection using data form endomyocardial biopsy using supervised machine learning tool versus manual identification.	Neural networks with regularization and dropout yielded a significantly reduced model overfitting, and improved stable accuracy of the automated diagnostic process for patient's classification.	Low, NO, 58%
Zhu Y et al.	2019	38	Cohort study for model validation	Clustering and classification of images, from endomyocardial biopsies, to classify patients with preclinical organ rejection after heart transplantation.	By deep learning-based image processing method, after features extraction by stacked convolutional autoencoder followed by multiple instance learning with dimensionality reduction and unsupervised clustering, unsupervised clustering achieved reliable classification results while preserving the capability for multi-class classification.	Low, NO, 63%
Castellani C et al.	2020	39	Cohort study for model validation, N = 90 (53 training cohort, 37 validation cohort)	Diagnosis of preclinical allograft rejection by non-invasive evaluation of patterns in extracellular vesicles of nucleic acids, proteins and lipids in combination with endomyocardial biopsies.	With more features of graft rejection, the concentration and diameter of extracellular vesicles increased, with a significant trend of associations for both antibody-mediated rejection and acute cellular rejection. Automated classification accuracy in external validation cohort reached 87%, and showed potential for reducing the number of surveillance biopsies.	Low, YES, 70%
Peyster EG et al.	2021	40	Cohort study Observational, N = 2,472 endomyocardial biopsies from 3 major US transplant centers	Demonstrate that automated grading of cellular rejection based on computational histological analysis was as reliable as that from expert pathologist.	Trained deep learning machine with 154 specimens resulted in approximately 62% agreement with pathologist, and a sensitivity for high-grade rejection up to 74% vs. 40% with pathologists.	Low, YES, 77%
Wei D et al.	2022	41	Cohort study Observational, N = 217 (35% with cardiac allograft vasculopathy)	Identify a urinary proteomic signature for cardiac allograft vasculopathy.	Within participants grouped randomly and evenly into a derivation (n = 108) and validation (n = 109) cohort, decision tree-based machine learning methods (extreme gradient boost) constructed a signature (27 peptides) for allograft vasculopathy based on urinary proteomic, with a sensitivity, specificity and accuracy of 68%, 73%, 72% respectively, in the validation cohort. Adding signature from logistic model including clinical risk factors improved the diagnostic performance further more.	Low, YES, 77%
Domain: Prognosis						
Oztekin A et al.	2009	42	Cohort study for model validation, N = 16,604 cases	Improve the prediction of outcomes following combined heart–lung transplantation by proposing an integrated data-mining methodology.	Develop machine learning predictive models and extract most relevant predictive factors comparing 3 methods: a) machine learning using decision trees, neural network or logistic regression; b)	Low, NO, 83%

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Table 1 (*continued*)

Author	*Year of Pub*	*Reference #*	*Type of Study, N*	*Objective*	*Results*	*Risk of bias, External validation, Quality of reporting by % of the Items traced*
					literature review and expert decision; common sense. Predictive models' performance − 10-fold cross-validation accuracy rates for two multi-imputed datasets - was between 79% and 86% for neural networks, 78% − 86% for logistic regression, and 71% − 79% for decision trees. The study suggested a set of variables useful for pre-transplant evaluation.	
Delen D et al.	2010	43	Cohort study for model validation	Exploring risk groups of thoracic transplant recipients through machine learning-based methods to mine large and feature-rich data to explore highly complex, non-linear relationships	Machine learning radial basis Kernel function predicted the survival time with R(2) value of 0.879; the artificial neural network (multilayer perceptron-MLP-model) reached R(2) value of 0.847; M5 algorithm-based regression tree model yielded R(2) value of 0.785. Using the prognosis indices in a Cox survival model revealed 3 group of subjects with sufficiently separated prognosis (clusters).	Low, NO, 87%
Nilsson J et al.	2015	24	Cohort study for model validation, N = 56,625 heart transplanted patients over time.	Develop and validate a flexible risk model for prediction of survival after heart transplantation using the largest transplant registry in the world.	The receiver operating characteristic area under the curve to predict one-year mortality was 0.650 (95% CI: 0.640–0.655) for the novel algorithm, it reached 0.56 (95% CI: 0.56–0.57) for the donor risk index, and 0.61 (95% CI: 0.60–0.61) for the index for mortality prediction after cardiac transplantation, respectively. The novel decision-tree yielded an expected survival time 2.8 years longer for recipients matched to a donor younger than 38 years. Donors could be increased in number by up to 22% by the novel funciton.	Low, YES, 67%
Medved D et al.	2017	44	Retrospective cohort study for model validation	Study of the outcome having patients in transplantation waiting list by deep learning techniques.	A model of two-layer neural networks predicted the outcome as still waiting at 180, 365 and 730 days from the transplantation in a large cohort from United Network for Organ Sharing (UNOS) – time window 2000–2011. The training procedures using the Keras framework, improved the F1 macro scores up to 0.674, 0.680, and 0.680 at the 3 follow-ups as compared to a baseline of F1 of 0.271, and 10 most significant parameters predicting outcomes were extracted from the neural network.	Low, NO, 77%
Medved D et al.	2018	45	Retrospective cohort study for model validation, N = 27,860	Compare the accuracy of the International Heart Transplantation Survival Algorithm (IHTSA) deep learning technique-based prediction model versus accuracy of the Index for Mortality Prediction After Cardiac Transplantation (IMPACT) to predict survival after heart transplantation.	In the United Network for Organ Sharing (UNOS) – time window 1997–2011, as compared to a mortality rate of 10% at year-1 follow-up, the IHTSA model predicted a mortality rate of 12% while the IMPACT predicted a mortality rate at 22% with the validation cohort.	Low, YES, 80%
Medved D et al	2018	10	Retrospective cohort study for model validation	A discrete event model and a neural network algorithm simulated the heart allocation process in a transplant queue.	The prediction performances of a discrete event model, and a neural network algorithm -the Lund Deep Learning Transplant Algorithm (LuDeLTA)- were compared to the performance of the International Heart Transplant Survival Algorithm (IHTSA) model to predict short-term survival pot heart transplantation. LuDeLTA was superior to IHTSA model utilized to predict the survival of the patients both in the queue and after transplant.	Low, YES, 80%

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Table 1 (*continued*)

Author	*Year of Pub*	*Reference #*	*Type of Study, N*	*Objective*	*Results*	*Risk of bias, External validation, Quality of reporting by % of the Items traced*
Yoon J et al.	2018	21	Cohort study for model validation, N = 22,780	Develop a novel risk prediction algorithm and test its performance on the database of all patients who were registered for cardiac transplantation in the United States during 1985–2015.	Built on the principle of trees of predictors to be used for specific clusters within the patient population, the 3-year survival/mortality predictions post-transplantation (versus best clinical standard) yielded a specificity at 80.0%, so that the novel algorithm increased prediction of survival of 14% and due to sensitivity at 80.0%, increased prediction of mortality of 13.0%.	Low, YES, 83%
Kransdorf EP et al.	2019	46	Cohort study for model validation	To predict 1-year mortality after heart transplant and assess the effect of size match on donor heart turn down for size by Investigation of 5 size match metrics-predicted heart mass, weight, height, body mass index, and body surface area.	Severe donor-recipient mismatch due to allograph undersize experienced increased mortality, which was not detected by common anthropometric parameters. Of heart offers and turned down due to donor size, 32% would have been acceptable using a novel approach.	Low, NO, 77%
Miller PE et al.	2019	47	Retrospective cohort study for model validation. N = 56,477	Prediction of 1-year survival among patients undergoing cardiac transplantation, within the Unified Network for Organ Sharing (UNOS) database (1987–2014). Comparing machine learning methodologies neural networks, naïve-Bayes, tree-augmented naïve-Bayes, support vector machines, random forest, and stochastic gradient boosting, with standard statistical methods logistic regression, ridge regression, and regressions with LASSO (least absolute shrinkage and selection operator).	The neural network-derived model showed highest C-statistic (0.66), which was slightly superior to that (0.65) derived from simple logistic regression, ridge regression, and regression with LASSO models.	Low, NO, 70%
Miller R et al.	2019	48	Cohort study for model validation, N = 3,502 (validation sample N = 700)	Evaluate algorithms predicting mortality after pediatric HTx among patients < 18 years of age who received cardiac transplantation between 2006 and 2015 in the UNOS.	Mortality was explored at year-1, −3, and −5. Models were trained by cross-validation, then validated in a separate sample. Machine learning algorithms demonstrated fair predictive utility in both training and testing data, but sensitivity was poor across models (training: 0.22–0.58; testing: 0.07–0.49).	Low, NO, 66%
Mark E et al.	2019	49	Observational Retrospective, N = 240,163	Use of machine learning to estimate survival at 5 years in patients receiving organs at increased risk of disease transmission (heart, liver, or lung) versus outcome among those awaiting a standard organ	Cox proportional hazards model was compared to random survival forests with conditional inference trees, based on Harrell's concordance index. The random survival forest models each used 500 trees. Higher chance of 5-year survival occurred when the patient received an increased risk of disease transmission organ versus when the patient remained on the waitlist.	Intermediate, NO, 50%
Hsich EM et al.	2019	22	Observational Retrospective, N = 33,069 (time window 2004–2015)	Predict survival post-heart transplantation to identify pre-listing variables essential to an accurate heart transplant allocation and maximize outcome.	Machine learning using random survival forests identified complex interactions among estimated glomerular filtration rate, serum albumin, extracorporeal membrane oxygenation, ventricular assist device, mechanical ventilation, peak oxygen capacity, hemodynamics, inotrope support, and type of heart disease. Some interactions were gener-specific.	Low, NO, 80%
Agasthi P et al.	2020	50	Retrospective cohort study for model validation, N = 15,236	Develop a risk prediction model of survival and graft failure 5 years after orthotopic heart transplant.	Machine learning, using gradient-boosted machine, identified 342 variables, 87 of which were used to develop a risk prediction model to predict 5-year mortality and graft failure post-heart transplantation. Ten-fold cross-validation was used to estimate model's external performance and optimize the hyperparameters simultaneously. Areas under the curves	Low, NO, 70%

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Table 1 (*continued*)

Author	*Year of Pub*	*Reference #*	*Type of Study, N*	*Objective*	*Results*	*Risk of bias, External validation, Quality of reporting by % of the Items traced*
					to predict 5-year mortality and graft failure were 0.72 (both), with length of stay, recipient and donor age, recipient and donor body mass index, and ischemic time as factors with the highest impact on outcomes.	
Hsich EM et al.	2020	23	Retrospective cohort study for model validation, N = 30,606	Understand the complex factors affecting heart transplant survival and determine possible sex-specific risk factors.	Early post-transplantation, constant, and late post-heart transplant mortality risk was not associated with recipient sex; complex interactions predicting early-, mid-, and late-mortality existed and were identified with machine learning (i.e., elevated bilirubin, mechanical ventilation, and dialysis).	Low, NO, 80%
Ayers B et al.	2021	51	Retrospective cohort study, N = 33,657 (time window 2000–2019)	To investigates predictors of post-heart transplantation mortality and improve 1-year survival.	Multiple machine learning algorithms were combined. Discriminatory capability, evaluated by means of area under receiver-operating-characteristic curve (AUROC), was with singular logistic regression 0.649, compared to 0.691 with random forest, 0.691 (95% CI, 0.671–0.712) with deep neural network, and 0.653 (95% CI, 0.632–0.674) with Adaboost, and reache 0.764 with a final ensemble machine learning model, which improved predictive performance by 73% ±4% ($p < 0.001$) (net reclassification index compared to logistic regression).	Low, YES, 80%
Zhou Y et al.	2021	54	Retrospective cohort study for model validation, N = 381	Establish a risk-prediction model for assessing prognosis of heart transplantation using machine-learning approach.	Least absolute shrinkage and selection operator method for variables selection. Seven different machine-learning approaches were employed to develop the risk-prediction model. Bootstrap method was used for model validation. Shapley Additive exPlanations (SHAP) method was used for model interpretation. Random Forest model achieved the best area under curves (0.801) and gradient boosting machine showed the best sensitivity (0.271). SHAP method best described the Random Forest model's predicting processes of "survival" or "death" at individual level.	Low, NO, 77%
Kampaktsis PN et al.	2021	53	Retrospective cohort study, N = 18,625 (time window 2010–2018)	Develop and validate machine learning models to increase accuracy of 1-year prediction of mortality after heart transplantation.	Of 134 pre-transplant variables, 39 were predictive of 1-year mortality based on feature selection algorithm and were used to train five machine learning models. Machine learning models showed good predictive accuracy of outcomes after heart transplantation. For the prediction of 1-year survival, area under the curve was 0.69, 0.64, 0.65, 0.64, 0.53 for the Adaboost, Logistic Regression, Decision Tree, Support Vector Machine, and K-nearest neighbor models, respectively, whereas the Index for Mortality Prediction after Cardiac Transplantation (IMPACT) score had an AUC of 0.57.	Low, YES, 77%
Killian MO et al.	2021	54/55	Retrospective cohort study for model validation, n = 654 (32 heart transplantations)	Various logistic regression, naive Bayes, support vector machine, and deep learning methods were employed to predict 1-, 3-, and 5-year post-transplant hospitalization using patient and administrative data from a large pediatric organ transplant center.	Deep learning models predicted outcome with areas under the receiver operating characteristic curves values ranging from 0.750 to 0.851, and generally outperformed traditional ML models across organ-types and prediction windows.	Low, NO, 77%
Domain: Treatment						

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Table 1 (*continued*)

Author	*Year of Pub*	*Reference #*	*Type of Study, N*	*Objective*	*Results*	*Risk of bias, External validation, Quality of reporting by % of the Items traced*
Woillard JB et al.	2021	56	Cohort study	To estimate the area under the curve of mycophenolic acid in organ transplant patients using extreme gradient boosting (Xgboost R package) Machine Learning models.	ML provided models accurate in estimating areas under the curve estimation performances in the test datasets (relative bias < 5% and relative root mean standard error < 20%) and	Low, NO, 80%
Woillard JB et al.	2021	57	Cohort study	To estimate the area-under the blood concentration curve of tacrolimus (TAC) following b.i.d. or q.d. dosing in organ transplant patients, using Xgboost machine learning (ML) models	better performance than Bayesian estimation in the four independent full-PK datasets.	Low, NO, 80%

Risk of bias according to PROBAST (ref.# 33) was proportional to the number of items fulfilled among those indicated in the four domains of Participants selection, Predictors selection, Outcome definition, and Analysis). Empirically LOW risk of bias was assigned to studies fulfilling more than 66% of the items, whereas high risk of bias was assumed for a number of items fulfilled less than 33%, intermediate for % of the items comprised between 33 and 66%. External validation was extrapolated as specifical indicator of quality of reports. Overall quality of reporting was scored as % of the items traced among the 30 indicated by Cabitza F and Campagner A in 2021 (ref.#32).

55%-54% in the internal validation cohort; and 85% versus 84%, 73%-76%, and 58%-58% in the external validation cohort. The receiver operating characteristic area under the curve to predict one-year mortality was 0.650 (95% CI: 0.640–0.655) for the novel model, 0.56 (95% CI: 0.56–0.57) for the donor risk index, 0.61 (95% CI: 0.60–0.61) for risk stratification score, and 0.61 (0.61–0.62) for index for mortality prediction after cardiac transplantation, respectively. The decision-tree revealed that recipients receiving donation from a donor younger than 38 years had additional expected median survival time of 2.8 years. The number of suitable donors could be increased by up to 22%. Using data from the United Network for Organ Sharing, Medved D et al. [44] in 2017 refined outcome prediction using AI in patients awaiting HTx at 180 days, 365 days, and 730 days, and further validated the prediction function in a subsequent study in 2018 [45]. In addition, ML-approach was also reported to be more reliable than traditional methods [10] in predicting longer post-HTx survival, moving the target of AI in HTx from allograft rejection to best allocation mechanisms to maximize prognosis. Yoon J. et al. [21] reported in 2018 a trees-of-predictors method to identify clusters and personalize prediction of survival, which resulted in an average accuracy of 67%. In 2019, Kransdorf et al. [46] used AI to optimize donor-recipient anthropometric best match to predict post-HTx survival. Miller P.E. et al. [47] and Miller R et al. [48] reported in 2019 the performances of ML to predict early and mid-term survival after HTx, with accuracy comprised between 66% and 72%, and poor sensitivity mostly due to missing data for long-term survival. On a different aspect, because prolongation of waitlist time may also be related to rejection of organs due to increased, acceptable, risk of disease transmission in HTx, Mark et al. [49] reported that ML-related survival models in a simulation based on 20,000 potential different scenarios, predicted a survival rate at 5-year follow-up post-HTx higher with patients accepting organ-related acceptable increased risk for disease transmission (heart, liver and lung) than in those who refused transplantation. The study indirectly validated the notion that irrational prolongation of waitlist time worsen prognosis in candidates to HTx. Hsich EM et al. [22] in 2019 reported that waitlist mortality was higher with lower glomerular filtration rate, and more so with lower serum albumin, use of extracorporeal membrane oxygenation, previously implanted ventricular assist device, mechanical ventilation, low body mass index and hemodynamic conditions characterizing patients in status 1A/1B United Network for Organ Sharing (UNOS), whereas lower peak exercise oxygen consumption was an important predictor of waitlist mortality among ambulatory patients. In adults and pediatric patients, in 2020, Agasthi P et al. [50] analyzed by ML a large set of variables (above 300) in 15,236 patients who underwent HTx from January 2005 to December 2009 (International Society of Heart and Lung Transplant (ISHLT) registry data), and found that length of stay, recipient and donor age, recipient and donor body mass index, and ischemic time had the highest relative influence in predicting 5-year mortality and graft failure, with an overall accuracy of 71%. In 30,606 adults in the Scientific Registry of Transplant Recipients database, who received isolated HTx between January 1, 2004, and July 1, 2018, Hsich EM et al. in 2020 [23] reported several interactions predicting early mortality such as pre-HTx mechanical ventilation, end-stage liver and kidney dysfunctions, and interactions predicting later mortality such as diabetes and older age (donor and recipient), with increasing and complex interactions predicting early-, mid-, and late-mortality identified by machine learning. Ayers et al. [51] employed ML-based multiple algorithms to predict mortality in a total of 33,657 patients who had undergone HTx, with accuracy at year-1 follow-up that was close to 76%. In a single center from China, Zhou Y. et al. used multiple ML and a random forest method to discriminate at the level of single patient between alive or dead at year-1 follow-up post HTx [52] with an accuracy of 80%. Only a few of the variables predicting events were common to other investigations (i.e., age of the recipient, previous cardiac surgery, albumin, prolonged post-HTx invasive mechanical ventilation). ML-based method was crucial to elaborate a large amount of data from various sources in the perspective of optimal organ utilization and longevity after HTx [53]. DL sharply increased the accuracy of algorithmic outcome prediction to 85%, and was proposed as standard tool in support to clinical decision-making for identification of those patients who have least likelihood to benefit from HTx at a specific time of the clinical history, given specific clinical conditions and donors characteristics [54,55]. Post HTx Treatments of rejection: ML can also be applied in monitoring of therapeutic levels of immunosuppressive drugs, such as mycophenolic acid and tacrolimus [56,57]. Simulation of application of prediction function in real-world.: as example of testing reproducibility, calibration, and validation of prediction algorithms, the difference between the theoretical and actual post-HTx time-to-event within the first year of observation was evaluated (Fig. 3). Mortality rate was not explained by novel prognostic functions derived from predefined database [24]. Further analyses revealed that prolonged ventilation, post-HTx dialysis, and infections requiring multiple intravenous antibiotics were significant correlates of the difference between the actual and the theoretical time-to-event in persons who underwent HTx in our Institution, as expected [24,58].

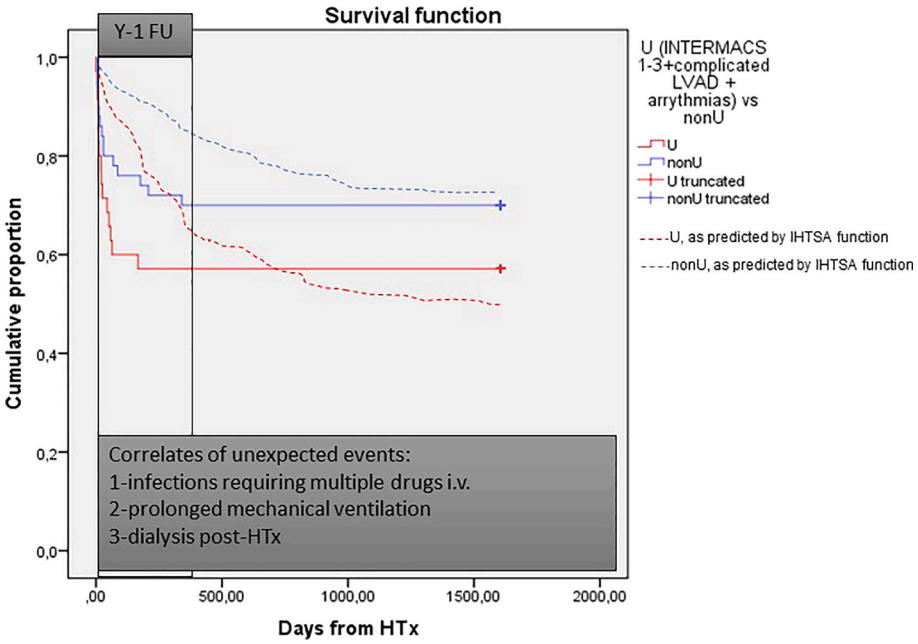

Fig. 3. Survival curves, actual (continuous) versus predicted (dashed), factored based on standardized urgent vs nonurgent criteria for htx. ai-based function described by nilsson et al. (ref.# 24) was unable to predict early outcome, which was indeed related to infections requiring intravenous multiple antibiotics and vasopressors, and prolonged mechanical ventilation, and post-htx unpredicted dialysis as in part or all identified by others (see ref. # 23, 52, 53).

4. Discussion

As to date, AI was generally found to be more accurate in the process of identification of the relevant variables to prognosis, and generating prognostic and diagnostic functions potentially turning into tools for common clinical practice. Yet, even with AI-base algorithms, AUCs were rarely above 0.80, a threshold for defining acceptable performance of discrimination functions in medicine [59]. Looking at reports on AI-based diagnostic and prognostic functions, issues could be identified with the procedures of predictors selections, population characterization, prediction function calibration, management of missing data, errors, and outliers, lack of external validation and discussion of limits of released prediction faction. Indeed, one of the available AI-based algorithms was found inaccurate in predicting the difference between real and expected mortality in cases from our center, a paradigm of the limits of application of functions generated from a selected context to the unselected context of the real-world. Nevertheless, predictors of fatal events in our small series were identified as powerful predictors of prognosis in different and larger datasets [22,23,50], demonstrating that large, high-quality and less selected data remain a key-factor also in the case of AI employed to develop tools thought to be applied in the general context.

AI has the potential to grant a boost to knowledge [29], and optimal management of the supply chain and outcome in HTx by working on BD (Fig. 1), as already suggested in medicine [60,61]. Recently, Naruka et al.[62] reviewed current evidence of application of ML in the field of HTx, focusing on prediction of graft failure, mortality and aids from imaging. In our overview, we reported studies classified in the 4 domains of etiology, diagnosis, prognosis, treatments, based on prevalent results. We also searched specifically for the use of BD in the fields, and found that none of the studies selected was actually based on BD. The lack of BD in the field of THx may be seen as a limitation to the performance of AI to develop reliable, precise and calibrated diagnostic and prognostic algorithms. However, while AI usually takes advantage from the use of BD, in itself BD does not automatically guarantee the quality of the process. BD does not mean just large datasets, and BD available to date are often not intended as fuel for medical AI. In fact, there is need for high-quality, unbiased and large, time-varying data, transparency of the procedures and methodologies applied, understanding and minimizing bias, and high-quality validation processes, in order to improve the reliability and generalizability of the AI-based prognostic and diagnostic functions [32–34]. BD is made of integrated and dynamic databases from multiple sources with multiple inter-relations, complex aggregation and potentialities for non-parametric and unbiased cases discrimination [63]. BD analyses by AI is usually oriented to reveal patterns, trends, clusters, or define models characterizing and aggregating cases and persons [63], implying associations more than cause-effect relationships. In medicine, specifically generated BD including high quality medically oriented information from the real-world, may balance complexity and costs of sophisticated data analyses through the medical AI, and supporting network medicine in the real world [64,65].

Network medicine may represent a wishful horizon in HTx supply chain and outcome optimization [28], which requires major shifts in information technology (IT) in health care, and health care organization and workflow. IT is one of the key factors able to generate BD with information of good-quality from real-world [64], to fuel specifically medical AI to develop algorithms with minimal biases, to train machine and derived refined and externally validated probabilistic tools for managing uncertainty and identify patterns in unselected group of persons. Electronic Health Record (EHR) and administrative data, medical images stored in pixels or voxels, provide a large spectrum of analytic information despite risk of misclassification and the impact of the missing data [66]. Also, genome, proteomic, transcriptomic, epigenomic, and metabolomic data may contribute to with additional important sources to BD [67]. Managing high-quality and medical oriented BD requires significant investments in large and independent storage systems, complex computing such as neural networks to operate LM and DL, immediate access and relational databases, highly qualified personals.

In such a new potential paradigm of AI contributing to knowledge building in HTx, data source and analyses modality are key factors. Grounded and “true” data are key elements for all analyses of data feeding AI, and deal with the key element of responding precisely and timely to right inquiries, with specific therapeutic options readily applicable. Such a process is inductive more than hypothetical or deductive, and has root into reality more than in randomized controlled

trials. To date, EHR systems perpetuate the document model of health care, thus affected frequently by missing data and often unprecise. Transforming health care systems to implement AI applied to BD, and build complex and dynamic algorithms supporting in decision making (Fig. 1), holds if investment and culture changes, including the use of medical terminology and data collections oriented to requirements from optimal employment of machines. Standardized, ubiquitarian and quantitative computational approaches should be oriented to captured and describe consistently clinical scenarios for simulations, discriminations and decision making by AI in a context of network medicine. Hence, clinicians need to adhere to a standardized terminology and semantic (definitions, meanings, relationships among words, cognitive structures, allowed value sets); specific infrastructure is needed to be converted by informaticians into technical representations suitable for database storage and computations; IT functions are to be known so that a public control is applied to systems processing BD, impacting clinical decisions; and finally, resources and results must be reachable by the majority, with defined rules of sharing, engagement and utilizations from a large communities. Promoting capturing of well-defined, high-quality data, integrated into clinical workflow, and grounded in real world, requires significant investments in health systems structures. After all, AI most likely identifies associations among variables with a various degree of strength or weakness, which varies over time, and identifies interactions among variables varying overtime. Yet, associations are not necessarily proofs of cause-effect relationships.

While IT systems grow-up structured, there are also growing responsibilities of professional societies representing doctors, to mediate and agree for standards, act as arbiters of the lexical component, dealing with organizations managing health-care-oriented IT, such as the Clinical Information Modeling Initiative at HL-7 building frameworks and systems data collection, database inter-relations, data quality monitoring; finally, health IT should become an absolute requirement for all actors of the health care systems, oriented to produce documentation able to be shared. The fact that, as today, health care related equity funds oriented to AI have almost doubled in a few years, reaching 3 billion of USD, is a sign of the general sentiment on how important is and will be the issue of AI applied to BD for a more and more precise medicine.

Limitations: As we selected a relatively small number of studies by our search options applied to electronic libraries, we may have been limited in reporting all the spectrum of the possible scientific contributions in the field of medical AI applied to the supply-chain and outcome in HTx. A summary of the quality of the selected reports has been attempted and reported in Table 1, which should be considered as an empiric, indicative and essential process without a specific validation. In addition, while composing the empiric overall score of the quality of the reports as in Table 1, we weighted equally different items, which might limit further the attempt to fully represent the quality of each study, and their comparisons. For each of the selected studies, we extrapolated specifically the information related to eventual external validation of the results, as single nonanalytic item potentially representing one aspect of the quality of each study, and applicability/deployment. Yet, we did not describe specifically the procedures and the details of external validations reported in the studies, which limits the absolute value of such an item as indicator of quality, and its value for comparing studies beyond the simple information in objective. The report on the difference between predicted and observed mortality post-HTx in our HTx center, as example of real-world applicability of prognostic algorithms developed through AI, may be considered anecdotical and is not meant to support any conclusive scientific statements. Nevertheless, a number of clinical variables closed the gap between predicted and observed mortality as reported in our experience from real-world, which were identified as important prognosticators later on by others [22,23,50].

5. Conclusions

To date, a relatively small number of studies reported on AI applied to the field of HTx, mostly in the domains of prediction of outcome while awaiting HTx, or post-HTx, and optimal organ allocation as relevant step to improve HTx outcome. In general, AI-based algorithms showed a tendency to perform better than those developed by traditional statistic tools using pre-defined datasets. None of those algorithms were developed using high-quality BD, and frequently lacked of external validation. Current performance of AI-based tools, and their applicability in the real world, may also be limited by relatively poor transparency of methodologies, risk of bias, and lack of generalizability as external validation lacks frequently. Integrated and dynamic databases generated with the aid of appropriate IT, of good quality, intended for medical AI, from multiple sources with multiple inter-relations, complex aggregation and potentialities for non-parametric and unbiased cases discrimination, may generate high quality standards for AI-based prediction models. Transparency and procedure quality in machine training, and appropriate validation sections demonstrating reproducibility and calibration are additional critical key-point to deploy medical AI in the field of HTx, with high biological and nonbiological costs, and reach in ethical issues.

6. Summary table

- A systematic overview was performed on studies published in English on peer-revied journals referring to heart transplantation (HTx), artificial intelligence (AI), and big data (BD) in HTx, identified as December 31st, 2022, through PUBMED-MEDLINE-WEB of Science.
- Twenty-seven studies were grouped in 4 domains (etiology, diagnosis, prognosis, treatment), representing the 0.02% of the studies identified by the key-words.
- AI has been mostly used for an algorithmic prediction and discrimination in cohort studies and registries while BD-based studies were not available.
- AI-based algorithms appeared superior to probabilistic functions to predict patterns.
- The majority of the reports did not provide external validation of the proposed prediction functions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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