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Stratification du risque cardio-vasculaire et de mortalité chez le patient transplanté cardiaque

Thèse de doctorat d'épidémiologie clinique

Dirigée par Le Professeur Xavier JOUVEN

Présentée et soutenue à Paris, le 6 décembre 2021

Par Guillaume BONNET

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Titre : Stratification du risque cardio-vasculaire et de mortalité chez le patient transplanté cardiaque

Plus de 5000 transplantations cardiaques sont réalisées chaque année dans le monde, avec une survie médiane après la transplantation supérieure à 12 ans. La stratification du risque de résultats post-transplantation est devenue une priorité pour la communauté de transplantation notamment face au nouveau système français d'allocation et suite à la récente révision du système américain d'allocation cardiaque. L'objectif de ce travail était d'identifier des pistes d'amélioration de la stratification du risque d'événements cardio-vasculaires et de mortalité chez les patients transplantés cardiaques.

Tout d'abord, dans notre analyse d'une cohorte contemporaine de l'UNOS (United Network for Organ Sharing - USA), nous avons montré que le statut d'assistance circulatoire au moment de la transplantation était associé à des différences majeures dans les caractéristiques des patients et leur pronostic, et avait une influence sur les modèles prédictifs post-transplantation. Cependant, le développement de modèles prédictifs spécifiques pour chaque type d'assistance circulatoire a eu un impact limité sur la performance statistique des modèles prédictifs.

Au-delà des limitations que peuvent représenter ces approches sur de grandes bases de données nationales (faible niveau de granularité avec l'absence de données immunologiques, données manquantes dans le suivi), nous avons constitué une base francilienne prospective multicentrique et hautement phénotypée de transplantés cardiaques. Au sein de cette population spécifique et suite à une relecture médicale détaillée des causes de décès, nos résultats retrouvaient que la mort subite était une cause majeure de décès au-delà de la première année post-transplantation. Nous avons démontré que l'incidence annuelle de la mort subite était 25 fois plus importante que dans la population générale. Le risque de mort subite était nettement plus élevé chez les plus jeunes receveurs. Cinq variables étaient indépendamment associées à la mort subite : l'âge du donneur plus élevé, l'âge du receveur plus jeune, l'origine ethnique, les anticorps préexistants spécifiques au donneur et la fraction d'éjection ventriculaire gauche. Nos résultats fournissent des

données nouvelles concernant l'épidémiologie de la mort subite après transplantation cardiaque.

Enfin, nous avons identifié, pour la première fois, 4 trajectoires distinctes de la progression à long terme de la coronaropathie du greffon en utilisant une approche innovante non supervisée. Ces 4 trajectoires étaient cohérentes et validées dans des cohortes géographiquement distinctes (Europe et États-Unis). Nous avons constaté que ces trajectoires étaient associées à des caractéristiques spécifiques du donneur et du receveur, aux processus pathologiques en cours dont le rejet et aux profils immunologiques précoces après la transplantation. Ainsi, l'évaluation de la trajectoire des patients qui peut être effectuée à un stade précoce après la transplantation peut optimiser la stratification du risque post-transplantation.

Ces différentes pistes permettent d'aboutir au développement de nouveaux outils de stratification du risque, parfois transposables à la pratique quotidienne. L'identification de sous-groupes de patients à haut risque nous amènerait à des stratégies préventives plus agressives afin d'améliorer la survie globale à long terme.

Mots-clés : Transplantation cardiaque, allo-immunisation, rejet d'allogreffe, maladie coronaire du greffon, biologie moléculaire, stratification pronostique

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A l'ensemble des intervenants du centre d'épidémiologie et du Paris Transplant Group, formant un environnement si propice à la recherche et à l'apprentissage.

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A Mathilde.

Mes remerciements s'accompagnent d'un profond respect et d'une grande reconnaissance envers vous tous.

J'ai appris de vous la véracité de cet aphorisme :

« Quand rien ne semble aider, je regarde un tailleur de pierre qui frappe une pierre peut-être cent fois sans qu'aucune marque n'apparaisse. Et puis, au 101e coup, elle se fend en deux et je sais que ce n'est pas le dernier coup qui a tout fait, mais tous ceux d'avant »

Publications

Articles acceptés:

- Identification and characterization of Trajectories Of Cardiac Allograft Vasculopathy After Heart Transplantation: A Population Based Study. A Loupy*, G Coutance*, **G Bonnet*** (equal contribution), J V Keer, M Raynaud, MC Bories, M Racapé, D Yoo, JP Duong, P Bruneval, S Varnous, P Leprince, R Guillemain, Ryan Levine, Jig Patel, J Kobashigawa and X Jouven. ***Circulation. 2020 Jun 16;141(24):1954-1967.***

- Development and validation of specific post-transplant risk scores according to the circulatory support status at transplant: A UNOS cohort analysis. Guillaume Coutance, **Guillaume Bonnet**, Evan P. Kransdorf, Alexandre Loupy, Jaime Moriguchi, Pascal Leprince, Jon A Kobashigawa, Jignesh K Patel. ***J Heart Lung Transplant. 2021 Oct;40(10):1235-1246.***

Articles soumis:

- Sudden Cardiac Death After Heart Transplantation: A Population Based Study.
G Bonnet, G Coutance, O Aubert, V Waldman, M Raynaud, A Asselin, MC Bories, R Guillemain, P Bruneval, S Varnous, P Leprince, P Achouch, E Marijon, A Loupy, X Jouven. ***JAMA Cardiology submitted***

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ABREVIATIONS

AMR : Rejet médié par les anticorps

CAV : Coronaropathie du greffon

DAI : Défibrillateur automatique implantable

DSA : Anticorps spécifiques du donneur

FEVG : Fraction d'éjection ventriculaire gauche

HTx : Transplantation cardiaque

SCD : Mort subite

UNOS : United Network for Organ Sharing

Introduction

Intro-A. Insuffisance cardiaque avancée et transplantation cardiaque

Intro-A-1. Insuffisance cardiaque

L'insuffisance cardiaque est un syndrome clinique caractérisé par des symptômes typiques (par exemple, essoufflement, oedème des chevilles et asthénie) qui peuvent être accompagnés de signes causés par une anomalie cardiaque structurelle et/ou fonctionnelle, entraînant une réduction du débit cardiaque et/ou une élévation des pressions intracardiaques au repos ou à l'effort.[1]
La prévalence de l'insuffisance cardiaque dans les pays industrialisés est estimée entre 1 et 2%, ce qui fait de cette maladie un véritable problème de santé publique, souligné par un récent livre blanc à l'initiative de la Société Française de Cardiologie.[2] La prise en charge thérapeutique de l'insuffisance cardiaque a été révolutionnée au cours des vingt dernières années. Cependant, certains patients sont affectés par cette maladie à un point tel que ces traitements restent insuffisants.

Intro-A-2. Insuffisance cardiaque avancée

L'insuffisance cardiaque avancée désigne ces patients instables et sévères. Sa définition repose sur l'association de la persistance de symptômes et/ou de signes d'insuffisance cardiaque malgré une prise en charge médicale et électrique optimale et la présence de critères de gravité cliniques, biologiques, électrocardiographiques ou échographiques.[3,4]
La prévalence de l'insuffisance cardiaque avancée est estimée à 1% de la population des patients insuffisants cardiaques, ce qui représente plusieurs dizaines de milliers de patients en Europe ou aux Etats-Unis. Le pronostic de ces patients est mauvais. La mortalité des patients dépendants d'un support inotrope est estimée à 75% à 1 an[5] et celle des patients INTERMACS 4 à 50%.[6]

Intro-A-3. La transplantation cardiaque : Épidémiologie, survie post-transplantation

Malgré le développement des techniques d'assistance circulatoire de longue durée, la transplantation cardiaque (HTx) reste l'option thérapeutique de référence pour les patients atteints d'insuffisance cardiaque avancée.[7,8] Actuellement, plus de 5 000 greffes cardiaques sont réalisées chaque année dans le monde, dont près de 500 interventions en France (Figure 1).[9,10]

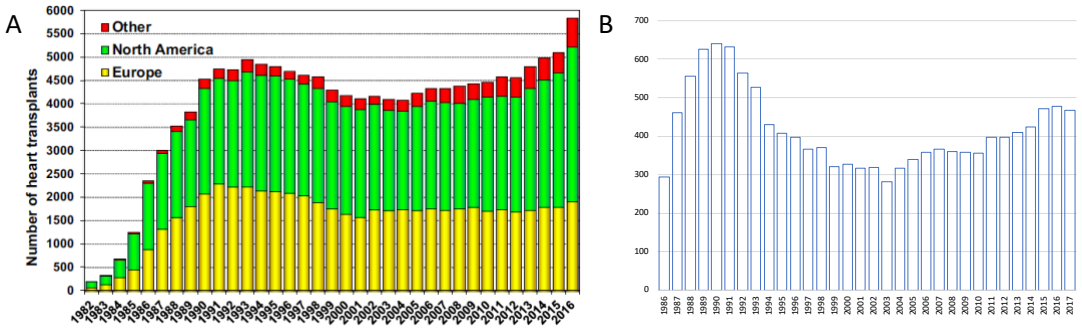

Figure 1. Évolution du nombre de transplantations cardiaques. (A) Données de l'ISHLT, (B) Données de l'Agence de la Biomédecine.

La survie à un an est d'environ 88 % et la survie médiane après transplantation cardiaque dépasse désormais 12 ans selon les données de l'ISHLT.[9] En France, la survie à un an est de 79 % pour la période 2013-2016 et la survie médiane après transplantation cardiaque dépasse 10 ans (Figure 2).[10]

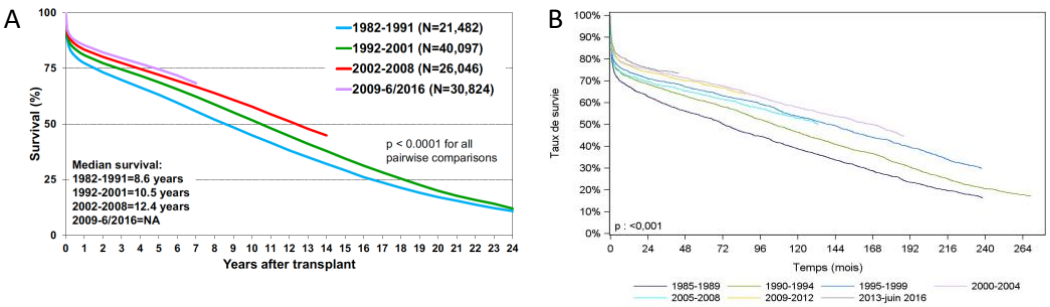

Figure 2. Survie post-transplantation. (A) Données de l'ISHLT, (B) Données de l'Agence de la Biomédecine.

L'amélioration de l'immunosuppression et les assistances circulatoires mécaniques de courte durée ont permis une amélioration continue de la survie après une

transplantation cardiaque. Cependant, seule la survie précoce a été significativement améliorée. La pente des courbes de survie au-delà de la première année reste stable dans le temps, ce qui fait des causes de décès tardives un défi majeur pour l'amélioration du pronostic des transplantés cardiaques.

Notre objectif sera d'accroître notre connaissance sur les outils actuellement disponibles de prédiction de la survie de patients transplantés.

Intro-B. La prédiction d'évènement en transplantation cardiaque.

Intro-B-1. Politique d'allocation et le concept de greffe futile

Un système optimal d'allocation devrait garantir un bénéfice de la transplantation équitable, en équilibrant la liste d'attente et la mortalité post-transplantation. Cependant, dans la plupart des pays, les systèmes d'attribution des cœurs donnent actuellement la priorité aux patients qui sont plus susceptibles de mourir pendant qu'ils sont sur la liste d'attente, sans tenir compte de leur mortalité post-transplantation.[11] Cette politique d'allocation "à mi-chemin" peut s'expliquer par la capacité modérée des scores de risque existants à discriminer les survivants post-transplantation parmi les transplantés.[12]

Le bénéfice de survie (différence entre la survie après HTx et la survie sur la liste d'attente sans HTx) semble être une métrique clinique de plus en plus pertinente qui peut aider à prioriser les candidats.[13] Les taux de transplantation sont limités par une pénurie de cœurs de donneurs. Dans ce contexte, une stratification précise du risque de décès après HTx est essentielle pour éviter les transplantations futiles, allouer de manière appropriée une ressource rare et rationaliser l'appariement complexe entre donneur et receveur.[14]

Intro-B-2. Le score de risque post-transplantation : une première française

Certains systèmes d'allocation, comme le système français d'allocation de greffon cardiaque, comprennent une procédure de notation individuelle visant à stratifier le risque de décès précoce après la transplantation.[15,16] Ce score de risque post-

transplantation développé par l'Agence de la Biomédecine est une étape majeure dans le monde de la transplantation. Ce score français comprend un modèle de perte de greffon prévue à un an dans l'allocation, empêchant l'offre de greffons aux candidats dont la survie prévue à un an après la transplantation est de 50 % ou moins.

Ainsi La prédiction de la survie individuelle au cours de la première année post-transplantation apparait comme un challenge toujours à relever face à des modèles prédictifs non suffisamment précis.[17]

Intro-B-3. Des raisons des mauvaises performances des scores

Plusieurs facteurs peuvent expliquer les mauvaises performances des différents scores disponibles de prédiction post-transplantation.[18] Tout d'abord, les grands registres multicentriques, comme l'ensemble de données de United Network for Organ Sharing (UNOS), ont été la principale source de cohorte pour les modèles dérivés. Le manque de granularité des données incluses dans ces registres peut être la limitation la plus importante.[19] Le comité thoracique de l'UNOS a récemment décidé d'étendre la collecte de données pour saisir davantage de marqueurs pronostiques afin d'améliorer la stratification du risque. De plus, des variables prédictives importantes comme l'albumine sérique manquaient dans environ la moitié de la cohorte, ce qui limitait la taille de l'échantillon de la cohorte de validation du score.[20]

Pour rappel, plusieurs scores ont été développés il y a 10-20 ans, lorsque le pronostic post-greffe était moins favorable et que les dispositifs d'assistance ventriculaire pré-greffe étaient moins usuels que dans la période actuelle. De même, la démographie des donneurs a évolué, notamment en ce qui concerne l'âge du donneur qui a augmenté dans la plupart des régions de transplantation. Le changement spectaculaire du paysage de la HTx suite à la mise en œuvre du nouveau schéma d'attribution aux États-Unis souligne l'évolution rapide du profil des candidats à la HTx et la nécessité d'un modèle prédictif régulièrement mis à jour.[21]

Enfin, des critères de sélection plus stricts sont systématiquement appliqués aux donneurs à haut risque (par exemple, les donneurs âgés). Ce biais de sélection d'origine clinique peut altérer la performance statistique des scores dans les sous-groupes à haut risque.

Au niveau méthodologique, la plupart des scores considèrent les variables continues comme des variables catégorielles dans leur modèle, ce qui entraîne une perte importante d'informations (par exemple, l'âge du donneur). Des modèles statistiques plus complexes peuvent améliorer la stratification du risque. L'analyse des interactions complexes entre les variables prédictives peut améliorer la stratification du risque (par exemple, l'âge du donneur et le temps ischémique).[22,23]

Le développement d'un score d'allocation cardiaque qui inclurait la stratification du risque de résultats post-transplantation est donc une réalité en France et est devenu la prochaine priorité américaine suite à la récente révision du système d'allocation cardiaque de l'UNOS. Cependant, nous semblons arriver à la limite de cette approche méthodologique « traditionnelle » avec des scores de risque post-transplantation souffrant d'une mauvaise performance statistique.[18] Leur faible discrimination ne permet pas une stratification précise et individuelle du risque de mortalité post-transplantation.

En développant un seul score pour tous les patients, ces scores négligent l'hétérogénéité entre les patients. **Nous avons émis l'hypothèse que le développement de modèles pronostiques spécifiques pour chaque statut d'assistance (aucune assistance, assistance durable, assistance temporaire) pourrait améliorer leur performance statistique.**

Intro-C. Place du DSA et de l'AMR après une transplantation cardiaque

Intro-C-1. Limites du succès à long terme de la transplantation : le rôle central de l'allosensibilisation et du rejet médié par les anticorps.

Au-delà de la première année de transplantation, deux causes majeures sont à l'origine de la majorité des décès : les complications de l'immunosuppression chronique (cancers et infections) et les maladies spécifiques du greffon : coronaropathie du greffon (CAV), rejet de l'allogreffe et dysfonctionnement du greffon (Figure 3).[9,24] Le terme "dysfonctionnement du greffon" est un terme générique utilisé dans les grands registres. En dehors de la dysfonction primaire du greffon survenant

très tôt après la transplantation, cette entité reflète à la fois des dysfonctions aiguës liées au rejet de l'allogreffe ou à une coronaropathie non diagnostiquée, et des dysfonctions chroniques liées à une évolution restrictive des allogreffes cardiaques ou à des coronaropathies non diagnostiquées.

Les maladies spécifiques du greffon (CAV, rejet, dysfonctions tardives, physiologie restrictive) représentent la première cause de décès au-delà de la première année de transplantation. L'allosensibilisation et le rejet médié par les anticorps (AMR) sont au centre de toutes ces maladies spécifiques du greffon en raison des lésions aiguës et chroniques, micro et macrovasculaires qu'elles peuvent induire.[25] L'amélioration de la gestion de l'allosensibilisation et de l'AMR est donc une priorité en transplantation cardiaque.

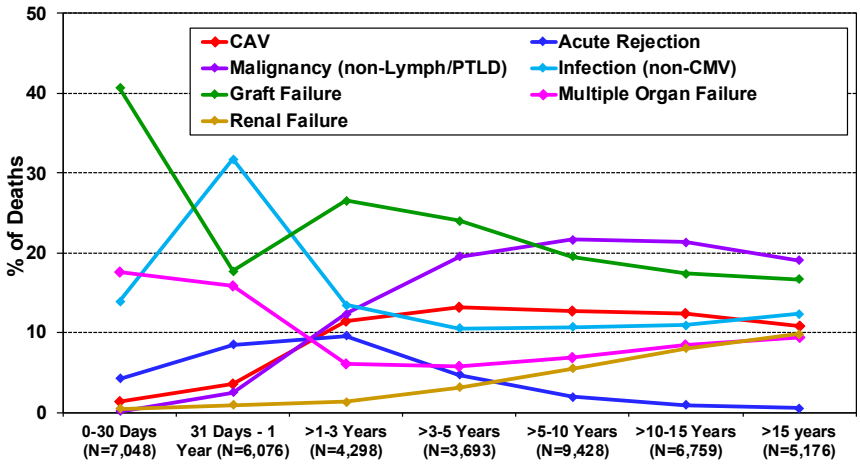

Figure 3. Dynamique des causes de décès après une transplantation cardiaque (ISHLT)

Le système vasculaire du donneur, présent à l'interface entre le tissu du donneur et le système immunitaire du receveur, est la principale cible de la réponse allo-immune. La physiopathologie complexe de l'AMR est de mieux en mieux comprise et implique i) la production d'anticorps spécifiques du donneur (DSA), principalement des anticorps anti-HLA, en tant que réponse allo-immune à la transplantation d'organes ou à des événements sensibilisants avant la transplantation, ii) la fixation de ces DSA sur les cellules endothéliales du donneur, iii) responsable de l'activation des voies dépendantes et indépendantes du complément conduisant à des dommages cellulaires et au rejet de l'allogreffe.

Depuis la découverte par Terasaki et al. de l'importance du crossmatch et de la cytotoxicité dépendante du complément pour prédire le rejet hyperaigu d'une allogreffe, les preuves du rôle central de l'activation du complément dans la physiopathologie de l'AMR se multiplient.[26]

Intro-C-2 Voie indépendante du complément

La composante cellulaire joue également un rôle majeur dans l'AMR. Ainsi, à l'instar du rejet cellulaire aigu, dont la " synapse immunologique " entre le lymphocyte T et la cellule présentatrice d'antigène dans le secteur interstitiel est la pierre angulaire du processus pathologique, une " synapse immunologique " est également l'un des mécanismes fondamentaux de l'AMR, mais dans le secteur vasculaire, entre la cellule Natural Killer (NK) et les cellules endothéliales via le FCGRIIIA (récepteur Fc gamma, CD16A) et le DSA.[27] L'activation de la cellule NK va entraîner :

- la production et la libération d'interféron-gamma (IFNG), du facteur de nécrose tumorale (TNF) et du facteur de stimulation des colonies de granulocytes-macrophages (CSF2), augmentant i) la cytotoxicité des monocytes environnants (TNF-, IL-1, IL-6) et ii) les expressions de CXCL9 et CXCL10, ce qui facilite le recrutement de nouvelles cellules NK,
- la production et la libération de chimiokines pro-inflammatoires favorisant le recrutement des monocytes (CCL3 et CCL4),
- la libération du contenu des granules des cellules NK (perforine, granulysine granzymes A et B) responsables des lésions endothéliales via le mécanisme de cytotoxicité à médiation cellulaire dépendant des anticorps.

La figure 4 résume les connaissances actuelles sur la physiopathologie de l'AMR.

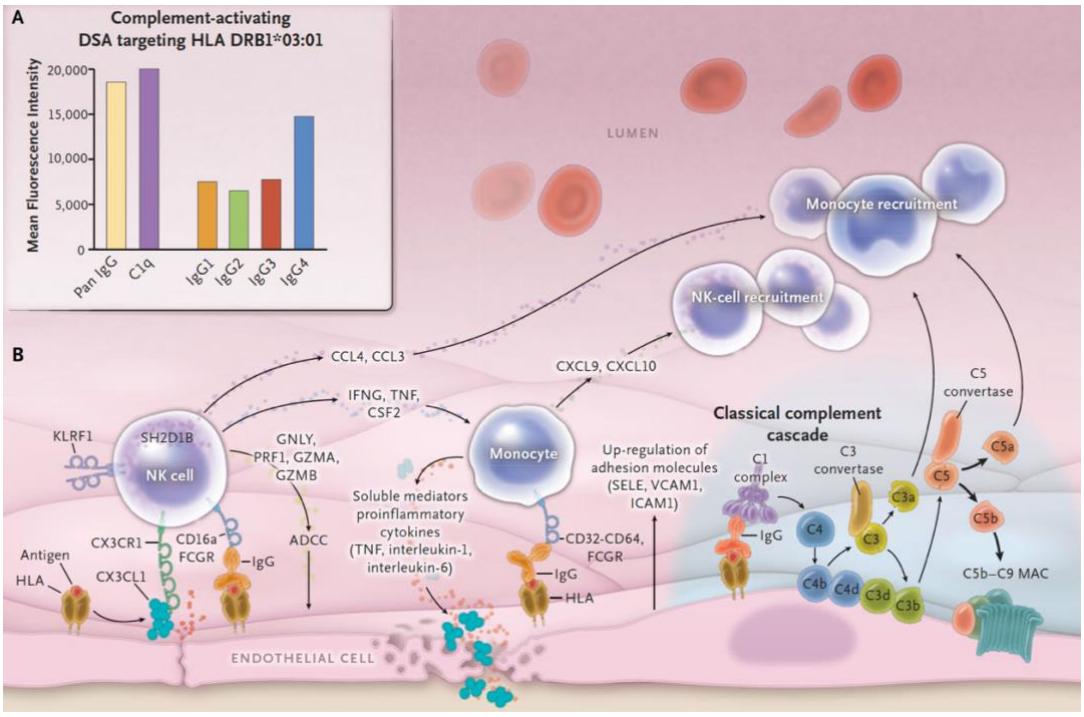

*Figure 4 : Pathophysiologie du rejet médié par les anticorps (**25**)*

Cette figure résume la pathophysiologie du rejet médié par les anticorps dans la transplantation d'organes solides. Côté gauche : voies indépendantes du complément ; côté droit : voies dépendantes du complément.

Intro-C-3. Le diagnostic d'AMR et le concept de rejet chronique sub-clinique

La prise en charge médicale actuelle, très hétérogène entre les centres, présente trois limitations majeures : i) la difficulté du diagnostic pathologique, ii) l'absence d'outil de stratification pronostique capable d'aider à la décision clinique et, en conséquence, iii) l'absence de consensus concernant la prise en charge thérapeutique.[28–30]

Contrairement aux épisodes manifestes et aigus de rejet médié par les anticorps qui contribuent au rejet chronique, il est maintenant reconnu que des anomalies microvasculaires indolentes peuvent survenir sans compromettre de façon aiguë la fonction de l'allogreffe chez les receveurs de greffe ayant des anticorps anti-HLA spécifiques du donneur. Un tel rejet subclinique médié par les anticorps a été observé chez des receveurs de greffes de rein,[31] de cœur,[32] de foie[33] et de poumon.[34] Cette approche de l'histoire naturelle du rejet médié par les anticorps est soutenue par des études chez l'animal, comme le modèle de primate non humain de

rejet chronique d'allogreffe rénale médié par les anticorps,[35] ainsi que par des analyses longitudinales de biopsies protocolaires réalisées chez des receveurs humains de rein et de cœur, qui révèlent des oscillations substantielles des niveaux d'activité de la maladie.[36] Le rejet médié par les anticorps est maintenant considéré comme un processus pathologique avec un continuum de gravité, qui commence à tout moment après la transplantation et se poursuit à des niveaux d'intensité variables, conduisant progressivement au développement de dommages, de dysfonctionnements et de pertes chroniques de l'allogreffe. Une meilleure compréhension de l'histoire naturelle du rejet médié par les anticorps a conduit à une interprétation plus complexe des divers scénarios cliniques rencontrés dans la pratique clinique, étant donné l'hétérogénéité, le polymorphisme et la dépendance temporelle des manifestations cliniques et histologiques du rejet médié par les anticorps.

Nous faisons l'hypothèse que la présence d'anticorps anti-HLA spécifiques du donneur est un facteur potentiel d'un phénomène parfois sub-clinique de rejet médié par anticorps, pouvant être associé à des complications à long terme post-transplantation.

Intro-D. Transplantation cardiaque et complications

Intro-D-1. Lésion aiguë : dysfonctionnement aigu du greffon lié au rejet de l'allogreffe.

Le rejet de greffon reste une cause importante de décès après une transplantation cardiaque. Si les traitements immunosuppresseurs d'induction ou d'entretien sont particulièrement efficaces pour la prévention et le traitement du rejet cellulaire aigu, la prise en charge thérapeutique du rejet médié par les anticorps (AMR) reste beaucoup plus complexe. L'incidence du rejet cellulaire aigu a diminué au fil du temps.[37] Il n'entraîne plus que rarement une dysfonction grave du greffon et n'est plus associé à une augmentation de la mortalité cardio-vasculaire, contrairement à l'AMR.[38] Dans de nombreux cas cliniques rapportés, les cas les plus sévères de dysfonction aiguë du greffon responsable d'un choc cardiogénique étaient liés à un

AMR, soulignant le rôle important de ce type de rejet dans la genèse de la dysfonction aiguë du greffon.[39]

Intro-D-2. Lésion chronique : coronaropathie du greffon

La coronaropathie du greffon (CAV) est une affection fréquente et grave après une HTx. Elle est caractérisée par un épaississement intimal responsable d'un rétrécissement diffus des artères coronaires. Malgré les progrès réalisés en terme de prévention, l'incidence de la CAV reste élevée, 50% à 10 ans après la transplantation.[40] La présence d'une CAV est un facteur de risque significatif de morbidité et de mortalité, même à un stade subclinique diagnostiqué par une augmentation de l'épaisseur intimale à l'échographie intravasculaire.[41,42] Outre les facteurs de risque cardio-vasculaire habituels des donneurs et des receveurs, de nombreuses études expérimentales et cliniques ont établi un lien étroit entre les anticorps anti-HLA spécifiques du donneur (DSA) et l'AMR, d'une part, et l'apparition ou la progression d'une CAV, d'autre part.[43–46] La cytotoxicité cellulaire dépendante des anticorps semble jouer un rôle majeur dans la physiopathologie de la CAV.[47,48]
Le dépistage de la CAV et du rejet d'allogreffe repose sur des tests invasifs, itératifs et protocolés, respectivement la coronarographie et la biopsie endomyocardique.[49,50] L'histoire naturelle et les facteurs de risque de ces complications n'étant pas profondément décrits, la fréquence des tests de dépistage est appliquée de la même manière à tous les patients, quel que soit leur risque de développer la maladie. Il en résulte un mauvais rapport coût-efficacité diagnostique ainsi qu'un risque de complications inhérent à ces tests invasifs.
Nous faisons l'hypothèse qu'une meilleure connaissance de l'épidémiologie, de l'histoire naturelle et des facteurs de risque de la CAV, basée sur l'utilisation d'outils statistiques innovants et sur une approche populationnelle, permettrait une meilleure stratification pronostique de ces maladies ; un premier pas vers la rationalisation des tests invasifs de dépistage.

Intro-D-3. Lésion chronique : physiologie restrictive du greffon

L'évolution progressive vers des troubles du remplissage ventriculaire, en rapport avec une physiologie restrictive du transplant cardiaque, est une cause importante

de dysfonctionnement tardif du greffon et de retransplantation. Ces anomalies seraient responsables d'un tiers des cas d'insuffisance cardiaque au-delà d'un an de transplantation[51] et de 15% des retransplantations.[52] L'altération de la microcirculation coronaire est probablement un mécanisme important de ce type de dysfonctionnement. Plusieurs études ont établi un lien entre DSA/AMR et la physiologie restrictive. La présence d'un DSA pourrait être associée à des anomalies de la microcirculation coronaire et à une élévation des pressions de remplissage.[53] La plupart des patients retransplantés, quelle qu'en soit la raison, présentaient des signes d'AMR, le plus souvent subcliniques, tant sur les greffons explantés que sur les biopsies endomyocardiques réalisées au cours du suivi habituel.[54]

Intro-D-4. Atteinte méconnue : la mort subite du transplanté cardiaque.

La fibrose myocardique a de nombreuses étiologies en transplantation cardiaque : fibrose préalablement présente chez le donneur, long temps d'ischémie lors de la transplantation, coronaropathie évoluée du greffon, rejet clinique ou sub-clinique. Cette fibrose myocardique est un modèle commun à diverses maladies cardiaques qui favorise les tachyarythmies ventriculaires en créant un substrat vulnérable pour l'activité réentrante et en favorisant l'émergence de déclencheurs.[55]

La mort subite d'origine cardiaque (SCD) est définie comme un décès inattendu survenant dans l'heure (ou dans les 24 heures en l'absence de témoin) qui suit l'apparition des symptômes. C'est un mode de décès fréquent chez les patients atteints d'insuffisance cardiaque. Avant l'utilisation des défibrillateurs automatiques implantables (DAI), plus de 50% des décès chez les patients atteints d'insuffisance cardiaque étaient soudains, avec un taux d'incidence de 6,1 pour 100 patients-années.[56] Dans l'insuffisance cardiaque avancée, la dysfonction sévère de la contractilité ventriculaire gauche +/- droite, avec les manifestations graves de stase pré-ventriculaire et de bas débit, est le mode de décès le plus fréquent. Cependant, la SCD est responsable de presque 40 % des décès chez les patients atteints d'une insuffisance cardiaque avancée inscrits sur la liste des transplantations cardiaques.[57]

Les données épidémiologiques concernant la SCD post-transplantation sont insuffisantes. Le mécanisme pathogène sous-jacent de la SCD post-transplantation est probablement multifactoriel et n'est pas complètement élucidé. Actuellement, il n'existe pas de directives pour l'implantation de DAI après une transplantation

cardiaque. Par conséquent, une évaluation de l'incidence de la SCD après HTx et l'identification de ses facteurs de risque spécifiques, y compris les facteurs immunologiques, sur la base de grandes cohortes de receveurs de cœur, pourraient améliorer le suivi et la gestion des patients.

Nous faisons l'hypothèse qu'une investigation approfondie des causes de décès des transplantés cardiaques au sein d'une base de données à haut de niveau de phénotypage, associée à une approche populationnelle, permettrait une description précise et une meilleure stratification du risque de mort subite post-transplantation.

Part I. Prédiction de la mortalité post-transplantation cardiaque.

I.A Méthodologie et stratification du risque

L'un des principaux objectifs de la recherche biomédicale est l'identification des facteurs de risque d'une maladie ou d'un événement clinique permettant de stratifier le risque de son apparition, au moins au niveau de la population. De nombreux modèles statistiques existent et dépendent du type d'événement ou de variables que l'on cherche à expliquer. Souvent, dans le domaine biomédical, le critère analysé est binaire (maladie / pas de maladie), et le moment de survenue de l'événement est ajouté à l'analyse. Dans ce cas typique, le modèle de Cox est le modèle le plus pertinent et le plus fréquemment utilisé. Ce modèle permet de déterminer des facteurs de risque indépendants de la survenue de la maladie auxquels on attribue un coefficient ß correspondant à l'importance de leur effet sur le moment de survenue de l'événement analysé.

I.A.1. Identification des facteurs de pronostic à l'aide d'un modèle statistique

I.A.1.a. Modèle semi-paramétrique de Cox

Ce modèle a été introduit en 1972 par David Cox et reste le modèle le plus utilisé dans les analyses de survie à censure droite et les études médicales. Ce modèle prend en compte plusieurs variables explicatives pour expliquer l'occurrence d'un événement (partie paramétrique) sans faire d'hypothèses sur les distributions de survie et la fonction de risque (partie non paramétrique). Le modèle exprime la fonction de risque comme le produit d'une fonction de risque de base $h_0(t)$ commune à tous les individus et considérée comme une fonction inconnue, et d'une fonction de régression paramétriquement explicite, $\exp(\beta' Z)$ où β' est un p-vecteur

de coefficient de régression inconnu. Le modèle de risque proportionnel de Cox s'écrit comme suit :

$$h(t, Z) = h_0(t) \exp(\beta' Z)$$

Ce modèle sous-tend deux hypothèses. Premièrement, la relation entre la fonction de risque et les covariables est log-linéaire. Il existe plusieurs méthodes pour évaluer l'écart de log-linéarité des variables continues (statistiques et/ou graphiques). Lorsque la variable ne satisfait pas l'hypothèse de log-linéarité, la pratique courante est de transformer la variable continue en une variable catégorielle. Deuxièmement, le rapport des risques instantanés pour deux sujets i et j de caractéristiques Z_i et Z_j ne dépend que de Z_i et Z_j et ne dépend pas du temps (hypothèse des rapports de risques proportionnels). En d'autres termes, si un individu a un risque de décès à un moment initial qui est deux fois plus élevé que celui d'un autre individu, alors à tous les moments ultérieurs, le risque de décès reste deux fois plus élevé. L'hypothèse des ratios de risques proportionnels peut être vérifiée par une méthode graphique ou une méthode statistique. La méthode statistique est la plus robuste et constitue la solution privilégiée. Elle est basée sur l'analyse des résidus de Schoenfeld. Les résidus sont calculés pour chaque date d'événement et correspondent à la différence entre le profil de l'individu avec l'événement et le profil des individus à risque à cette date. Si les résidus sont distribués de la même manière dans le temps, l'hypothèse de risques proportionnels est vérifiée. Si ce n'est pas le cas, alors : i) le modèle de Cox peut être stratifié sur cette variable (perte de l'estimation de l'impact de cette variable sur l'événement), ii) il est possible d'introduire une covariable dépendante du temps (la covariable est alors la même variable mais avec une interaction avec le temps), et iii) il est possible de créer un modèle divisé en deux parties en considérant l'analyse séparément sur deux périodes.

I.A.1.b. Interprétation des coefficients ß

L'interprétation des coefficients exponentiels est le rapport de risque pour l'augmentation d'une unité du covariant spécifique. La validité de ce rapport de risque est basée sur l'hypothèse de rapports de risques proportionnels. Si z1 est une

variable à deux modalités, $z1$ = {1/0} parmi les p variables explicatives, alors le rapport de risque (RR) pour cette variable s'écrit comme suit :

$$RR_{z1=1/z1=0} = \frac{h_0(t_i)\exp\,(\beta_{1)}\,\exp(\sum_{j=2}^{p}\beta_{jz_{i,j}})}{h_0(t_i)\,\exp(\sum_{j=2}^{p}\beta_{jz_{i,j}})} = \exp\,(\beta_1)\;\forall t_i$$

Les patients ayant la variable explicative {$z1$=1} ont un risque d'échec multiplié par $\exp\,(\beta_1)$ par rapport à ceux ayant la variable explicative {$z1$=0}. On dit que le risque relatif de la variable z1 est ajusté pour toutes les autres variables, c'est-à-dire avec toutes les autres variables constantes. Il est constant dans le temps puisqu'il ne dépend que du coefficient de régression β_1.

L'hypothèse H_0 nécessitait de tester l'égalité des fonctions de hasard de chaque modalité de la variable explicative $z1$: { β_1=0 $\Leftarrow\Rightarrow$ RR $z1$=1/$z1$=0}. L'hypothèse alternative H_1 est le plus souvent bilatérale : {β_1≠0 $\Leftarrow\Rightarrow$ RR $z1$=1/$z1$=0}. Si H_0 est rejetée, il existe une différence de survie entre les deux populations définies par la variable $z1$.

I.A.2. Du modèle vers le score prédictif

I.A.2.a. Discrimination du modèle statistique

Lorsqu'on teste un nouveau facteur pronostique, il est essentiel de tester sa valeur additionnelle. En effet, si ce facteur est associé de manière indépendante à l'événement, sa contribution par rapport aux modèles existants doit être déterminée. La question est de savoir si ce nouveau facteur apporte une information supplémentaire et complémentaire et si son application en pratique clinique est pertinente. Si tel est le cas, ce facteur est considéré comme discriminant. La capacité discriminante d'un modèle est définie par son aptitude à séparer les individus qui ont réalisé l'événement de ceux qui ne l'ont pas fait, et consiste donc à séparer des individus ayant des pronostics différents. L'une des méthodes classiques d'évaluation de la discrimination est l'analyse d'une courbe ROC. Il s'agit d'une représentation graphique de la sensibilité d'un facteur pour l'événement sur l'axe des ordonnées en fonction de la spécificité 1 sur l'axe des abscisses. Cela revient à

évaluer le taux de vrais positifs en fonction du taux de faux positifs. L'indice associé est l'aire sous la courbe ROC, appelée AUC. Elle renseigne sur la probabilité que le résultat du test pour deux personnes avec et sans l'événement permette de poser le bon diagnostic. Ainsi, le test est parfaitement discriminant si l'AUC est égale à 1. Dans ce cas, lors de l'évaluation de deux personnes, le test distinguera toujours la personne atteinte de la maladie de celle qui ne l'est pas. Un test qui n'est pas meilleur que le hasard aura une AUC de 0,5.

I.A.2.b. Construction d'outils de pronostic basés sur des modèles intégratifs

Après avoir identifié les facteurs indépendamment associés à l'événement et la valeur additive de nouveaux facteurs, l'étape finale est le développement d'outils de prédiction adéquats pour permettre la stratification du risque. Un score est créé en fonction des coefficients ß attribués par le modèle multivarié final à chaque variable. Ces coefficients représentent la contribution relative et individuelle des variables à la distribution de la survie.

I.A.2.c. Performance du score de prédiction

L'analyse de la performance du modèle passe par l'étude de sa calibration et de sa discrimination, déjà abordées dans les paragraphes précédents.
Pour quantifier la performance globale d'un modèle, il est essentiel de prendre en compte sa calibration correspondant à la distance entre les événements prédits et les événements observés. Ces distances entre les événements observés et prédits sont liées à la notion de qualité d'ajustement d'un modèle, les meilleurs modèles ayant des distances plus faibles entre les résultats prédits et les résultats observés. La calibration est essentielle puisqu'elle fait référence à la capacité du modèle à produire des prédictions précises et non biaisées dans des groupes de patients similaires. Il s'agit d'une étape préliminaire indispensable avant l'étude de la discrimination des modèles, car un modèle discriminant, mais mal calibré, a une valeur clinique limitée. La calibration peut être mesurée par une méthode graphique à l'aide de courbes de calibration ou par une méthode statistique, comme celle de Hosmer-Lemeshow pour les modèles de survie. Le modèle statistique de Hosmer-Lemeshow ou son extension pour les données de survie est dérivé de n groupes équilibrés de patients définis par les quantiles de la probabilité prédite par le modèle.

Le biais mesuré est défini comme la somme des différences entre la moyenne des probabilités prédites et la moyenne des probabilités observées dans chaque groupe de patients similaires. La calibration du modèle est alors appréciée par la p-value du test qui est basé sur cette somme. Lorsque cette somme est inférieure à 0,1, la calibration n'est pas adéquate.

Comme défini précédemment, la discrimination est la capacité du modèle à distinguer les individus qui ont réalisé l'événement de ceux qui ne l'ont pas fait, et donc la capacité du modèle à séparer des individus ayant des pronostics différents.

I.B Développement et validation de scores de risque spécifique post-transplantation en fonction du statut d'assistance circulatoire lors de la transplantation : Une analyse de cohorte UNOS

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I.B.1. Problématique

L'utilité, la justice et le respect des personnes sont les trois piliers éthiques sur lesquels repose tout système d'attribution d'organes.[58] En particulier, lorsqu'il s'agit d'une ressource vitale remarquablement limitée, telle que la transplantation cardiaque, l'équilibre entre l'utilité - c'est-à-dire une intervention qui a une forte probabilité d'apporter un bénéfice au patient - et la justice - c'est-à-dire permettre un accès équitable et juste à la transplantation aux patients présentant le risque de décès le plus élevé - représente un défi non résolu, de même que la nécessité de donner aux patients les moyens de faire un choix éclairé fondé sur des données concernant leurs résultats potentiels. En effet, les patients qui ont le plus de risque de mourir en attendant une transplantation sont généralement ceux qui ont le plus de risque d'avoir de mauvais résultats post-opératoires. Par conséquent, déterminer si une procédure est futile ou non est un défi pour les cliniciens, qui prennent souvent des décisions avec un manque de preuves.[59]

Dans ce contexte, les organismes de réglementation des transplantations ont développé plusieurs systèmes d'allocation principalement axés sur le principe de justice, permettant de donner la priorité aux patients les plus graves afin de minimiser la mortalité sur liste d'attente.[17] En 2018, l'UNOS a révisé sa politique d'allocation, passant à un système à 6 niveaux conçu pour mieux prioriser les patients en fonction de la mortalité prévue sur la liste d'attente. Ce nouveau système, similaire au précédent, n'aborde pas la question du résultat post-transplantation, et ne traite donc pas du concept de bénéfice de la transplantation.[60]
Plusieurs tentatives ont été faites pour stratifier le pronostic des candidats à la transplantation en fonction des caractéristiques du donneur et du receveur : une revue systématique récente a identifié 21 scores de risque différents, prenant en compte jusqu'à 28 variables relatives au donneur et 48 variables relatives au receveur.[61] La pertinence des scores de risque repose sur leur capacité à soutenir la prise de décision clinique, à fournir des informations pour un conseil et un consentement appropriés aux patients et aux familles, et à orienter les politiques d'attribution d'organes. Malheureusement, la performance globale de ces scores est faible, avec une C-statistique allant de 0,54 à 0,77. Un défi majeur dans ce contexte est d'identifier des marqueurs de gravité clinique qui ne dépendent pas de la stratégie de traitement développée par l'équipe de soins (par exemple, la décision d'utiliser des inotropes ou une contre-pulsion par ballon intra-aortique peut dépendre de la pratique spécifique du centre plus que de la gravité du patient). En outre, la proposition de marqueurs prédictifs devrait conserver sa validité une fois qu'une assistance circulatoire mécanique temporaire ou à long terme a été implantée.

Ainsi, le développement d'un score d'allocation cardiaque qui inclurait la stratification du risque de résultats post-transplantation est devenu la prochaine priorité suite à la récente révision du système d'allocation cardiaque de l'UNOS. Cependant, les scores de risque post-transplantation souffrent d'une mauvaise performance statistique.[18] Leur faible discrimination ne permet pas une stratification précise et individuelle du risque de mortalité post-transplantation. En développant un seul score pour tous les patients, ces scores négligent l'hétérogénéité entre les patients.

Nous avons émis l'hypothèse que le développement de modèles pronostiques spécifiques pour chaque statut d'assistance (aucune assistance, assistance durable, assistance temporaire) pourrait améliorer leur performance statistique.

I.B.2. Article original

Dans ce contexte, notre contribution repose sur une analyse d'une cohorte contemporaine de l'UNOS avec une analyse statistique approfondie

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Development and validation of specific post-transplant risk scores according to the circulatory support status at transplant: A UNOS cohort analysis

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KEYWORDS:
heart transplantation;
mechanical circulatory support;
prognosis;
survival;
risk score

BACKGROUND: The clinical use of post-transplant risk scores is limited by their poor statistical performance. We hypothesized that developing specific prognostic models for each type of circulatory support at transplant may improve risk stratification.

METHODS: We analyzed the UNOS database including contemporary, first, non-combined heart transplantations (2013-2018). The endpoint was death or retransplantation during the first year post-transplant. Three different circulatory support statuses at transplant were considered: no support, durable mechanical support and temporary support (inotropes, temporary mechanical support). We generated 1,000 bootstrap samples that we randomly split into derivation and test sets. In each sample, we derived an overall model and 3 specific models (1 for each type of circulatory support) using Cox regressions, and compared, in the test set, their statistical performance for each type of circulatory support.

RESULTS: A total of 13,729 patients were included; 1,220 patients (8.9%) met the composite endpoint. Circulatory support status at transplant was associated with important differences in baseline characteristics and distinct prognosis (p = 0.01), interacted significantly with important predictive variables included in the overall model, and had a major impact on post-transplant predictive models (type of variables included and their corresponding hazard ratios). However, specific models suffered from poor discriminative performance and significantly improved risk stratification (discrimination, reclassification indices, calibration) compared to overall models in a very limited proportion of bootstrap samples (<15%). These results were consistent across several sensitivity analyzes.

CONCLUSION: Circulatory support status at transplant reflected different disease states that influenced predictive models. However, developing specific models for each circulatory support status did not

Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygenator; eGFR, estimated glomerular filtration rate; HR, hazard ratio; HTx, heart transplantation; IABP, intra-aortic balloon pump; IDI, integrated discrimination improvement; ISHLT, International society for heart and lung transplantation; IQR, interquartile range; MCS, mechanical circulatory support; NRI, net reclassification improvement; UNOS, united network for organ sharing; VAD, ventricular assist device

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significantly improve risk stratification.
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In most countries, the allocation of heart allografts is based on a clinical stratification of the risk of poor pre-transplant outcomes, as assessed by the clinical condition and treatment received by the patient. Important limitations to this approach include the risk of influencing medical practice[1,2] and the lack of consideration of the risk of post-transplant mortality, thus neglecting the potential survival benefit of transplantation.[3] The development of a heart allocation score that would include the stratification of the risk of post-transplant outcomes has become the next priority following the recent revision of the United Network for Organ Sharing (UNOS) heart allocation system. However, all post-transplant risk scores suffer from poor statistical performance.[4,5] Particularly, their discrimination has been reported to be too low to allow an accurate and individual stratification of the risk of early post-transplant mortality.[6] By developing 1 score for all patients, these scores neglected heterogeneity between patients.

The increasing use of durable mechanical circulatory support (MCS) before HTx[7,8] and the recent increase in use of temporary MCS have dramatically contributed to this underlying heterogeneity.[2] Circulatory support status at transplant reflects different disease states that may influence post-transplant predictive models. As a reflection, the discrimination of risk scores has been shown to vary greatly according to the type of circulatory support at transplant.[6] We hypothesized that developing specific prognostic models for each support status may improve their statistical performance. We aimed to (1) identify independent risk factors for early post-transplant outcomes for each circulatory support status, (2) develop specific risk models for each status and (3) compare the statistical performance (discrimination, reclassification indices, calibration) of specific risk scores to a unique overall model for all patients.

Materials and methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. We followed the STROBE guidelines for data reporting of observational studies.

Definitions and selection of variables

We defined 3 circulatory support statuses at transplant: none, durable MCS (left ventricular assist device [VAD], right VAD, bi-VAD and total artificial heart) and temporary support (extracorporeal membrane oxygenator [ECMO], Impella, intra-aortic balloon pump [IABP], and inotropes). The clinical endpoint analyzed in this study was a composite endpoint of death and/or retransplantation during the first year post-HTx.

The severity of disease was assessed using the UNOS status at transplant and categorized as urgent (UNOS status 1A or 1-2-3 in the new allocation scheme) and nonurgent HTx (UNOS status 1B-2 or 4-5-6 in the new scheme).

We considered the predictive variables previously identified as independently associated with post-transplant outcomes in previously published risk models. We identified 16 independent risk scores.[6,9-23] The detailed search methodology has been published previously and is summarized in Supplementary Methods.[6] These models included a total of 70 different predictive variables. Among them, we selected a subset of 43 variables to avoid variables with ≥33% of missing values and redundant or obviously collinear variables (selection process detailed in Supplementary Table S1).

Patients and databases

We analyzed a contemporary UNOS cohort to take into account the rapidly evolving epidemiology of circulatory support status at transplant. All adult patients who underwent HTx between January 1, 2013 and December 31, 2018 were selected from the UNOS registry. Patients were excluded if they were 18 years or younger, underwent dual organ transplantation or redo-HTx, or if their vital status was not available. A flowchart is provided in Supplementary Figure S1. Studies using this dataset have been determined to be exempt from review by the Institutional Review Board of Cedars-Sinai Medical Center. We attest our strict compliance with the International Society for Heart and Lung Transplantation (ISHLT) ethics statement.

Statistical analysis

Qualitative variables were described as their frequencies and compared with the chi-squared test. Quantitative variables were described as the mean values with the standard deviation and compared with the Student t-test or ANOVA. Cumulative survival curves for the time-to-event analyses were constructed according to the Kaplan-Meier method and compared with the log-rank test. Using univariate and then multivariate Cox models (candidate factors selected when the univariate likelihood ratio test p value was ≤0.10; backward elimination, complete-case analysis), we first built an overall predictive model and analyzed the interactions between significant predictive variables and circulatory support status at transplant (complete-case analysis). We then randomly generated 1,000 bootstrap samples (random sample with replacement, stratified by type of circulatory support at transplant). For each sample, we (1) randomly split the overall cohort in a derivation set (2/3) and a test set (1/3); (2) developed, in the derivation set, 4 distinct predictive models (complete-case analysis): an overall model including all patients and 3 specific models, 1 for each circulatory support status at transplant using multivariate Cox regression with automatic selection of variables and backward elimination; and (3) analyzed and compared, in the test set, the statistical performance (a- discrimination: concordance statistic compared using the STATA's "somersd" package, b- reclassification indices: net reclassification improvement [NRI] and integrated discrimination improvement [IDI], c- calibration: graphical evaluation) of the specific and overall models for each type of circulatory support status. We analyzed the consistency of our

results by performing several sensitivity analyses: analysis of continuous variables as categorical variables, analysis of a broader set of predictive variables and limitation of the sample size of the derivation set for the overall model (an overall model was derived in a subset of randomly selected patients, which equals the number of patients in the derivation set of each specific model). Statistical significance was set at $p \leq 0.05$. All tests were 2-sided. Statistical analyses were performed using STATA 15.1 (StataCorp LP, College Station, TX, USA).

Results

Characteristics of patients

A total of 13,729 patients were included. Their main characteristics are summarized in Table 1. At transplant, 2,135 (15.5%), 6,695 (48.8%) and 4,899 (35.7%) patients were on no, durable and temporary circulatory support, respectively. We observed important differences in the main clinical characteristics between support status at transplant, including recipient gender, ethnicity, etiology of heart failure, diabetes and pre-transplant infection, and donor gender and cause of death.

During the first year post-transplant, a total of 1,220 patients (8.9%) met the composite endpoint of death or retransplantation (Supplementary Figure S2-A). Post-transplant survival significantly differed across circulatory support status at transplant (no support: reference; temporary support: HR = 0.92, 95%CI = 0.77-1.12; durable support: HR = 1.19, 95%CI = 1.01-1.41, p = 0.01) (Supplementary Figure S2-B).

Overall model and analysis of interaction

Among the 43 selected variables, 25 variables were associated with post-transplant outcomes in univariate Cox regression analysis ($p < 0.10$). After multivariate analysis, 12 predictive variables were independently associated with the occurrence of the primary endpoint (Table 2, concordance statistic = 0.676), including 9 recipient-related variables (age, body mass index, etiology of heart failure, prior

Table 1 Characteristics of Patients

Recipient characteristics	N	Overall	No support	Durablesupport	Temporarysupport	*p* value
Age, years — mean (SD)	13,729	53.8 ± 12.6	53.9 ± 13.4	53.6 ± 12.2	54.1 ± 12.8	**0.05**
Female gender — no. (%)	13,729	3,646 (26.6)	777 (36.4)	1,339 (20.0)	1,530 (31.23)	**<0.001**
Ethnicity	13,729					
Caucasian		8,918 (65.0)	1,480 (69.3)	4,288 (64.1)	3,150 (64.3)	
African American		3,008 (21.9)	339 (15.9)	1,636 (24.4)	1,033 (21.1)	**<0.001**
Hispanic		1,146 (8.3)	193 (9.0)	510 (7.6)	443 (9.0)	
Others		657 (4.8)	123 (5.8)	261 (3.9)	273 (5.6)	
Body mass index, kg/m^2 — mean (SD)	13,723	27.6 ± 4.9	26.9 ± 4.8	28.7 ± 4.8	26.5 ± 4.7	**<0.001**
Etiology of heart failure — no. (%)	13,729					
Dilated / idiopathic		7,681 (55.9)	949 (44.5)	4,070 (60.8)	2,662 (54.3)	
Ischemic		4,510 (32.9)	650 (30.4)	2,384 (35.6)	1,476 (30.1)	**<0.001**
Congenital		407 (3.0)	140 (6.6)	52 (0.8)	215 (4.4)	
Other		1131 (8.2)	396 (18.5)	189 (2.8)	546 (11.2)	
Pre-transplant diabetes — no. (%)	13,722	3,851 (28.1)	473 (22.2)	2,048 (30.6)	1,330 (27.2)	**<0.001**
Mechanical ventilation at transplant — no. (%)	13,729	104 (0.8)	10 (0.5)	24 (0.4)	70 (1.4)	**<0.001**
eGFR at transplant, mL/min/1.73m^2 — mean (SD)	13,727	72.9 ± 33.5	72.7 ± 31.3	72.8 ± 29.7	73.1 ± 38.9	0.86
Dialysis after listing — no. (%)	13,727	243 (1.8)	19 (0,9)	150 (2.2)	74 (1.5)	**<0.001**
Total bilirubin at transplant, mg/dL — mean (SD)	13,715	0.94 ± 1.39	0.93 ± 1.64	0.88 ± 1.16	1.01 ± 1.55	**<0.001**
Pre-transplant infection — no. (%)	13,558	1,338 (9.9)	72 (3.4)	826 (12.5)	440 (9.1)	**<0.001**
Donor characteristics						
Age, years — mean (SD)	13,729	32.2 ± 11.2	32.7 ± 11.8	31.8 ± 10.7	32.6 ± 11.5	**<0.001**
Female gender — no. (%)	13,729	4,162 (30.3)	801 (37.5)	1,586 (23.7)	1,775 (36.2)	**<0.001**
Pre-transplant diabetes — no. (%)	13,662	519 (3.8)	97 (4.6)	238 (3.6)	184 (3.8)	0.11
Cause of death — no. (%)	13,460					
Traumatic		6,459 (48.0)	916 (43.8)	3,334 (50.7)	2.209 (46.1)	
Cerebrovascular		2,520 (18.7)	410 (19.6)	1,131 (17.2)	979 (20.4)	**<0.001**
Anoxia		2,875 (21.4)	468 (22.4)	1,399 (21.3)	1,008 (21.1)	
Other		1,606 (11.9)	297 (14.2)	714 (10.8)	595 (12.4)	
Transplant characteristics						
Ischemic time, hour — mean (SD)	13,729	3.11 ± 1.04	3.13 ± 1.11	3.10 ± 1.06	3.10 ± 0.98	0.41

Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation.

Table 2 Overall Predictive Model (Multivariable Cox Model)

Variables	Label	Number of patients	Number of events	HR	95%CI	p
RECIPIENT CHARACTERISTICS						
Age	per 10-year increment	13,169	1,164	1.18	[1.11-1.24]	<0.001
Prior history of	No	6,348	443	1	-	
cardiac surgery	Yes	6,821	721	1.40	[1.23-1.58]	<0.001
Diabetes mellitus	No	9,461	770	1	-	
	Yes	3,708	394	1.16	[1.02-1.32]	0.02
Etiology of	Dilated	7,357	584	1	-	
Heart Failure	Ischemic	4,328	425	0.99	[0.87-1.14]	
	Congenital	392	59	2.30	[1.73-3.07]	<0.001
	Other	1,092	96	1.16	[0.94-1.45]	
Body Mass Index	≤18.5 kg/m2	291	29	1.38	[0.94-2.02]	
	18.5-25 kg/m2	4,053	306	1	-	
	25-30 kg/m2	4,834	411	1.12	[0.96-1.30]	<0.001
	≥30 kg/m2	3,991	418	1.37	[1.18-1.59]	
Dialysis after listing	No	12,938	1,115	1	-	
	Yes	231	49	2.20	[1.65-2.95]	<0.001
Transfusion after	No	10,087	811	1	-	
Listing	Yes	3,082	353	1.25	[1.10-1.43]	0.001
Mechanical	No	13,071	1,140	1	-	
ventilation	Yes	98	24	2.77	[1.84-4.17]	<0.001
Total bilirubin	per 1-mg/dL increment	13,169	1,164	1.085	[1.07-1.10]	<0.001
DONOR CHARACTERISTICS						
Age	per 10-year increment	13,169	1,164	1.075	[1.02-1.14]	0.011
Cause of death	Traumatic	6,330	529	1	-	
	Cerebrovascular	2,477	280	1.26	[1.08-1.48]	
	Anoxia	2,802	228	0.96	[0.82-1.12]	0.005
	Other	1,560	127	0.92	[0.76-1.12]	
TRANSPLANT CHARACTERISTICS						
Ischemic time	per 1-hour increment	13,169	1,164	1.18	[1.12-1.24]	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

history of cardiac surgery, diabetes, total bilirubin, dialysis after listing, transfusion after listing, and mechanical ventilation at transplant), 2 donor-related variables (age and cause of death) and 1 transplant-related variable (ischemic time).

We found significant interaction between the circulatory support status at transplant and 5 out of 12 predictive variables selected in the multivariate model (Supplementary Figure S3), including donor age ($p = 0.01$), transfusion after listing ($p = 0.01$), dialysis after listing ($p = 0.04$), body mass index ($p = 0.05$), and total bilirubin ($p = 0.06$).

Development of specific predictive models

First, we developed specific predictive models for each circulatory support status at transplant on the overall cohort. We found important differences between models in terms of both the predictive variables included and their respective weight in the multivariate model (Table 3, concordance statistic = 0.696, 0.641 and 0.660 for no support, durable support and temporary support models, respectively).

Then, we developed an overall model and 3 specific models (no support, durable support and temporary support models) in the derivation set of each one of the 1,000 bootstrap samples generated. As described in Figure 1, we observed important differences in the set of variables independently associated with post-transplant outcomes between models. However, the overall models represented a mix ~~average~~ of specific models. Most variables among the 10 most selected variables for each specific model were also among the 10 most selected variables in the overall models (no support model: $n = 7/10$; durable support model: $n = 7/10$; and temporary support model: $n = 6/10$).

Comparison of overall and specific models: discrimination, reclassification indices and calibration

In the test set of the 1,000 bootstrap samples, the median concordance statistic of the specific models was 0.613 (IQR = 0.573-0.653), 0.615 (IQR = 0.595-0.634) and 0.600 (IQR = 0.574-0.621) compared to 0.67 (IQR = 0.597-0.708), 0.630 (IQR = 0.586-0.652) and 0.630 (IQR = 0.606-0.652) for the overall models in patients with no, durable and temporary support, respectively (Figure 2). The specific model significantly outperformed the discrimination of the overall model in only 0.9%, 3% and 1.6% of the bootstrap samples in patients with no, durable and temporary support, respectively. The discrimination of specific models was mostly driven by variables already included in the overall model. The addition of variables exclusively present in

Table 3 Multivariable Predictive Model for Each Circulatory Support Status at Transplant

Variables	Label	No support	Durable support	Temporary support
RECIPIENT CHARACTERISTICS				
Age	per 10-year increment	1.21 [1.02-1.42]	1.23 [1.14-1.34]	1.10 [1.001-1.22]
Ethnicity	Caucasian			1 -
	Af. American			1.56 [1.11-2.19]
	Hispanic			0.88 [0.65-1.20]
	Other			0.86 [0.51-1.43]
Blood group	A		1 -	
	B		1.13 [0.87-1.46]	
	0		0.91 [0.75-1.11]	
	AB		0.42 [0.21-0.82]	
Prior cardiac surgery				1.53 [1.22-1.92]
Diabetes mellitus				1.30 [1.03-1.66]
Steroids use			0.40 [0.22-0.68]	
Etiology of	Dilated	1 -		
Heart Failure	Ischemic	1.14 [0.73-1.77]		
	Congenital	3.97 [2.07-7.61]		
	Other	1.68 [1.05-2.67]		
Time on the	≤31			1 -
waitlist, days	32-109			0.80 [0.61-1.06]
	110-306			0.96 [0.71-1.31]
	≥307			1.34 [0.96-1.86]
Body Mass Index	≤18.5 kg/m2	4.61 [2.08-10.18]	1.34 [0.59-3.06]	
	18.5-25 kg/m2	1 -	1 -	
	25-30 kg/m2	1.28 [0.82-1.99]	1.13 [0.88-1.45]	
	≥30 kg/m2	1.42 [0.89-2.27]	1.45 [1.14-1.85]	
Mean pulmonary	≤19		1 -	
artery pressure,	19-25		1.01 [0.79-1.28]	
mmHg	25-33		1.11 [0.87-1.42]	
	>33		1.44 [1.12-1.85]	
Dialysis after listing				

(*continued on next page*)

Table 3 (*Continued*)

Variables	Label	No support	Durable support	Temporary support
		5.91 [2.45-14.24]	1.97 [1.25-3.09]	2.39 [1.32-4.31]
Transfusion				1.67 [1.21-2.30]
Mech. ventilation		5.22 [1.27-21.51]	2.78 [1.15-6.74]	2.08 [1.11-3.91]
Total bilirubin	per 1-mg/dL increment	1.12 [1.08-1.17]	1.12 [1.09-1.15]	1.06 [1.03-1.10]
DONOR CHARACTERISTICS				
Age	per 10-year increment	1.29 [1.12-1.50]		1.17 [1.06-1.28]
Cause of death	Traumatic		1 -	
	Cerebrovasc		1.28 [1.02-1.61]	
	Anoxia		0.82 [0.64-1.05]	
	Other		0.98 [0.72-1.31]	
TRANSPLANT CHARACTERISTICS				
Ischemic time	per 1-hour increment	1.22 [1.05-1.41]	1.21 [1.12-1.30]	

Abbreviations: Af American, African American; CI, confidence interval; HR, hazard ratio; Mech. Ventilation, mechanical ventilation.

specific models resulted in a marginal improvement in discrimination (Figure 3).

The NRI (event, no event and global) and IDI of specific models compared to the overall models are presented in Figure 4A and B. Compared to the overall models, specific models significantly improved risk stratification in a limited number of samples (NRI: 11.1, 13.4 and 13.4%; IDI: 9.6, 4.9 and 6.7% of samples for no support, durable support and temporary support models, respectively).

A graphical evaluation of calibration of the specific and overall models is provided in Figure 5. We observed a trend towards an overestimation of the risk of event in high-risk patients which was more important in specific models, particularly for the no support model.

Sensitivity analyses

First, we analyzed continuous variables as categorical variables (categorized into quartiles or validated classifications). The specific models significantly outperformed the discrimination of overall models in less than 2% of samples. Similarly, specific models improved risk reclassification in a very limited number of samples (Supplementary Table S2).

Second, we considered a broader set of variables of interest by including all variables included in the 16 prognosis scores. The improvement in discrimination and risk reclassification with specific models compared to overall models remained marginal (Supplementary Table S2).

Third, when limiting the sample size of the derivation set for the overall model, the specific models had a significantly greater discrimination than the overall model in less than 10% of the samples (Supplementary Figure S4) and improved reclassification in less than 20% of samples (Supplementary Table S2).

Finally, when taking into account the severity of disease as assessed by the UNOS status at transplant, specific models significantly outperformed overall models in a minority of cases (Supplementary Table S2).

Discussion

In our analysis of a contemporary UNOS cohort of adult first non-combined HTx, we found that circulatory support status at transplant was associated with major differences in baseline characteristics and distinct prognosis, presented significant interactions with important predictive variables included in an overall predictive model, and had a major influence on post-transplant predictive models (type of variables and their associated hazard ratios). However, the development of specific predictive models for each type of circulatory support had limited impact on the statistical performance of predictive models. Our results do not support the development and the use of a specific post-transplant prognostic model for each circulatory support status at transplant.

While the development of a heart allocation score has become the next priority following the recent revision of the UNOS heart allocation system, it has become necessary to counterbalance the prioritization of patients based on the assessment of the risk of death on the waitlist by accurate stratification of the risk of death after HTx in order to avoid futile transplantations. We recently reported the poor

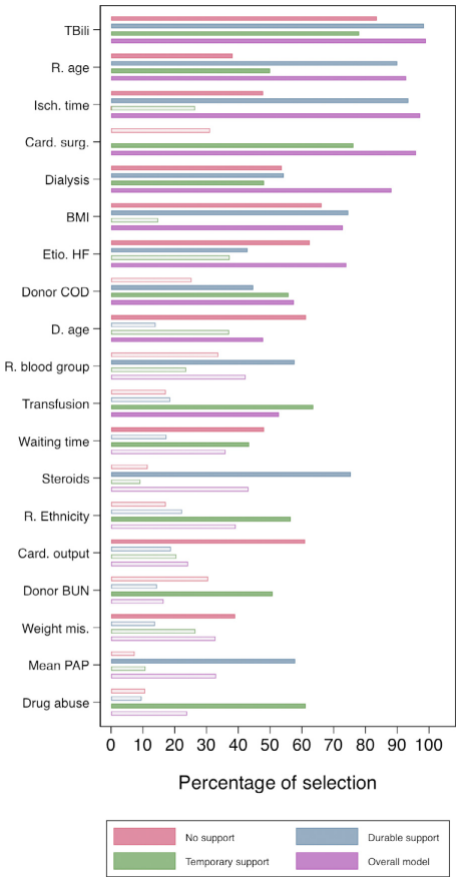

Figure 1 Most selected predictive variables according to the circulatory support status at transplant. This figure represents the percentage of bootstrap samples (n = 1,000) in which the variable of interest was found to be independently associated with post-transplant outcomes (the 10 most selected variables in all models are presented). Important differences in the set of selected variables were observed between models. Opaque bars: variable among the 10 most selected for this model. Transparent bars: variable not among the 10 most selected for this model. BMI, body mass index; BUN, blood urea nitrogen; Card. Surg, prior history of cardiac surgery; Card. output, cardiac output; COD, cause of death; D, donor; eGFR, estimated glomerular filtration rate; Etio. HF, etiology of heart failure; HF, heart failure; Isch. Time, ischemic time; PAP, pulmonary artery pressure; R, recipient; TBili, total bilirubin.

statistical performance of 16 post-transplant risk scores, particularly concerning their discrimination abilities.[6] These models do not allow a precise and individual stratification of the risk of early post-transplant mortality or retransplantation, thus limiting the evaluation of the individual transplant benefit. Developing more accurate models is an essential step before considering using these scores in clinical practice. Taking into account part of the heterogeneity between patients by developing risk models for specific populations may be an interesting approach.

Several prognostic models have been specifically developed in patients on durable MCS at transplant. The bridge to transplant risk score was developed in patients on left VAD at transplant (UNOS database, transplantation from 2008 to 2014).[11] The transplantation Risk Index in Patients with MCS was developed in patients on any type of MCS excluding ECMO (UNOS database, transplantation from 2000-2013).[14] Both multivariate predictive model included common predictive variables previously identified as independent risk factors for post-transplant mortality in patients without MCS at transplant. In line with our results, these 2 models were less discriminant than several models developed on non-VAD patients to predict outcomes in patients on durable MCS.[6]

We found that the specific models included different combinations of predictive variables. While total bilirubin and eGFR were similarly selected in all specific models, several variables were clearly imbalanced between models. Ischemic time, recipient age and mean pulmonary artery pressure were much more selected in durable support models that in the other specific models. On the other hand, donor cause of death, transfusion after listing and prior history of cardiac surgery were more often selected in the temporary support models, while donor age and etiology of heart failure were more frequently included in the no support model. These important differences between models may reflect (1) a different donor/recipient matching process according to the circulatory support at transplant, (2) differences in baseline characteristics and sample size and (3) different impacts of predictive variables on outcomes according to the circulatory support status.

As observed and discussed previously for all previously published predictive models, the overall discrimination of specific and overall models in our study was limited.[6,24] Additionally, the development of specific models for each circulatory support status did not result in improved statistical performance compared to that in overall models. First, the relatively limited number of variables taken into account for our primary analysis may limit statistical discrimination. However, this set of variables gathered all variables already included in previous prognostic models and ISHLT annual reports. The consideration of additional variables in the development of the model resulted in marginal improvement in discrimination. The lack of granularity of data in the UNOS registry may be the underlying explanation. The UNOS Thoracic Committee recently decided to expand the collection of data to capture more prognostic markers in order to improve risk stratification. Second, the overall models were an average of all specific models and included their most discriminant predictive variables. The addition of variables that were specific of a particular circulatory support model did not improve discrimination. Third, each circulatory support subpopulation included less patients and events than those in the overall population, thus limiting the number of independent predictive variables selected in the specific models compared to those in the overall model. However, developing specific predictive

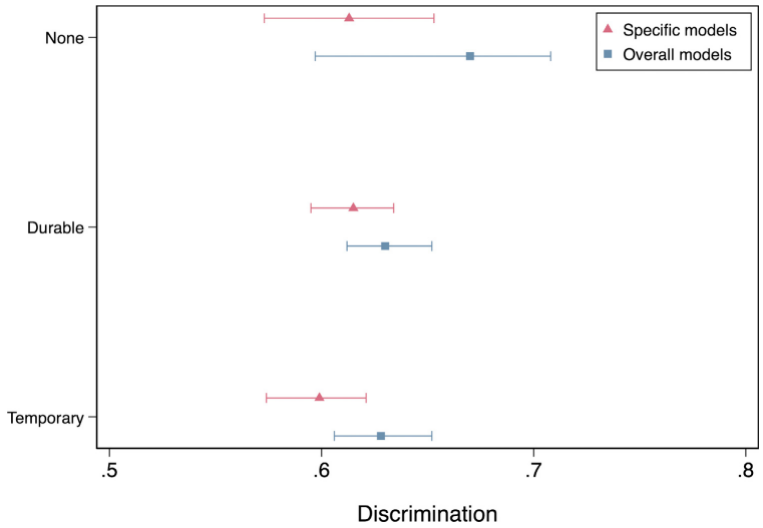

Figure 2 Discrimination of the overall and specific models for each circulatory support status. This figure represents the median and interquartile range of the concordance index observed in the test set of each bootstrap sample (n = 1,000). For each type of circulatory support at transplant, the discrimination of the specific model and of the overall model are given.

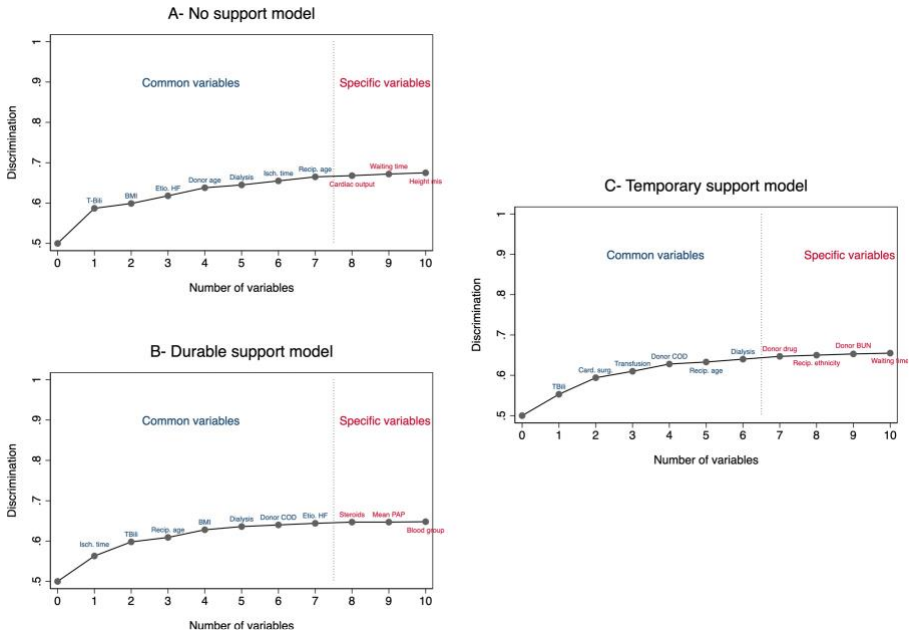

Figure 3 Evolution of discrimination according to the number and type of variables included in the specific models. The evolution of discrimination is described after progressive inclusion of the most selected variables in specific models. (A) No support model. (B) Durable support model. (C) Temporary support model. "Common variables" designs variables among the 10 most selected in the specific model and in the overall model. "Specific variables" designs variables among the 10 most selected in the specific models but not in the overall model. BMI, body mass index; BUN, blood urea nitrogen; Card. surg, prior history of cardiac surgery; Donor COD, donor cause of death; Etio. HF, etiology of heart failure; Isch. Time, ischemic time; PAP, pulmonary artery pressure; Recip, Recipient, T-Bili, total bilirubin.

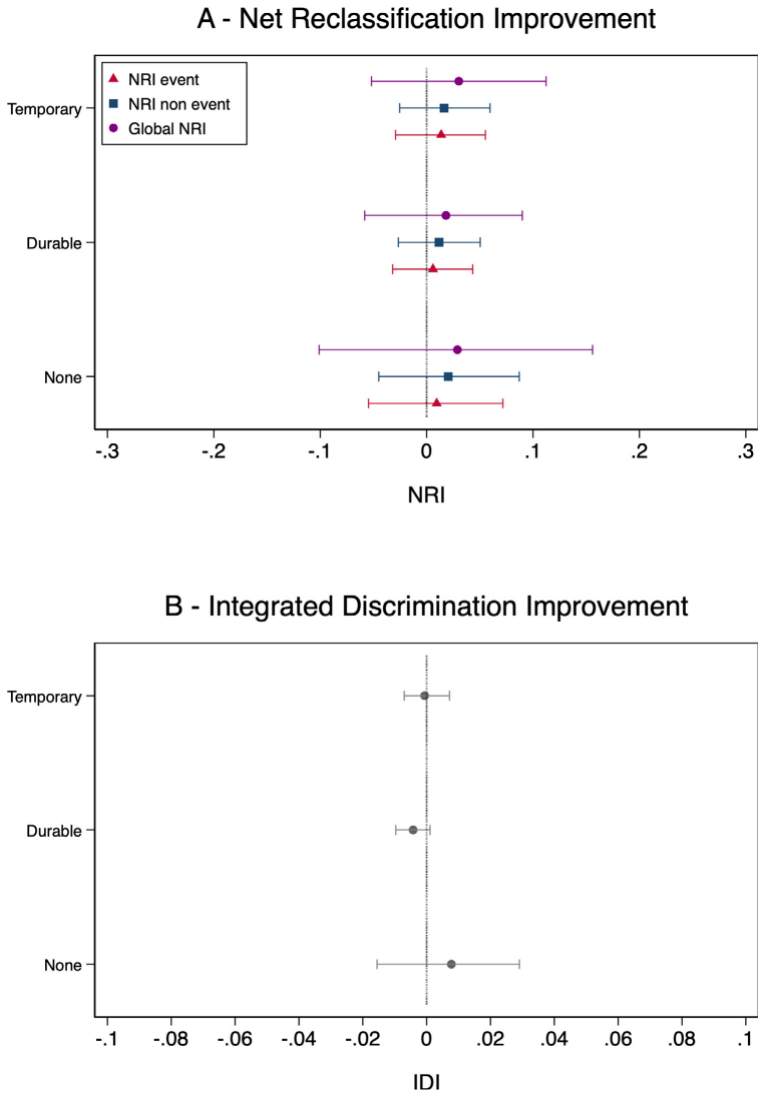

Figure 4 Net reclassification improvement and integrated discrimination improvement. Comparison of specific and overall models for each type of circulatory support. This figure represents the median and interquartile range of the Net reclassification improvement (A) and integrated discrimination improvement (B) observed in the test set of each bootstrap sample (n = 1,000).

models in similar derivation set sample sizes than those in the overall model resulted in marginal improvement of discrimination with specific models. Finally, circulatory support subgroups at transplant may include a wide heterogeneity of illness intensity. However, taking into account disease severity as assessed by the UNOS status at transplant did not modify our results.

Our results show that current predictive models do not allow a precise and individual stratification of the risk of early post-transplant mortality. However, we believe that considering post-transplant outcomes remains crucial in an allocation scheme based on the "sickest first" principle to avoid futile procedures. Pending the development of more accurate predictive models, we believe that post-transplant mortality risk scores should only be seen as a way to avoid very high-risk procedures associated with unacceptable outcomes and not as a continuous score aimed at evaluating precisely and individually the transplant benefit.

Our study should be interpreted in the context of its limitations. First, we analyzed a very limited number of patients transplanted with the 2018 allocation scheme, thus representing an important limitation to the clinical applicability

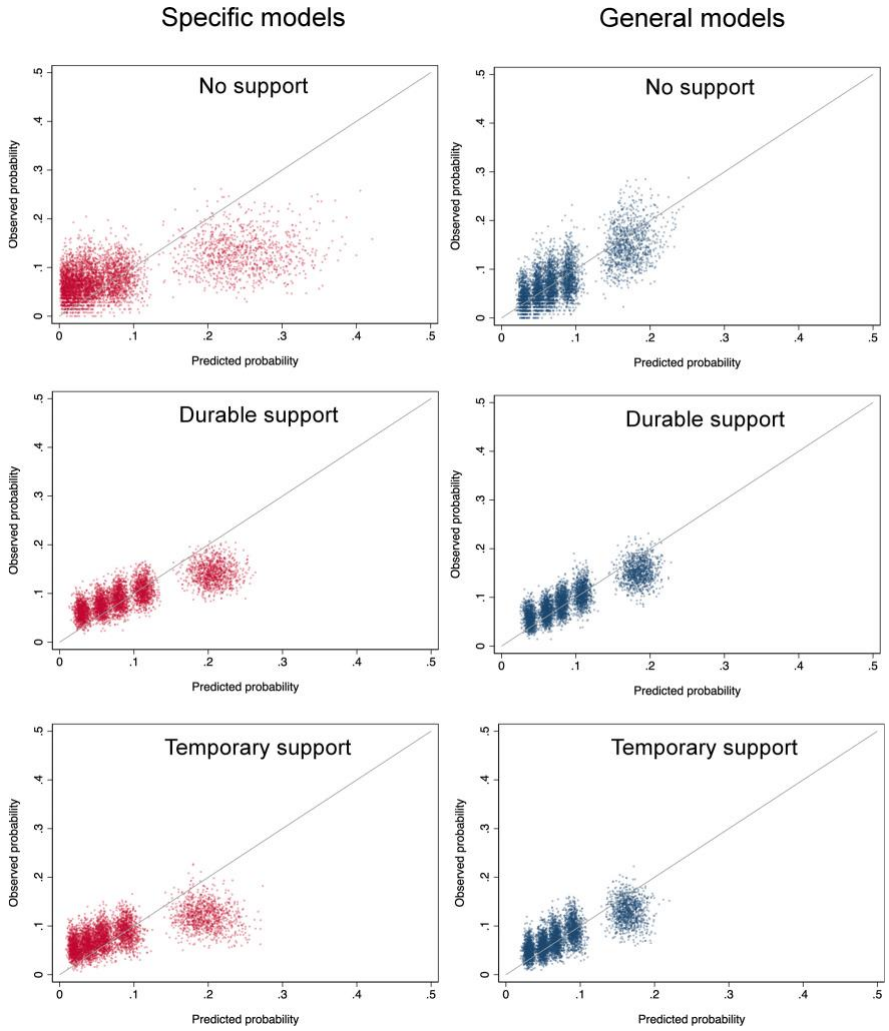

Figure 5 Calibration of the specific and overall models for each type of circulatory support at transplant. Test set: graphical evaluation of the calibration of each model by plotting predicted and observed probability of events (quintiles of predicted probability). Each circle represents 1 bootstrap sample (n = 1,000).

of our results. Important changes in the frequencies of mechanical support at transplant have followed the implementation of the new scheme, particularly concerning a dramatic increase in temporary MCS at transplant.[2,25,26] The limited number of patients on ECMO and IABP in the 2013-2018 UNOS cohort did not allow for the development of specific models for this subpopulation. However, recent data suggest that the profile of risk of patients transplanted with the new allocation scheme do not differ significantly compared to that in patients transplanted earlier, thus making it unlikely to improve discrimination by developing new specific models for these subgroups of patients.[2] Second, the use of the c-statistic as a measure of discrimination has been criticized for its low sensitivity in comparing models from different datasets and for the arbitrary selection of acceptable thresholds. However, the concordance index is a commonly accepted way to assess the discrimination of a model, and we applied it to analyze the discrimination ability of multiple risk scores on the same set of data. Third, an important limitation of all of the scores included in the analysis is that only the outcomes of patients that were actually transplanted were assessed and wait-list mortality was not accounted for.

Conclusion

Circulatory support status at transplant reflects different disease state of heart failure and had a major influence on post-transplant predictive models, concerning both the type of variables and their associated hazard ratios. However, developing specific models for each type of circulatory support did not result in improved statistical performance.

Author contributions (ICJME)

GC contributed to the design and analysis, drafted the work, approved the final version and agreed to be accountable for all aspects of the work.

GB contributed to the acquisition and analysis, drafted the work, approved the final version and agreed to be accountable for all aspects of the work.

EK contributed to the design, drafted the work, approved the final version and agreed to be accountable for all aspects of the work.

AL contributed to the conception and interpretation, revised the manuscript critically for important intellectual content, approved the final version and agreed to be accountable for all aspects of the work.

JM contributed to the interpretation, revised the manuscript critically for important intellectual content, approved the final version and agreed to be accountable for all aspects of the work.

PL contributed to the conception, revised the manuscript critically for important intellectual content, approved the final version and agreed to be accountable for all aspects of the work.

JAK contributed to the design and interpretation, revised the manuscript critically for important intellectual content, approved the final version and agreed to be accountable for all aspects of the work.

JKP contributed to the conception and interpretation, revised the manuscript critically for important intellectual content, approved the final version and agreed to be accountable for all aspects of the work.

Disclosure statement

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Supplementary materials

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I.B.3. Synthèse & Perspectives

Dans notre analyse d'une cohorte contemporaine de l'UNOS sur plus de 13 000 patients, nous avons constaté que le statut d'assistance circulatoire au moment de la transplantation était associé à des différences majeures dans les caractéristiques de base et le pronostic distinct, présentait des interactions significatives avec des variables prédictives importantes incluses dans un modèle prédictif global, et avait une influence majeure sur les modèles prédictifs post-transplantation (type de variables et leurs rapports de risque associés). Cependant, le développement de modèles prédictifs spécifiques pour chaque type d'assistance circulatoire a eu un impact limité sur la performance statistique des modèles prédictifs. Nos résultats ne soutiennent pas le développement et l'utilisation d'un modèle pronostique spécifique post-transplantation pour chaque statut d'assistance circulatoire lors de la transplantation.

Au niveau méthodologique, notre analyse était basée d'abord sur un modèle général, incluant tous les patients, qui a identifié les variables prédictives sur la base d'analyses univariées et multivariées de Cox. Dans cette première étape de l'analyse, nous avons identifié un score général basé sur 12 variables, qui étaient indépendamment associées aux résultats post-transplantation (par exemple, l'âge du donneur et du receveur, la bilirubine du donneur, le besoin de dialyse après l'inscription, la ventilation mécanique, l'indice de masse corporelle, le temps ischémique, etc.). La capacité prédictive était acceptable, mais pas grande, avec une statistique C de 0,67. Dans la deuxième étape, nous avons généré de manière aléatoire 1000 échantillons bootstrap stratifiés en fonction de l'utilisation de l’assistance (pas d’assistance vs. assistance à court terme vs. assistance de longue durée).

Dans l'ensemble, cette étude nous ramène au point de départ : même avec les approches de pointe les plus sophistiquées sur le plan statistique, il reste difficile de développer des scores de prédiction du risque en transplantation cardiaque qui soient précis et utiles pour guider la prise de décision, le conseil aux patients et les stratégies d'allocation.

Les défis à relever pour développer un score de risque validé pour la mortalité post-transplantation sont les suivants : 1) les scores de risque sont dérivés rétrospectivement et sont donc biaisés par un processus décisionnel qui a présélectionné les patients qui ont été transplantés ; 2) il existe une grande variabilité dans la pratique clinique entre les centres de transplantation dans la gestion de l'insuffisance cardiaque avancée (c'est-à-dire les indications de l'assistance ou d'inotropes). Par conséquent, cette variabilité brouille la taille de l'effet des variables qui peuvent être incluses dans un score de risque ; et 3) il existe probablement de nombreux facteurs importants qui influencent la survie après la transplantation et qui ne sont souvent pas pris en compte dans les grandes bases de données.

Devons-nous donc abandonner la recherche de scores de risque pour prédire les résultats post-transplantation ? En tant que cliniciens, nous devons reconnaître que les scores de risque sont imparfaits, néanmoins nous pouvons en tirer des enseignements. Les scores de risque apportent toujours une contribution importante à notre compréhension de la trajectoire de l'insuffisance cardiaque avancée et de la transplantation, et peuvent servir de guide pour de futures recherches.
Une des pistes de réflexion avancé par le score développé par l'Agence de la Biomédecine est le fait de combiner le risque du donneur et du receveur dans le modèle de prédiction. Les implications du système français sont qu'un donneur à haut risque amplifiera le statut de risque d'un receveur à haut risque. Par ailleurs, un donneur à faible risque pourrait minimiser les variables de risque du receveur à haut risque.[17]

Part II. Stratification du risque d'événements cardio-vasculaires post-transplantation cardiaque

II.A Introduction

Dans la quête d'une médecine personnalisée, la transplantation cardiaque doit améliorer ses normes de suivi des patients. Le meilleur exemple de cette problématique est le protocole de dépistage des complications de l'allosensibilisation impliquant des tests itératifs et invasifs, qu'il s'agisse de la coronarographie pour détecter la CAV ou des biopsies endomyocardiques pour détecter le rejet d'allogreffe. Des données épidémiologiques récentes ont montré que l'incidence de ces deux complications a diminué avec le temps.[37,62] Le rapport coût-efficacité actuel de ces tests de dépistage est faible et doit être comparé à leurs complications potentielles. De nombreux facteurs/marqueurs de risque pour le développement de la CAV ou du rejet d'allogreffe ont été décrits dans la littérature. Cependant, l'absence d'un outil intégré permettant d'estimer le risque d'événements pour un individu rend impossible le passage d'une médecine de protocole à une médecine personnalisée.

II.B Mort subite d'origine cardiaque après une transplantation cardiaque

Article soumis à JAMA Cardiology et présenté en tant que communication orale complète lors du congrès de l'ESC 2021

II.B.1. Problématique

En pratique quotidienne du suivi d'un patient transplanté, la mort subite (SCD) n'apparait pas comme une complication à dépister ou à prévenir. En effet, l'épidémiologie de la mort subite post-transplantation n'est pas clairement établie.[63] De petites séries de cas et des registres font état d'un taux important de SCD ainsi

que d'une variété de facteurs prédictifs significatifs.[64] Les données actuellement disponibles viennent aussi de grands registres aux données avec un faible niveau de granularité. Par exemple, au sein de la base de données UNOS, le diagnostic précis sur la cause du décès peut être absent, car souvent le décès a été déclaré par des équipes différentes de celles du suivi de la transplantation.[65] Plutôt qu'un mode de décès, la mort subite semble être une cause de décès à part entière, qui peut se superposer à d'autres causes de décès.[63] Cependant, plusieurs problèmes ont gravement entravé une compréhension approfondie de ces associations, notamment le nombre limité de patients, un suivi court, des cohortes mal phénotypées, et de grands registres et des données administratives manquant de granularité et de comparaison avec des patients non transplantés.[66] L'ensemble de ces lacunes a conduit à une épidémiologie et une stratification imprécise du risque de SCD post-transplantation.[67] Par conséquent, une évaluation de l'incidence de la SCD après HTx et l'identification de ses facteurs de risque spécifiques, y compris les facteurs immunologiques, sur la base de grandes cohortes de receveurs de cœur, pourraient améliorer le suivi et la gestion des patients.

Nous avons émis l'hypothèse qu'une investigation approfondie des causes de décès des transplantés cardiaques au sein d'une base de données à haut niveau de phénotypage, associée à une approche populationnelle, permettrait une description précise et une meilleure stratification du risque de mort subite post-transplantation.

II.B.2. Article original

Dans ce contexte, nous avons analysé deux grands registres prospectifs provenant de la même zone géographique et réalisés par le même groupe d'investigateurs : (i) une cohorte profondément phénotypée de 1,246 transplantés cardiaques consécutifs et (ii) le registre du Centre d'expertise sur la mort subite de Paris (étude prospective complète basée sur la population, n=19 706 SCD).

Sudden Cardiac Death After Heart Transplantation: A Population Based Study

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Brief title: Sudden Cardiac Death After Heart Transplantation

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ABSTRACT

IMPORTANCE The epidemiology of sudden cardiac death (SCD) after heart transplantation (HTx) remains imprecisely described.

OBJECTIVE To assess the incidence and determinants of SCD in a large cohort of HTx recipients, compared to the general population.

DESIGN, SETTING, AND PARTICPANTS Consecutive HTx recipients (n=1,246, 2 centers) transplanted between 2004 and 2016 were included. Clinical, biological, pathologic and functional parameters were prospectively assessed. SCD was centrally adjudicated. The SCD incidence was compared to the incidence of SCD observed in the general population of the same geographic area (registry carried out by the same group of investigators; n=19,706 SCD). A competing risk multivariable Cox analysis was used to identify variables associated with SCD.

MAIN OUTCOME AND MEASURE Sudden cardiac death.

RESULTS The annual incidence of SCD was 12.5 per 1,000 person-years [95%CI, 9.7-15.9] in the HTx recipients cohort compared to 0.54 per 1,000 person-years [95%CI, 0.53-0.55] in the general population (p<0.001). The risk of SCD was markedly elevated among the youngest HTx recipients with standardized mortality ratios for SCD up to 837 for recipients ≤30 years. Beyond the first year, SCD was the leading cause of death. Five variables were independently associated with SCD: older donor age (p=0.003), younger recipient age (p=0.001) and ethnicity (p=0.034), preexisting donor-specific antibodies (p=0.009) and last left ventricular ejection fraction (p=0.048).

CONCLUSIONS AND RELEVANCE HTx recipients, and particularly the youngest, were at very high risk of SCD compared to the general population. The consideration of specific risk factors may help identify high-risk subgroups.

Keywords : Heart transplantation, Sudden cardiac death, Donor-specific antibodies

ABBREVIATIONS

AMR: antibody-mediated rejection

CI: confidence interval

DSA: Donor-specific antibodies

HR: hazard ratio

HTx: heart transplantation

ICD: implantable cardiac defibrillator

IQR: interquartile range

LVEF: left ventricular ejection fraction

SCD: sudden cardiac death

SD: standard deviation

SMR : standardized mortality ratio

INTRODUCTION

The prevalence of heart failure continues to rise over time with the aging of the population. Currently, 26 million individuals are affected by heart failure worldwide.[1] Despite major advances in pharmacological and interventional treatments, heart transplantation (HTx) remains the ultimate treatment for terminal heart failure.[2] Approximately 5,500 HTx are performed annually worldwide,[3] and post-transplant survival now exceeds 12 years. This progressive improvement in post-transplant outcome is mainly driven by the decrease in early post-transplant mortality, while survival beyond the first year post-HTx has remained unchanged over time. The prevention of complications that can compromise long-term patient survival is an unmet medical need.

In this setting, sudden cardiac death (SCD) has been suggested to be an important cause of late mortality after HTx.[4] Rather than a mode of death, sudden death appeared to be a cause of death in its own, which may be overlapped with other causes of death.[5] However, several issues have severely hampered a thorough understanding of those associations, including limited numbers of patients, short follow-up, poorly phenotyped cohorts, and large registries and administrative data lacking granularity and comparison with non-HTx patients.[6] Together, these shortcomings have led to an imprecise epidemiology and risk stratification of SCD after HTx.[7] Therefore, an evaluation of the incidence of SCD after HTx and the identification of its specific risk factors including immulogical factors based on large cohorts of heart recipients may improve patient monitoring and management.

In this study, we aimed to assess the incidence and determinants of SCD in a large cohort of HTx recipients, compared to the general population.

METHODS

Data, methods, and materials used to conduct the research are available from the corresponding author upon reasonable request.

Heart transplant cohort

All consecutive HTx recipients over 18 years of age between January 1, 2004 and December 31, 2016 were enrolled in the multicenter prospective Paris Transplant Group cohort (La Pitié-Salpêtrière Hospital, Paris, and Georges Pompidou European Hospital, Paris), which represented 72.8% of all HTx procedures performed during this period in Paris and its suburbs. We focused our analysis on SCD beyond the first year post-transplant as i) the epidemiology of early deaths is very different from late deaths, both concerning the incidence (higher risk of death during the early post-transplant period) and the causes of death[3,7] (early deaths mainly due to primary graft dysfunction and infection), ii) early SCD are mostly in-hospital SCD, thus raising concerns about the comparison of the incidence of SCD with the general population, and iii) to avoid survival bias when evaluating the effect of rejection and cardiac allograft vasculopathy as patients dying early post-transplant may have not had the opportunity to have rejection or be diagnosed with CAV.

The design of this prospective cohort has been previously described.[8] All data were anonymized and entered at the time of transplantation, at three months, six months, one year post-transplant and at subsequent annual visit evaluations using a standardized protocol to ensure harmonization across study centers. In addition, clinically-driven events such as symptomatic rejection were collected. Day of transplant and one year post-transplant visits included an extensive clinical, biological and functional evaluation (See Supplementary Appendix for detailed data collection procedures). Data were retrieved from the database in December 2019. The study was conducted in accordance with the

ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The institutional review board of the Paris Transplant Group (https://paristxgroup.weebly.com/#) approved the study.

Procedure and clinical protocols

All patients were followed from HTx until retransplantation, death, loss of follow up or date of final data extraction. Patient baseline information included donor characteristics, baseline recipient characteristics, immunological treatments, transplantation parameters, immunologic parameters, histological data, interventional and echocardiographic reports (**Supplementary Appendix**). Circulating donor-specific antibodies (DSA) against HLA-A, HLA-B, HLA-Cw, HLA-DR, HLA-DQ and HLA-DP were assessed using single-antigen flow bead assays as previously described (**Supplementary Methods**). Endomyocardial biopsies (EMB) were performed, processed and examined according to current standards.[9] The EMB results were classified as cellular (ACR 0 to 3R) or AMR (pAMR 0 to 3) according to the ISHLT guidelines (n = 13,676).[10,11] The detailed routine EMB protocol and the histological analysis are detailed in the **Supplementary Methods**. Echocardiography was routinely performed on all patients by a senior cardiologist and the left ventricular ejection fraction (LVEF) was reported and established by the biplane method of disk summation (modified Simpson's rule). Cardiac allograft vasculopathy angiographies were recorded per center protocol for all patients after transplantation. The routine evaluation included a first evaluation at one-year post-transplant followed by additional evaluations every other year or in case of clinical indication. Cardiac allograft vasculopathy was graded according to the current International Society for Heart and Lung Transplantation (ISHLT) classification as CAV 0

(not significant), 1 (mild), 2 (moderate) or 3 (severe).[12] The last LVEF measure and Cardiac allograft vasculopathy grade were considered as potential risk factors for SCD.

Adjudication of the causes of death

A pre-specified protocol was applied to analyze the causes of death by cross-checking multiple sources of data including medical reports, death certificates and information reported by the general practitioner and the family (see the **Methods section in the Supplementary Appendix**). Each cause of death was centrally adjudicated by two senior cardiologists blinded to patient characteristics (GB, GC). In case of discrepancies between observers or an inconclusive report, the cases were re-analyzed to reach an agreement with a third expert. Causes of death were classified as follows: infection, graft failure (including primary graft dysfunction and late graft failure due to rejection, cardiac allograft vasculopathy or from unknown causes), SCD, cardiovascular (including major adverse cardiovascular events), malignancy, others (including renal failure, bleeding complications, multiple organ failure and surgical complications) and unknown causes. According to the latest international guidelines, SCD was defined as an unexpected sudden death without obvious extracardiac cause, occurring with a rapid witnessed collapse within 1 hour after the onset of symptoms, or if unwitnessed, occurring within 24 hours after the last contact, in the absence of a prior terminal condition.

Paris Sudden Death Expertise Center registry

To compare the incidence of SCD, we used data from the Paris Sudden Death Expertise Center (SDEC) registry, a prospective population-based registry, recruited all consecutive SCD in the general population, in the same geographic area (Paris and its suburbs, comprising 6.7 million inhabitants, [approximately 10% of the total French population]

[13–15], and coordinated by the same group of investigators (Paris Cardiovascular Research Center).

The SDEC registry is an ongoing study that has been described previously.[14–16] Briefly, it is a comprehensive, prospective population-based registry comprising Paris and suburbs. Owing to a close collaboration with all the pre-hospital emergency medical services (EMS), 48 hospitals and forensic units, every case of out-of-hospital cardiac arrest aged ≥ 18 years occurring in the area is systematically enrolled in the SDEC registry, since May 2011. Exclusion criteria include age less than 18 years and cardiac arrest occurring outside the geographical area of interest. Regular external audits on the registry have shown that 99% of cardiac arrest cases are detected. The diagnosis of SCD was centrally adjudicated according to definition described above by two independent investigators. In cases of divergent opinion, a third expert was asked to arbitrate.

To calculate the annual incidence of SCD in the general population, we combined data from the Paris-SDEC with regional demographical data from the French National Institute of Statistics and Economic Studies. Patients analyzed were included from May 2011 to May 2017.

Statistical analysis

The analysis were performed in compliance with the STROBE checklist for observational studies.[17] Continuous variables were described as means and standard deviations (SD) for normally distributed data and as median and interquartile range (IQR) for non-normally distributed data. Categorical variables were reported using absolute and relative frequency distributions. We compared means and proportions between groups by using Student's t-test, analysis of variance (Mann-Whitney test for mean fluorescence intensity), or the χ^2 test (or Fisher's exact test if appropriate).

Incidence of sudden cardiac death

The incidence of SCD per 1,000 person-years was calculated for the entire cohort and then after stratification by age categories for both the HTx cohort and the general population. The incidence of SCD between cohorts was compared using the Mid-P Fisher exact test. The standardized mortality ratio (SMR) was computed by dividing the observed number of SCD in the cohort of HTx patients by the expected number based on rates observed in the general population (Paris-SDEC registry).

Competing risk models

Causes of death and respective cumulative incidences were analyzed using competing risk models. The cumulative incidence function represents the probability of occurrence by time of a particular type of death in the presence of other causes of death. The survival analysis was performed from one year after HTx to the maximum follow-up with SCD as the event of interest. Survival probability was assessed with Kaplan-Meier curves and compared using a log-rank test. Censoring occurred in the event of loss to follow-up, heart retransplantation or non-sudden death.

Determinants of sudden cardiac death

Cox proportional hazards models were applied to identify the clinical, immunological, histological, echocardiographic and angiographic parameters independently associated with SCD. In the univariate analysis, parameters were selected on the result of bivariate analyses (variables with a p value <0.1) and clinical relevance. The final multivariable model was selected based on the stepwise backward selection, with the competitive risk modeling of Fine and Gray. A two-tailed P<0.05 was considered statistically significant. All data were analyzed using STATA (version 15, Data Analysis and Statistical Software) and R software (version 3.6.3, R Project for Statistical Computing, Vienna, Austria).

RESULTS

Study population

A total of 1,220 patients were included from two French referral HTx centers (n=1,024 in La Pitié-Salpêtrière Hospital, Paris, and n=222 in Georges Pompidou European Hospital, Paris, **Supplementary Table 1**). During the first-year post-transplant, 315 patients died, mostly due to infection (n=112, 35.6% of causes of death) and graft failure (n=82, 26.0% of causes of death, **Supplementary Figure 1**), leaving 905 patients alive at one year post-transplant. Their baseline characteristics are presented in **Table 1.** The mean recipient age at transplant was 47.9±13 years and the mean donor age was 45.4±13.2 years. Two-thirds of the recipients were males. A total of 261 patients (30%) were transplanted with preexisting DSA. Median post-transplant follow-up was 6.8 years (IQR 4.2-10.1). A total of 209 (23.1%) patients died during follow-up. The overall 5- and 10-year survival rates were 83.6% (95%CI: 80.8-86.1) and 67.7%, (95%CI: 63.3-71.8) respectively. During follow-up, 35 patients (3.9%) were implanted with a pacemaker or defibrillator.

Causes of death beyond the first year post-transplant and incidence of sudden cardiac death

The cumulative incidence of the different causes of death beyond the first year post-transplant are presented in **Figure 1**. Overall, 46 deaths met the definition criteria of SCD, representing 22% of causes of death. SCD was the leading cause of death, ahead of malignancy and infection. With the detailed review of the medical records of the sudden deaths, we reported that only two patients had a known cardiac allograft vasculopathy and seven patients had a history of diagnosed rejection. The median time between HTx and SCD was 5.3 years (IQR 2.9-8.6). Characteristics of patients with SCD and non-sudden

death are provided in **Supplementary Table 2**. The crude annual incidence of SCD was 12.5 per 1,000 person-years (95%CI 9.7-15.9). We observed a stepwise increase in the risk of SCD with decreasing recipient age (incidence of SCD=38.6 per 1,000 person-years in recipients <30 years at transplant compared to 3.8 per 1,000 person-years in those >70 years at transplant, **Figure 2**).

Comparison of the incidence of sudden cardiac death with the general population

In the Paris-SDEC registry, a total of 23,086 out-of-hospital cardiac arrests were recorded from May 2011 to May 2017, among which 19,706 cases fit the SCD definition. The mean age of patients presenting SCD in the general population was 70.8 ±16.9 years, and 14,105 (61.1%) were males. Considering the average number of inhabitants in this area during the same period, the crude annual incidence of SCD was 0.54 per 1,000 person-years (95%CI 0.53-0.55). The incidence of SCD was significantly higher for HTx recipients compared to the general population from the same geographic area (p<0.001).

In contrast to the heart transplant recipients cohort, the incidence of SCD was higher in older patients in the general population (0.04 per 1,000 person-years in patients <30 years compared to 2.4 per 1,000 person-years in those >70 years, **Figure 2**). The corresponding SMR increased from 1.3 in HTx patients >70 years to 2.2 between 60 and 70 years, 10.8 between 50 and 60 years, 53.7 between 40 and 50 years, 107.9 between 30 and 40 years, and 837.6 in patients <30 years.

Identification of the determinants of sudden cardiac death after heart transplantation

Variables associated with SCD beyond the first year post-HTx after the univariate Cox analysis are reported in **Table 2** and included donor age (per 10-year increment, HR 1.34,

95%CI: 1.04-1.74), recipient age (per 10-year increment, HR 0.73, 95%CI 0.60-0.90), non-Caucasian ethnicity of the recipient (HR 2.35, 95%CI 1.30-4.25), presence of preexisting anti-HLA DSA (HR 2.78, 95%CI 1.52-5.09), antibody-mediated rejection (AMR) ≥ pAMR2 (HR 9.97, 95%CI 3.08-32.3), last LVEF evaluation (per 10-percent decrement, HR 1.43, 95%CI 1.05-1.92) and cardiac allograft vasculopathy grade at 4 years post-transplant (p=0.009).

In the competing risk multivariable analysis, five variables were independently associated with SCD (**Table 3**): donor age (per 10-year increment, HR 1.44, 95%CI 1.13-1.83, p=0.003), recipient age (per 10-year increment, HR 0.71, 95%CI 0.57-0.87, p=0.001), non-Caucasian ethnicity of the recipient (HR 1.88, 95%CI 1.05-3.38, p=0.034), presence of preexisting anti-HLA DSA (HR 2.28, 95%CI 1.22-4.26, p=0.009) and last LVEF evaluation (per 10-percent decrement, HR 1.32, 95%CI 1.01-1.69, p=0.048). The incidences of sudden death for each sub-population group defined by the presence of one of the risk factors are reported in **Supplementary Table 3**.

Sensitivity analyses

Various sensitivity analyses were performed to test the robustness of the final model of candidate variables associated with SCD.

i) Antibody-mediated rejection (AMR) grade >2 and SCD: When histological antibody mediated rejection grade>2 was forced in the final multivariable model instead of pre-formed DSA, it showed an association (p=0.001) with SCD (**Supplementary Table 4**), but it was outperformed by the circulating anti-HLA DSA status. *ii) Multivariable analysis with competitive risks of all cause of deaths including unknown causes of death:* By considering unknown causes of death as potential competitive risks, the final multivariable model

remained unchanged (**Supplementary Table 5**). *iii) Multivariable analysis stratified by center*: To take into account a possible bias in the assessment of the determinants of the SCD, the center was also entered in the final multivariable model and did not modify the set of independent parameters associated with SCD (**Supplementary Table 6**).

DISCUSSION

Based on the analysis of two large prospective cohorts, we showed that the risk of SCD was substantially increased in HTx recipients compared to the general population from the same geographic area. The youngest HTx recipients were at particularly high risk of SCD. In the competing risk analysis, SCD appeared to be the leading cause of death beyond the first year post-HTx. We identified five independent variables associated with SCD, including older age of donor, younger age of recipient, circulating DSA, LVEF and ethnicity. Our study represents the first step towards an improvement of the description of the epidemiology and risk factors of SCD after HTx and has several strengths including the large prospective and deeply phenotyped cohort of HTx recipients, the large exhaustive registry of SCD in the general population from the same geographic area and the competing risk analysis allowing a precise analysis of the specific determinants of SCD.

High incidence of sudden cardiac death

In our cohort, SCD was the leading cause of death beyond the first year after HTx, accounting for 22% of all causes of death. Data from the UNOS registry suggest that SCD may be less prevalent in the US.[18] However, in a recent meta-analysis including 47 901 patients, the pooled incidence rate of SCD has been described to be as high as 13.0 per 1,000 person-years (95% CI: 10.8-15.2) compared to 12.5 per 1,000 person-years (95% CI: 9.7-15.9) post-transplant in our study,[7] suggesting that the incidence of SCD after HTx has not been overestimated in our study. Additionally, the lack of granularity of large international registries may lead to an underestimation of the exact incidence of SCD after HTx. Finally, the distribution of risk factors differed between our cohort and international data. Compared to the ISHLT registry, donors in our cohort were older, recipients were

younger and the proportion of patients transplanted with pre-formed DSA was as high as 30%.

Sudden cardiac death: a similar risk before and after heart transplantation

In patients with non-ischemic cardiomyopathy and severe left ventricular dysfunction, the incidence of SCD was 15.0 per 1,000 person-years and significantly reduced by ICD in the DANISH trial, although the trial results were negative regarding the primary outcome.[19] In our cohort, all patients with at least one identified risk factor had an annual incidence of sudden death between 14.9 and 24.0/1,000 person-years (**Supplementary Table 3**). Our findings suggest that the strategies engaged before HTx to prevent SCD should probably be continued after HTx, and that specific identified risk factors may help with screening for high-risk patients in whom aggressive preventive strategies should be implemented. The prevention of SCD after HTx is however challenging and the potential impact of ICD in this setting remains to be evaluated, as electrocardiographic recordings at the time of SCD have shown a significant proportion of brady-arrhythmias, asystole, and electrical-mechanical dissociation.[7]

Importance of patient age on the risk of sudden cardiac death

Compared to the general population, heart transplant recipients were at high-risk of SCD. We found an opposite association between patient age and the risk of SCD in heart transplant recipients (stepwise increase of the risk of SCD with decreasing recipient age) compared to the general population (stepwise increase of the risk of SCD with increasing age). The increasing risk of SCD with patient age in the general population and with donor age in the heart transplant cohort is likely to reflect the increasing incidence of coronary artery disease with increasing age. On the opposite, the increased risk of SCD in young

recipients may reflect the importance of underlying immune processes as cause of allograft injury and arrhythmogenic substrate.

Immune determinants of sudden cardiac death after heart transplantation

We found marginal associations between allograft rejection and the risk of SCD in our cohort, contrasting with the robust association with the presence of HLA-DSAs. HLA-DSAs may be a more sensitive marker of allosensitization than AMR. Although acute and severe rejection has been associated with SCD, this entity is rare and chronic allograft inflammation induced by allosensitization may be a trigger of chronic allograft injury at the population level. Circulating HLA-DSAs have been shown to be a major determinant of premature and accelerated allograft fibrosis following kidney,[20] liver[21] and heart transplantation.[22] Interestingly, myocardial fibrosis is a common pattern of various heart diseases that promotes ventricular tachyarrhythmias by creating a vulnerable substrate for reentrant activity and by favoring the emergence of triggers [23,24]. In heart transplant recipients, myocardial fibrosis has been shown to be an intermediate pro-arrhythmogenic substrate with various etiologies,[25] including cardiac allograft vasculopathy, allograft rejection,[26] ischemic time[27] or donor-transmitted fibrosis.[28]

Cardiac allograft vasculopathy and sudden cardiac death

In accordance with previously published data,[7] we found a significant association between CAV and sudden cardiac death in univariable analysis. However, CAV was not independently associated with SCD in our study in contrary to circulating anti-HLA DSA and LVEF, two variables usually not included in previous epidemiologic study of post-transplant SCD. DSA have been shown to be an independent risk factor of CAV[8] and may be a more sensitive predictive variable at the population level. Among patients diagnosed

with CAV, the presence of a significant systolic graft dysfunction may reflect the severity of underlying coronary lesions and ischemic myocardial damages and therefore be a stronger predictor of SCD than the presence of coronary stenosis alone. Additionally, CAV may have been underestimated as a component of sudden death due to the long interval between two coronary angiograms (thus underestimating the potential evolution of CAV between two tests) and the limited diagnostic value of standard angiograms without endocoronary imaging (underdiagnosis of early forms of CAV).

Limitations

Our study should nevertheless be interpreted in the context of its limitations. First, despite a pre-specified protocol and an exhaustive research, the precise cause of 49 out-of-hospital deaths (9.4%) could not be found, including potential sudden deaths. It is likely that SCD was underestimated. However, this rate appeared to be low compared to previous studies. Second, the limited number of events did not allow us to develop an accurate predictive score. However, in our cohort, the incidence of SCD in patients with at least one risk factor was greater that the commonly accepted thresholds for primary prevention ICD implantation in various cardiac conditions. This simple approach may be used in clinical practice to refine risk stratification of SCD. Third, we were not able determine the precise mechanisms of SCD in our cohort since a minority of patients had a pacemaker/ICD or underwent autopsy.

Conclusion

The risk of SCD was substantially increased in HTx recipients compared to the general population. The youngest HTx recipients were at particularly high risk. Five independent variables were associated with the risk SCD. The consideration of specific risk factors may

help with identifying a high-risk subgroup that could benefit from more aggressive preventive strategies in order to finally improve long-term overall survival.

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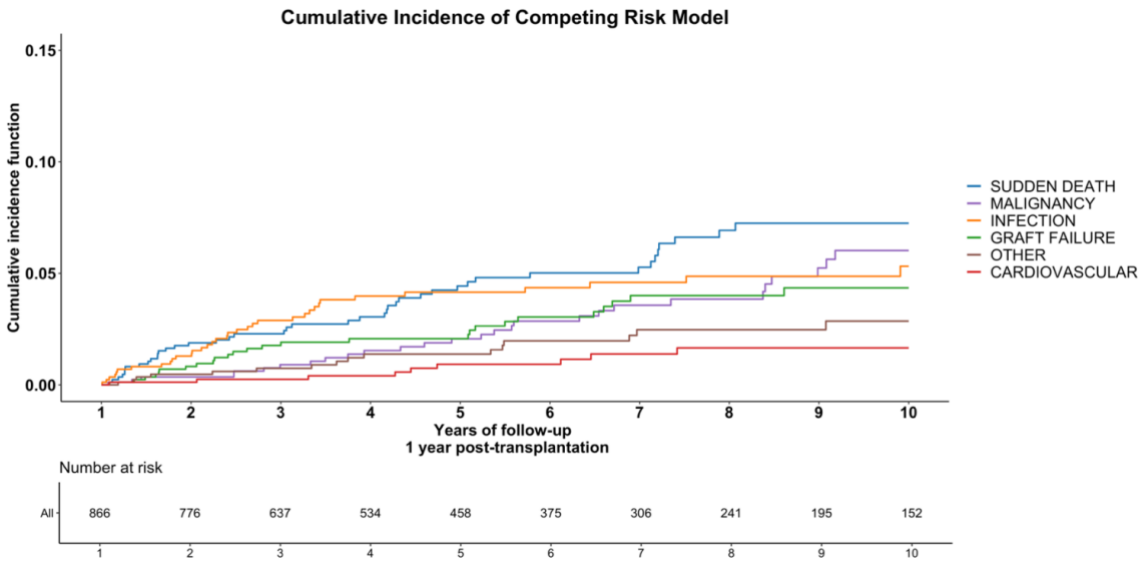
Figure 1. Cumulative incidence of death causes in heart transplant recipients beyond the first year (n=905). *

The curves represent the cumulative incidence of death by cause in surviving patients beyond the first year: sudden cardiac death, malignancy, infection, graft failure (including primary graft dysfunction and late graft failure due to rejection, cardiac allograft vasculopathy or from others causes), cardiovascular (including major adverse cardiovascular events), others (including renal failure, bleeding complications, multiple organ failure and surgical complications).



** Patients with unknown cause of death were excluded from the figure.*

Figure 2. Annual incidence of sudden cardiac death according to patient's age in the Paris general population (SDEC) and in the heart transplant cohort.

The annual incidence of sudden death was represented by 10-year age groups in the Paris general population through the Sudden Death Expertise Center registry (SDEC) and in the heart transplant patients in the same geographical area over the same period. The incidences were represented with a logarithmic transformation.

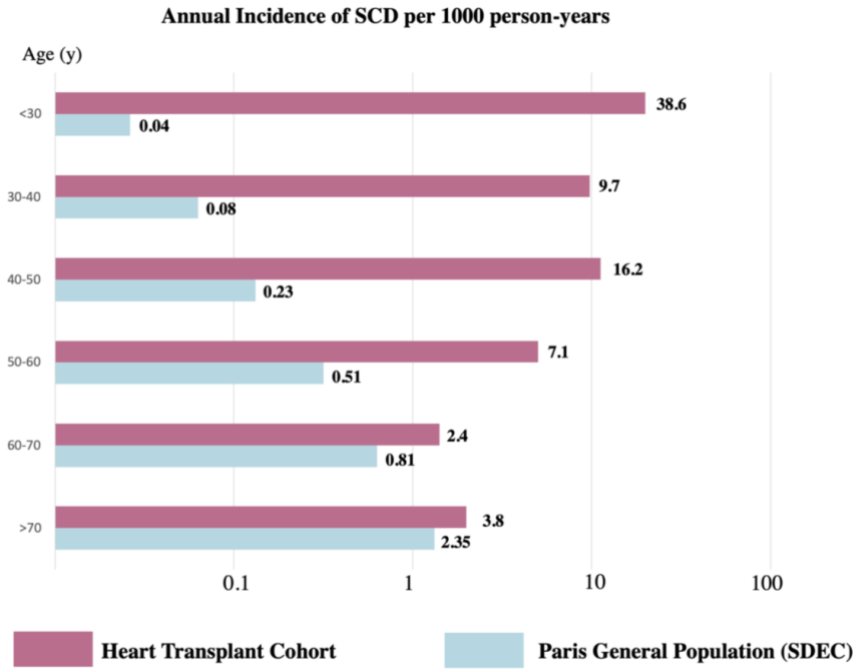


Table 1. Characteristics of patients among the one year survivors after transplantation.

	One year survivors *N=905*	N
Donor characteristics		
Age (years), mean (SD)	45.4 (13.2)	905
Gender (men), No (%)	597 (66.0%)	905
Tobacco, No (%)	315 (45.8%)	688
Hypertension, No (%)	123 (17.9%)	689
Diabetes mellitus, No (%)	19 (3.13%)	607
Alcohol, No (%)	214 (31.1%)	689
BMI (kg/m^2), mean (SD)	25.4 (4.79)	902
Creatinine clearance (mL/min/1.73m^2), mean (SD)	99.5 (25.4)	605
Recipient characteristics		
Age (years), mean (SD)	47.9 (13.0)	905
Gender (men), No (%)	711 (78.6%)	905
BMI (kg/m^2), mean (SD)	24.3 (4.16)	905
Non-Caucasian ethnicity, No (%)	255 (28.2%)	905
Primary heart disease, No (%)		905
Dilated cardiomyopathy	404 (44.6%)	
Ischemic cardiomyopathy	285 (31.5%)	
Retransplantation	21 (2.32%)	
Congenital	44 (4.86%)	
Other	151 (16.7%)	
Hypertension, No (%)	282 (32.2%)	875
Diabetes mellitus, No (%)	144 (16.0%)	902
History of smoking, No (%)	475 (53.1%)	895
Long term MCS, No (%)	122 (13.5%)	905
ECMO at transplant, No (%)	216 (23.9%)	905
Transplant baseline characteristics		
Cold ischemic time (min), mean (SD)	185 (58.2)	905
Induction therapy, No (%)		905
ATG	834 (92.2%)	
Others	10 (1.1%)	
IL2-R inhibitor	61 (6.7%)	
Gender mismatch (Df Rm), No (%)	192 (21.2%)	905
Combined transplantation, No (%)	43 (4.8%)	905
CMV mismatch (D+ R-), No (%)	171 (19.4%)	883
Immunology and histology		
HLA mismatches (A/B/DR), mean (SD)	4.99 (0.96)	880
Pre-formed DSA, No (%)	261 (29.0%)	899
TCMR at 1 year, No (%)	424 (47.2%)	898
AMR at 1 year, No (%)	75 (8.34%)	899

AMR: antibody-mediated rejection; ATG: antithymocyte globulin; BMI: body mass index; CMV: cytomegalovirus; Df Rm: femal donor and male recipient; DSA: donor-specific antibodies; ECMO: extracorporeal membrane oxygenation; HTx: heart transplantation; ID: immunodominant; IL2-r: Interleukin-2 receptor; LVEF: left ventricular ejection fraction; MCS: mechanical circulatory support; MFI: mean fluorescence intensity; MMF: mycophenolate mofetil.

Table 2. Factors associated with sudden cardiac death in the univariate Cox analysis in one-year survivors.

	All patients N=905	No SCD N=859	SCD N=46	HR	p value	N
Donor characteristics						
Age (years), mean (SD)	45.4 (13.2)	45.1 (13.3)	49.3 (10.8)	1.34 [1.04;1.74] *	0.026	905
Gender (men), No (%)	597 (66.0%)	564 (65.7%)	33 (71.7%)	1.32 [0.69;2.51]	0.397	905
Tobacco, No (%)	315 (45.8%)	301 (45.8%)	14 (45.2%)	1.02 [0.50;2.07]	0.961	688
Hypertension, No (%)	123 (17.9%)	119 (18.1%)	4 (12.9%)	0.67 [0.23;1.91]	0.448	689
Diabetes mellitus, No (%)	19 (3.1%)	19 (3.3%)	0 (0.0%)	-	0.495	607
Alcohol, No (%)	214 (31.1%)	202 (30.7%)	12 (38.7%)	1.25 [0.60;2.57]	0.548	689
BMI (kg/m²), mean (SD)	25.4 (4.8)	25.4 (4.8)	24.6 (4.1)	0.97 [0.91;1.03]	0.313	902
eGFR (mL/min/1.73m²), mean (SD)	99.4 (25.4)	99.2 (25.6)	107 (19.2)	1.02 [1.00;1.04]	0.096	605
Chronic kidney failure, No (%)	55 (9.1%)	55 (9.4%)	0 (0.0%)	-	0.138	605
Recipient characteristics						
Age (years), mean (SD)	47.9 (13.0)	48.3 (12.8)	40.7 (14.2)	0.73 [0.60;0.90] *	0.003	905
Gender (men), No (%)	711 (78.6%)	678 (78.9%)	33 (71.7%)	0.74 [0.39;1.40]	0.352	905
BMI (kg/m²), mean (SD)	24.3 (4.2)	24.3 (4.1)	24.8 (4.8)	1.04 [0.97;1.11]	0.301	905
Non-Caucasian ethnicity, No (%)	255 (28.2%)	236 (27.5%)	19 (41.3%)	2.35 [1.30;4.25]	0.004	905
Primary heart disease, No (%)						
Dilated cardiomyopathy	404 (44.6%)	388 (45.2%)	16 (34.8%)	Ref.		905
Ischemic cardiomyopathy	285 (31.5%)	274 (31.9%)	11 (23.9%)	1.03 [0.48;2.23]		
Retransplantation	21 (2.32%)	20 (2.33%)	1 (2.17%)	1.57 [0.21;11.8]	0.089	
Congenital	44 (4.86%)	39 (4.54%)	5 (10.9%)	2.78 [1.02;7.62]		
Other	151 (16.7%)	138 (16.1%)	13 (28.3%)	2.16 [1.04;4.50]		
Hypertension, No (%)	282 (32.2%)	267 (32.1%)	15 (34.9%)	1.14 [0.60;2.14]	0.691	875
Diabetes mellitus, No (%)	144 (16.0%)	136 (15.9%)	8 (17.4%)	1.15 [0.54;2.48]	0.714	902
History of smoking, No (%)	475 (53.1%)	455 (53.6%)	20 (43.5%)	0.84 [0.47;1.51]	0.567	895
Long term MCS, No (%)	122 (13.5%)	122 (14.2%)	0 (0.0%)	-	0.010	905
ECMO at transplant, No (%)	216 (23.9%)	204 (23.7%)	12 (26.1%)	1.32 [0.68;2.55]	0.416	905
Transplant baseline characteristics						
Cold ischemic time (min), mean (SD)	185 (58.2)	184 (58.4)	192 (53.8)	1.00 [1.00;1.01]	0.242	905
Induction therapy, No (%)					0.841	905
ATG	834 (92.2%)	792 (92.2%)	42 (91.3%)	Ref.		
IL2-r inhibitor	61 (6.7%)	58 (6.8%)	3 (6.5%)	1.06 [0.33;3.42]		
Other	10 (1.1%)	9 (1.1%)	1 (2.2%)	1.79 [0.25;13.1]		
Gender mismatch (Df Rm), No (%)	192 (21.2%)	184 (21.4%)	8 (17.4%)	0.79 [0.37;1.70]	0.554	905
Combined transplantation, No (%)	43 (4.8%)	40 (4.7%)	3 (6.52%)	1.70 [0.53;5.51]	0.371	905
CMV mismatch (D+ R-), No (%)	171 (19.4%)	166 (19.8%)	5 (11.4%)	0.47 [0.18;1.20]	0.106	883
Immunology and histology						
HLA mismatches (A/B/DR), mean (SD)	4.99 (1.0)	4.98 (1.0)	5.20 (0.9)	1.28 [0.91;1.79]	0.157	880
Pre-formed DSA, No (%)	261 (29.0%)	242 (28.4%)	19 (41.3%)	2.78 [1.52;5.09]	0.001	899
Histology during the first year						
TCMR, No (%)	424 (47.2%)	400 (46.9%)	24 (53.3%)	1.22 [0.67;2.21]	0.507	898

Number of TCMR, mean (SD)	0.93 (1.3)	0.92 (1.3)	1.13 (1.4)	1.08 [0.89;1.32]	0.434	898
TCMR≥2R, No (%)	124 (13.8%)	115 (13.5%)	9 (20.0%)	1.43 [0.68;2.97]	0.343	898
TCMR≥3R, No (%)	20 (2.2%)	19 (2.2%)	1 (2.2%)	0.65 [0.09;4.76]	0.675	898
AMR, No (%)	75 (8.3%)	69 (8.1%)	6 (13.3%)	2.04 [0.86;4.84]	0.098	899
Number of AMR, mean (SD)	0.14 (0.6)	0.13 (0.6)	0.40 (1.3)	1.46 [1.17;1.82]	0.001	899
AMR Grade≥2, No (%)	9 (1.0%)	6 (0.7%)	3 (6.7%)	9.97 [3.08;32.30]	<0.001	899
Echocardiography parameters						
Last LVEF (%), mean (SD)	64.9 (8.30)	65.0 (8.24)	62.2 (8.99)	1.43 [1.05;1.92] †	0.020	885
Cardiac allograft vasculopathy (CAV) Distribution						
CAV at 1 year, No (%)					0.196	769
Grade 0	628 (81.7%)	597 (81.8%)	31 (79.5%)	Ref.		
Grade 1	110 (14.3%)	104 (14.2%)	6 (15.4%)	1.39 [0.58;3.36]		
Grade 2	27 (3.5%)	26 (3.6%)	1 (2.6%)	0.69 [0.09;5.04]		
Grade 3	4 (0.52%)	3 (0.41%)	1 (2.56%)	6.12 [0.83;45.00]		
CAV at 4 years, No (%)					0.009	509
Grade 0	283 (55.6%)	277 (56.5%)	6 (31.6%)	Ref.		
Grade 1	155 (30.5%)	145 (29.6%)	10 (52.6%)	5.15 [1.75;15.1]		
Grade 2	55 (10.8%)	53 (10.8%)	2 (10.5%)	3.10 [0.60;16.0]		
Grade 3	16 (3.1%)	15 (3.1%)	1 (5.2%)	6.08 [0.71;52.2]		

AMR: antibody-mediated rejection; ATG: antithymocyte globulin; BMI: body mass index; CAV: cardiac allograft vasculopathy; CMV: cytomegalovirus; DSA: donor-specific antibodies; ECMO: extracorporeal membrane oxygenation; HTx: heart transplantation; ID: immunodominant; IL2-r: Interleukin-2 receptor; LVEF: left ventricular ejection fraction; MCS: mechanical circulatory support; MFI: mean fluorescence intensity; MMF: mycophenolate mofetil; ; eGFR: estimated Glomerular filtration rate

* 10-year increment
† 10-percent decrement

Table 3. Factors associated with sudden cardiac death in the multivariable Cox analysis with the competitive risk model.

This table shows the clinical, immunological, functional and structural parameters associated with sudden cardiac death in the multivariable Cox analysis, with competitive risks taking into account all other known causes of death.

	n=885	HR	p value
Donor characteristics			
Age (per 10-year increment)		1.44 [1.13;1.83]	0.003
Recipient characteristics			
Age (per 10-year increment)		0.71 [0.57;0.87]	0.001
Non-Caucasian ethnicity	**No**	1	-
	Yes	1.88 [1.05;3.38]	0.034
Immunology			
Pre-formed DSA	**No**	1	-
	Yes	2.28 [1.22;4.26]	0.009
Echocardiography parameters			
Last LVEF (per 10-percent decrement)		1.32 [1.01; 1.69]	0.048

DSA: donor-specific antibodies; LVEF: left ventricular ejection fraction

II.B.3. Synthèse & Perspectives

Sur la base de l'analyse de deux grandes cohortes prospectives, nous avons montré que le risque de SCD était considérablement accru chez les personnes ayant subi une HTx par rapport à la population générale de la même zone géographique. Les plus jeunes receveurs d'HTx présentaient un risque particulièrement élevé de SCD. Dans l'analyse des risques concurrents, la SCD est apparue comme la principale cause de décès au-delà de la première année suivant l'HTx. Nous avons identifié cinq variables indépendantes associées à la SCD, notamment l'âge plus élevé du donneur, l'âge plus jeune du receveur, les DSA circulants, la Fraction d'éjection ventriculaire gauche (FEVG) et l'origine ethnique. Notre étude représente la première étape vers une amélioration de la description de l'épidémiologie et des facteurs de risque de SCD après HTx. Elle présente plusieurs points forts, notamment la grande cohorte prospective et profondément phénotypée de receveurs d'HTx, le grand registre exhaustif de SCD dans la population générale de la même zone géographique et l'analyse en risques compétitifs permettant une analyse précise des déterminants spécifiques de la SCD.

Dans notre cohorte, la SCD était la principale cause de décès au-delà de la première année après HTx, représentant 22 % de toutes les causes de décès. Les données du registre UNOS suggèrent que les SCD pourraient être moins répandues aux États-Unis.[68] Cependant, dans une méta-analyse récente, le taux d'incidence global des SCD a été décrit comme atteignant 13,0 pour 1 000 personnes-années (IC à 95 % : 10,8-15,2), contre 12,5 pour 1 000 personnes-années (IC à 95 % : 9,7-15,9) après la transplantation dans notre étude, ce qui suggère que l'incidence des SCD après HTx n'a pas été surestimée dans notre étude.[67] Nos données en population générale sont aussi reproductibles avec une analyse récente des participants exempts de maladie cardio-vasculaire de l'étude « Framingham Heart Study » qui a montré que le risque de SCD était 3,3 fois plus élevé chez les hommes (0,53 pour 100 personnes-années) que chez les femmes (0,16 pour 100 personnes-années).

Un facteur de risque important de SCD post-transplantation est le rejet, associé à une augmentation de 50 % du risque de SCD.[68] A l'origine, des études de séries de cas rapportant les résultats post-mortem de transplantés cardiaques décédés de

SCD ont montré une fréquence similaire de patients présentant une CAV sévère ou un rejet cellulaire aigu comme causes potentiellement responsables du décès.[69–71] Par analyse multivariée, McGiffin et al[72] avaient rapporté que les patients ayant des antécédents récents de rejet traité au cours des deux dernières années avaient un risque annuel de SCD multiplié par cinq. De plus, chez ceux qui présentaient un rejet avec des conséquences hémodynamiques, le risque de SCD augmentait de manière significative pour atteindre ~8 % à un an.

La plupart des rapports de cas et des séries de cas étudiant les causes et les mécanismes des SCD post-transplantation proposent une étiologie arythmogène, potentiellement précipitée par l'ischémie, l'inflammation, le stress mécanique ou la fibrose.[69,70] Les causes non arythmiques (par exemple, les événements thrombo-emboliques ou les intoxications alimentaires) sont très rares.[73,74] Le type d'arythmies conduisant à une SCD après une transplantation cardiaque n'est pas bien décrit. Les études comportant des enregistrements électrocardiographiques réels au début de la SCD sont peu nombreuses et ont montré que les brady-arythmies, l'asystolie et la dissociation électromécanique sont les rythmes responsables de la SCD.[70,71] Les troubles de conduction de haut grade et le besoin d'un stimulateur cardiaque permanent sont plus fréquents au début de la période post-transplantation.[75,76] L'utilisation d'un stimulateur cardiaque permanent après une transplantation est associée à une meilleure survie globale après ajustement en fonction de l'âge du receveur et du donneur.[77] Heureusement, l'utilisation de l'anastomose chirurgicale bicavale a considérablement réduit la nécessité d’un stimulateur cardiaque au cours des dernières années. Des séries de cas plus récentes chez des transplantés ayant subi une implantation de DAI ont rapporté que ~25% des patients ont reçu des chocs appropriés de DAI pour une tachycardie ventriculaire ou une fibrillation ventriculaire, ce qui a permis de prévenir avec succès le traitement.[78,79]

Il n'est toujours pas certain que l'utilisation d'un DAI après une transplantation cardiaque apporte un bénéfice en termes de survie. L'une des principales raisons est que l'on ignore quelle population spécifique pourrait bénéficier d’un DAI. En outre, le risque « concurrent » d'autres modes de décès chez ces patients peut être suffisamment élevé pour limiter les avantages potentiels du traitement par DAI en termes de survie et de rentabilité. Des études d'observation identifiant les

transplantés présentant un risque accru de mort subite mais un pronostic global relativement bon sont nécessaires pour mieux déterminer qui, le cas échéant, peut bénéficier de l'implantation d'un DAI. Jusqu'à ce qu'un groupe spécifique de patients présentant un risque accru de SCD soit identifié, il semble peu probable que l'on puisse démontrer un bénéfice convaincant du DAI après une transplantation.

Avec un certain degré de sens clinique et physiopathologique, le risque de SCD semble accru chez les transplantés atteints de CAV. Deux études ont décrit la CAV comme un prédicteur indépendant de la SCD.[72,80] Paradoxalement, une analyse multivariée de la base de données UNOS n'a pas trouvé d'association entre la CAV et la SCD.[68] Au-delà des biais liés aux risques compétitifs, une raison possible de ces résultats contradictoires est que l'étude UNOS avait évalué la dysfonction du greffon comme un prédicteur indépendant de SCD. La CAV est l'une des principales causes de dysfonction tardive du greffon après la transplantation.[81] Il peut donc y avoir une corrélation significative entre ces deux facteurs. L'inclusion de deux variables colinéaires, comme la dysfonction de greffon et la CAV, dans le même modèle statistique pourrait amener une interprétation potentiellement erronée.[82]

II.C Identification et caractérisation des trajectoires de la coronaropathie du greffon: Une étude basée sur la population.

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II.C.1. Problématique

II.C.1.a Une problématique méthodologique

Les approches traditionnelles, dont le modèle de Cox, souffrent de plusieurs limitations. En particulier, les modèles de Cox sont limités à l'analyse de l'occurrence d'un premier événement clinique et ne peuvent appréhender ni la récurrence ni l'évolution de la sévérité de la maladie après son diagnostic. De plus, le modèle de Cox n'est pas en mesure de comprendre pleinement le caractère longitudinal des résultats des tests itératifs d'un même patient. Les modèles spécifiques à l'analyse des données longitudinales, tels que les modèles linéaires généralisés, peuvent être un moyen de comprendre les problèmes de la répétition des tests chez un même individu. Cependant, ils ne prennent pas en compte la variabilité des réponses entre les individus et, par conséquent, ne permettent pas une stratification du risque individuel.

L'objectif de notre recherche est donc de pouvoir généraliser nos résultats à tous les individus de la population, et pas seulement à ceux observés. Nous voudrions donc prendre en compte la variance inter-clusters (variabilité inter-sujets, inter-individus). L'objectif est de permettre à certains paramètres de régression de varier d'un cluster à l'autre, via l'introduction d'effets aléatoires. Ainsi, diverses sources d'hétérogénéité de la population peuvent être prises en compte. Un modèle mixte est un modèle statistique dans lequel on considère à la fois des effets fixes, qui vont intervenir au niveau de la moyenne du modèle et des effets aléatoires, qui vont intervenir au niveau de la variance du modèle. Un modèle est dit mixte lorsqu'il y a au moins un facteur de chaque nature. Dans une deuxième étude épidémiologique, nous allons

appliquer ces modèles. Nous utiliserons le cas particulier des modèles mixtes à classes latentes, adaptés à l'analyse de données longitudinales catégorielles (grade de sévérité de la CAV selon l'ISHLT). Ces modèles postulent l'existence de variables latentes, qui sont inobservables directement, mais dont les effets peuvent être mesurés ou observés. Cette approche permet la catégorisation non supervisée, c'est-à-dire sans a priori, de groupes de patients. Chaque classe comprend un groupe homogène d'individus partageant un profil évolutif commun.

Nous souhaitons définir précisément l'épidémiologie et l'histoire naturelle de la CAV et déterminer les facteurs de risque indépendamment associés. Pour ce faire, nous appliquerons des méthodologies innovantes à de grandes cohortes de transplantés cardiaques hautement phénotypés.

Nous formulons l'hypothèse de l'intérêt des modèles mixtes à classe latente appliqués à la transplantation cardiaque, qui permettent non seulement l'analyse de données longitudinales, mais aussi l'introduction d'effets aléatoires tels que la variabilité inter-clusters, ce qui constitue la première étape vers une stratification du risque individuel. C'est ce type de modèle que nous allons appliquer à l'étude de la CAV.

II.C.1.b Une étude des facteurs de risque

La situation de l'endothélium coronaire, à la frontière entre le donneur et le receveur, le place au centre d'interactions complexes entre de nombreux facteurs immunologiques et non immunologiques responsables d'agressions chroniques conduisant à une activation endothéliale, à des réponses inflammatoires chroniques, à des signaux de prolifération et finalement à un remodelage chronique et à un rétrécissement diffus des artères coronaires.[83,84]

De nombreux facteurs de risque pour le développement de la CAV ont été décrits. Cette littérature a été enrichie par l'utilisation des techniques d'imagerie endocoronaire, qui sont capables de détecter avec une grande sensibilité des changements minimes de l'épaisseur intimale entre deux examens. Plusieurs synthèses de cette abondante littérature ont été publiées.[85] Ces facteurs de risque de la CAV sont classiquement classés en (i) facteurs de risque cardio-vasculaire traditionnels du donneur responsables de l'athérosclérose transmise[86] (âge, sexe, diabète, consommation de tabac etc;[87,88] (ii) facteurs de risque cardio-vasculaire

traditionnels du receveur après la transplantation (notamment la dyslipidémie[89]) ; (iii) facteurs non immunologiques spécifiques à la transplantation (temps ischémique, cause de décès du donneur, infection à CMV[90,91]) et (iv) facteurs immunologiques spécifiques à la transplantation (rejet cellulaire aigu, AMR, DSA[45,46,87,92]).
Certains auteurs soulignent que la plupart des études analysant les facteurs de risque de la CAV se sont finalement concentrées sur l'étude d'un nombre limité de facteurs potentiels, limitant ainsi l'impact de leurs résultats.[85] L'approche épidémiologique habituellement appliquée à la détermination des facteurs de risque de la CAV est dichotomique (présence ou absence de la maladie, évolution ou non de l'épaisseur intimale), prenant parfois en compte le délai d'apparition de la maladie mais négligeant les profils évolutifs de la maladie.

II.C.1.c Revue systématique de la littérature

Nous avons donc effectué une revue systématique de la littérature pour trouver des études sur l'évaluation de la CAV basée sur la trajectoire chez les transplantés cardiaques. Nous avons recherché dans PubMed les publications du 1er janvier 2008 au 30 juin 2019 en utilisant les termes (((cardiac allograft vasculopathy) OR ((cardiac allograft vasculopathy) AND "Risk Factors"[Mesh]). Pour saisir les paramètres relatifs aux changements longitudinaux de la CAV, nous avons également utilisé les termes “repeated measure”, “repeated measures”, “repeated measurements”, “trajectory”, “trajectories”, and “slope.” AND ((("Natural History"[Mesh]) OR "Disease Progression"[Mesh]) OR "Latent Class Analysis"[Mesh]))). Pour concentrer la recherche sur la transplantation cardiaque, nous avons utilisé les termes “heart transplantation”, “heart transplant”. Sur la base de cette approche, une stratégie de recherche exhaustive a été menée en utilisant plusieurs bases de données (Medline, Embase, Cochrane et Scopus).

La recherche a donné lieu à 249 articles. Quatre-vingt-dix-huit d'entre eux ne traitaient pas de la CAV, y compris des études sur d'autres transplantations d'organes solides (n=46), d'autres domaines de la transplantation cardiaque (n=46) et des modèles animaux ou des études in vitro (n=8). Soixante-six études n'incluaient pas de données longitudinales sur la CAV, y compris des rapports de cas, des revues, des éditoriaux (n=36) et des études transversales (n=30), ce qui

laisse 85 études qui ont étudié la progression de la CAV. Parmi elles, 60 études ont considéré la CAV comme un critère dichotomique (présence ou absence), négligeant la gravité et la progression ultérieure de la CAV, et 24 petites études rétrospectives ont comparé l'évolution de la moyenne des paramètres dérivés de l'IVUS entre des groupes à deux moments, négligeant les caractéristiques longitudinales des données sur la CAV et la progression ultérieure de la CAV. Enfin, aucune étude n'était issue de grandes cohortes de patients avec un suivi systématique et une conception spécifique visant la stratification du risque et l'évaluation répétée de la CAV par protocole.

Les approches actuelles d'investigation de la CAV ont été limitées par les données des registres, y compris les échantillons de convenance avec un nombre limité de mesures pour un seul patient. Il est important de noter qu'à ce jour, aucune étude n'a été principalement conçue pour évaluer de manière prospective et standardisée la CAV, en même temps qu'une caractérisation approfondie du patient, y compris son profil immunologique et biologique, ses phénotypes histologiques et des informations sur les traitements.

Pour éviter de faire des hypothèses préalables sur le nombre et les formes des trajectoires de la CAV, nous avons utilisé une approche contemporaine non supervisée basée sur les trajectoires, connue sous le nom de modélisation mixte à classe latente.[93] Ce modèle a déjà démontré sa pertinence clinique dans différents contextes médicaux tels que la dépression, l'athérosclérose ou le handicap en révélant des profils méconnus de patients et en contribuant à une meilleure compréhension de l'évolution dans le temps des maladies chroniques.[94–96]

L'identification des trajectoires pertinentes de la CAV et de leurs déterminants respectifs est un besoin non satisfait et nécessite un niveau supplémentaire de compréhension et de caractérisation par rapport au paradigme actuel de 4 stades de CAV. Étant donné l'évolution à long terme du développement de la CAV après la transplantation, de telles informations pourraient être utiles pour fournir une image plus nuancée de la progression de la maladie, ce qui pourrait finalement contribuer à guider les soins des patients transplantés.

Notre objectif était d'appliquer un modèle statistique innovant capable d'analyser les données longitudinales d'angiographies coronaires dans une grande cohorte de patients, nous permettant de démasquer les profils évolutifs de la CAV au fil du temps, associés avec des facteurs de risque spécifiques.

II.C.2. Article original

Dans ce contexte, nous avons réalisé une étude de cohorte longitudinale prospective des transplantés cardiaques consécutifs provenant de différentes cohortes d'Europe et des États-Unis.

Circulation

ORIGINAL RESEARCH ARTICLE

Identification and Characterization of Trajectories of Cardiac Allograft Vasculopathy After Heart Transplantation

A Population-Based Study

Editorial, see p 1968

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BACKGROUND: Cardiac allograft vasculopathy (CAV) is a major contributor of heart transplant recipient mortality. Little is known about the prototypes of CAV trajectories at the population level. We aimed to identify the different evolutionary profiles of CAV and to determine the respective contribution of immune and nonimmune factors in CAV development.

METHODS: Heart transplant recipients were from 4 academic centers (Pitié-Salpêtrière and Georges Pompidou Hospital, Paris, Katholieke Universiteit Leuven, and Cedars-Sinai, Los Angeles; 2004–2016). Patients underwent prospective, protocol-based monitoring consisting of repeated coronary angiographies together with systematic assessments of clinical, histological, and immunologic parameters. The main outcome was a prediction for CAV trajectory. We identified CAV trajectories by using unsupervised latent class mixed models. We then identified the independent predictive variables of the CAV trajectories and their association with mortality.

RESULTS: A total of 1301 patients were included (815 and 486 in the European and US cohorts, respectively). The median follow-up after transplantation was 6.6 (interquartile range, 4–9.1) years with 4710 coronary angiographies analyzed. We identified 4 distinct profiles of CAV trajectories over 10 years. The 4 trajectories were characterized by (1) patients without CAV at 1 year and nonprogression over time (56.3%), (2) patients without CAV at 1 year and late-onset slow CAV progression (7.6%), (3) patients with mild CAV at 1 year and mild progression over time (23.1%), and (4) patients with mild CAV at 1 year and accelerated progression (13.0%). This model showed good discrimination (0.92). Among candidate predictors assessed, 6 early independent predictors of these trajectories were identified: donor age ($P<0.001$), donor male sex ($P<0.001$), donor tobacco consumption ($P=0.001$), recipient dyslipidemia ($P=0.009$), class II anti–human leukocyte antigen donor-specific antibodies ($P=0.004$), and acute cellular rejection ≥2R ($P=0.028$). The 4 CAV trajectories manifested consistently in the US independent cohort with similar discrimination (0.97) and in different clinical scenarios, and showed gradients for overall-cause mortality ($P<0.001$).

CONCLUSIONS: In a large multicenter and highly phenotyped prospective cohort of heart transplant recipients, we identified 4 CAV trajectories and their respective independent predictive variables. Our results provide the basis for a trajectory-based assessment of patients undergoing heart transplantation for early risk stratification, patient monitoring, and clinical trials.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04117152.

*Drs Loupy, Coutance, and Bonnet contributed equally.

†Drs Patel, Jouven, and Kobashigawa are co-senior authors.

The full author list is available on page 1966.

Key Words: allografts ■ antibodies ■ coronary artery disease ■ graft rejection ■ heart transplantation ■ latent class analysis

Sources of Funding, see page 1966

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Clinical Perspective

What Is New?

- By applying an unsupervised statistical method, 4 distinct trajectories of the long-term progression of cardiac allograft vasculopathy after heart transplantation were identified in a large and highly phenotyped European cohort.
- These cardiac allograft vasculopathy trajectories manifested consistently in an independent US cohort and were associated with all-cause mortality.
- Based on an integrative approach allowing the precise analysis of the independent association of each immune and nonimmune potential risk factor, 6 candidate variables independently associated with cardiac allograft vasculopathy were identified.

What Are the Clinical Implications?

- The robustness of the 4-trajectory pattern and the predictive variables in different healthcare systems supports the basis for a trajectory-based assessment.
- Trajectory-based monitoring could allow for the individualization of coronary angiogram monitoring and medical therapies, thus minimizing unnecessary angiograms in low-risk patients and intensifying treatment and angiogram monitoring in high-risk patients, and may inform the design and optimize end point definition of next-generation clinical trials.

The number of patients with end-stage heart failure is dramatically increasing worldwide and responsible for tens of thousands of deaths annually in Europe and in the United States.[1,2] Orthotopic heart transplantation (HTx) is the ultimate treatment but is dramatically limited in numbers.[3,4] Although the short-term survival after HTx has improved considerably in recent decades, the survival beyond 1 year after transplantation has remained unchanged over years despite important progress in immunosuppression and patient care.[5,6] In this setting, cardiac allograft vasculopathy (CAV) is the third leading cause of late mortality and the leading cause of late allograft dysfunction.[7–9]

The identification of relevant CAV-predicted progression or trajectories and their respective risk factors is an unmet need. The current gold standard for CAV monitoring after HTx relies on protocol angiograms that guide the clinical management of patients including prevention strategies, therapeutic changes, and end points for clinical trials.[10,11] Current approaches for CAV investigation have been limited to registry data. No study to date has been primarily designed toward a prospective protocol-based and standardized assessment of CAV together with ongoing patient characteristics including immunologic and biological profiles, histological phenotypes, and information on treatments. We conducted the present study to determine the characteristics and profiles of the development of CAV over the years with a specific aim: to early identify the factors that contribute the most to CAV development, which could become a target for guiding patient care.

To achieve this goal, we performed a longitudinal prospective cohort study including consecutive heart transplant recipients in different cohorts from Europe and the United States. We used information gathered by protocol-driven repeated CAV assessments performed together with clinical, biological, histological, and immunologic phenotyping. We determined whether a trajectory-based approach could identify robust prototypes of CAV course that could stratify patients into distinct CAV trajectories. Furthermore, we identified the respective contribution of immune and nonimmune candidate predictive characteristics on CAV progression over 10 years and its association with overall-cause mortality.

METHODS

Data, methods, and materials used to conduct the research are available from the corresponding author on reasonable request and in compliance with the European General Data Protection Regulation.

Study Design and Participants

Derivation Cohort

The derivation cohort included 815 consecutive European patients >18 years of age who were prospectively enrolled at the time of HTx in 2 French referral centers (La Pitié-Salpêtrière Hospital, Paris, n=510; Georges Pompidou European Hospital, Paris, n=99) and 1 Belgium center (Leuven University Hospital, n=206), who underwent transplantation between January 1, 2004 and December 31, 2016, and who were alive at 1 year after transplantation and had undergone at least 2 coronary angiographies during follow-up (from 1 to 10 years after transplantation). All data were entered at the time of transplantation, at 3 months, 6 months, 1 year after transplantation, and at subsequent annual visit evaluations using a standardized protocol to ensure harmonization across study centers. In addition, clinically driven events such as symptomatic rejection were collected. Day of transplant and 1-year posttransplant visits included an extensive clinical, biological, and functional evaluation (see Methods and the study protocol in the Methods in the Data Supplement for detailed data collection procedures). Data were retrieved from the database in June 2019. The institutional review boards of the Paris Transplant Group (https://paristxgroup.weebly.com/#), Leuven University, and Cedars-Sinai approved the study. Patients provided written informed consent at the time of transplantation (URL: https://clinicaltrials.gov; Unique identifier: NCT04117152).

US Independent Cohort

The robustness of the European trajectory pattern was evaluated in an independent cohort of 486 heart transplant

ORIGINAL RESEARCH ARTICLE

recipients >18 years of age from 1 US center (Cedars-Sinai Heart Institute, Los Angeles, 2008 and 2016). Data sets from the independent cohort were collected as part of routine clinical practice and entered in the center's databases in compliance with local and national regulatory requirements and sent anonymized to the Paris Transplant Group.

Procedures and Clinical Protocols

All patients were followed from time of transplant until retransplantation, death, or date of final data extraction.

We defined the baseline period at 1 year after transplantation where the recipients underwent concomitant evaluation of coronary angiography, allograft pathology, usual blood tests, and circulating anti–human leukocyte antigen (HLA) antibody assessment according to a prespecified protocol. All patients included in the study had at least 2 CAV measures after 1 year after transplantation (see Methods in the Data Supplement for the list of parameters assessed for the derivation cohort).

CAV angiographies were recorded per center protocol for all patients. CAV was graded per patient according to the International Society for Heart and Lung Transplantation classification as CAV 0 (not significant), 1 (mild), 2 (moderate), and 3 (severe).[12] European center protocols for follow-up data included CAV measurement at 1 year after transplantation and every 2 years thereafter, and at the time of any clinical indication, as well. The US center protocol included CAV measurement at 6 weeks and 1 year after transplantation, then every year thereafter, and at the time of any clinical indication, as well.

A prespecified protocol was applied to the analysis of coronary angiograms, including independent evaluation by senior cardiologists, complete review of cases with uncertain CAV grade, and additional analyses of random coronary angiograms. This detailed approach allowed the mitigation of the risk of CAV grade misclassification. In the European derivation cohort, a total of 2742 reports of coronary angiographies were retrospectively and independently reviewed by 3 senior cardiologists (G.B., G.C., M.-C.B.). In the case of discrepancies between observers or an inconclusive report, the coronary angiographies were reviewed to reach an agreement (n=454, 16.6%, mostly International Society for Heart and Lung Transplantation CAV1). In the US independent cohort, a total of 1968 coronary angiographies were analyzed. Two senior cardiologists graded all coronary angiographies according to the summarized report collected prospectively during patient follow-up.

Anti- HLA donor-specific antibodies (DSA) are antibodies developed by the recipient and directed against donor class I or class II HLA antigens. They can be either preexisting if present before transplantation or de novo if developed after transplantation. Circulating DSAs against HLA-A, HLA-B, HLA-Cw, HLA-DR, HLA-DQ, and HLA-DP were assessed by using single-antigen flow bead assays (Methods in the Data Supplement). Heart allograft pathology data were recorded and graded according to the International Society for Heart and Lung Transplantation classifications (acute cellular rejection classification: grade 0R to 3R; pathological antibody-mediated rejection classification: grade 0–3; Methods in the Data Supplement).[13,14] During the first year after transplantation, a total of 12 803 endomycardial biopsies were performed in the derivation cohort.

Outcome Measures

The primary outcome was CAV trajectories after transplantation. The secondary outcome was progression to all-cause mortality or retransplantation. The outcomes were prospectively assessed in both cohorts at each transplant anniversary, up to June 30, 2019.

Statistical Analysis

Continuous variables were described using means and SDs or median and the interquartile range, as appropriate. We compared means and proportions between groups using the Student *t* test, analysis of variance (Mann-Whitney *U* test for DSA mean fluorescent intensity) or the χ^2 test (or Fisher exact test, if appropriate).

Derivation of Posttransplantation CAV Trajectories

So that we would not identify trajectories that may be influenced by allocation systems and patient management across cohorts and countries, we conducted the analyses on Europe and in the United States separately. CAV trajectories were identified over 10 years after transplantation using latent class mixed models.[15] Latent class mixed models characterize trajectories in repeated measurements, with the assumption that several underlying subpopulations (ie, the latent classes) can be detected.[16] This approach requires neither the same number of measures per patient nor the same time points of measurement. Initial CAV grading (1 year after transplantation) and CAV slopes were specific to each subpopulation identified. We compared the linear trajectory models with nonlinear models, including quadratic (t^2 effect) and splines, and confirmed the suitability of linear models used for trajectory identification. Furthermore, we tested different link functions to identify the best fitting model.

At model convergence, each patient was assigned posterior likelihoods of belonging to each CAV trajectory. Patients were assigned the class to which they had the highest likelihood of belonging.

Definition of the Optimal Number of CAV Trajectories

The number of CAV trajectories was defined according to (1) the Bayesian Information Criterion and the Akaike Information Criterion, (2) the discrimination (ie, the ability of the model to specifically classify patients in the CAV trajectories), (3) the entropy (ie, the ability of the model to identify distinct CAV trajectories), and (4) the interpretability of the model, as previously published (see further details in the Appendix in the Data Supplement).[16–18]

Candidate Predictive Variables of CAV Trajectories

In the derivation cohort, the associations between CAV trajectories and clinical, histological, functional, and immunologic parameters at the time of transplantation, during the first year and at 1 year after transplantation were assessed using multinomial logistic regression. Parameters associated with trajectories in the univariate analysis with $P<0.10$ were

thereafter included in the multivariable model. Stepwise backward elimination was performed to obtain the final multivariable model (Methods in the Data Supplement).

Missing Data and Imputation

A total of 35 patients (4.29%) in the derivation cohort had at least 1 missing data element for the final multinomial model. Multiple imputation using chained equations was used (MICE R package, using 20 sets of imputations); continuous parameters were imputed with random forest, and categorical parameters were imputed with polynomial regressions.

CAV Trajectories and Association With All-Cause Mortality

Kaplan-Meier curves were used to report time to occurrence of all-cause mortality according to the identified CAV trajectories. The outcome of death or graft failure was defined when any patient died or had preemptive retransplantation at the date of final data extraction (June 1, 2019).

We used R (version 3.5.3, R Foundation for Statistical Computing) and STATA (version 15, Data Analysis and Statistical Software) for the descriptive and survival analyses. Values of $P<0.05$ were considered statistically significant, and all tests were 2-tailed. Details regarding the interpretation of important statistical concepts are given in the Methods in the Data Supplement.

RESULTS

Characteristics of the European Derivation and US Independent Cohorts

The European derivation cohort (n=815) and the US independent cohort (n=486) comprised a total of 1301 included patients from 4 transplant centers between January 1, 2004, and December 31, 2016 corresponding to 9298 patient-years. The median follow-up after transplantation was 6.59 years (interquartile range, 4–9.1). The summarized characteristics of patients, and the transplant procedures, policies, and allocation systems per participating center, as well, are detailed in Table 1 and Table I in the Data Supplement. Older donors were used in the European cohort in comparison with the US cohort (43.6±12.2 versus 34.8±12.9, $P<0.001$). Recipients were younger (48.1±12.8 versus 56.4±12.7, $P<0.001$) with fewer ischemic cardiomyopathy and cardiovascular risk factors at the time of transplant in the European cohort. Detailed baseline characteristics stratified by center in the derivation cohort are displayed in Table II in the Data Supplement.

The total number of CAV measures analyzed was 4710 (3.6±1.6 measures per patient), including 2742 coronary angiographies in the derivation cohort (3.4±1.3 per patient) and 1968 in the US independent cohort (4.0±1.8 per patient). The International Society for Heart and Lung Transplantation CAV grades were distributed as follows: 3354 CAV grade 0 (71.21%), 847 CAV grade 1 (17.98%), 358 CAV grade 2 (7.60%), and 151 CAV grade 3 (3.21%) from year 1 to year 10. The CAV grades were higher in the European cohort than in the US cohort (Table III in the Data Supplement). One hundred sixty-six of 1301 (12.76%) were diagnosed with CAV grade >0 in the first year after transplantation. The detailed results of coronary angiographies and their evolution across years are described in Table IV in the Data Supplement.

Two hundred eighteen patients (27.3%) and 89 patients (20.1%) had detectable anti-HLA DSA in the European and US cohorts, respectively, either preexisting or de novo with 69.81% of DSA being class II. Overall, 108 patients (13.3%) from the derivation cohort presented with acute cellular rejection ≥2R, and 76 patients (12.5%) from the French derivation cohort presented with antibody-mediated rejection ≥pathological antibody–mediated rejection 1. In the US independent cohort, where only the information "treated rejections" was available, 32 (6.6%) and 28 (5.8%) patients presented with treated acute cellular rejection ≥2R and treated antibody-mediated rejection ≥pathological antibody–mediated rejection 1, respectively. The detailed results of the 12 803 endomyocardial biopsies are provided in Table V in the Data Supplement.

Identification and Characterization of CAV Trajectories

Derivation Cohort

We identified 4 distinct CAV trajectories over 10 years after transplantation (Figure 1, Figures I and II in the Data Supplement); the model showed a good discrimination of 0.92 (0.96, 0.83, 0.93, and 0.88 for trajectory 1, 2, 3, and 4, respectively) and entropy of 0.82, meaning that the model adequately separated the trajectories (see details regarding the model in Table VI in the Data Supplement and in Figures III and IV in the Data Supplement).

US Independent Cohort

Latent class mixed models were applied in the independent US cohort. The best fitting model identified 4 profiles of CAV trajectories and confirmed the consistency of the 4 profiles previously demonstrated in the derivation cohort (Figure 2). In this geographically distinct cohort, the model showed an excellent discrimination of 0.97 (0.93, 0.97, 0.88, and 0.92 for trajectory 1, 2, 3, and 4, respectively; see details regarding the model in Table VII in the Data Supplement).

CAV trajectory 1 was composed of patients with no CAV at 1 year who remained stable over time (n=823, 63.26%, CAV slope per year=0.00±0.01). Of note,

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Table 1. Baseline Characteristics of Patients (European Derivation and US Independent Cohorts)

Characteristics	All Patients (4 Centers, n=1301)		European Derivation Cohort (3 Centers, n=815)		US Independent Cohort (1 Center, n=486)		*P* Value
	n		n		n		
Donor							
Age, y, mean (SD)	1299	40.29 (13.74)	815	43.56 (12.17)	484	34.77 (12.89)	<0.001
Sex male, n (%)	1202	833 (69.3)	815	556 (68.22)	385	340 (70.10)	0.48
Tobacco, n (%)	1220	390 (31.97)	783	348 (44.44)	437	42 (9.61)	<0.001
BMI, ≥25 kg/m², n (%)	1257	608 (48.37)	815	347 (42.58)	442	261 (59.05)	<0.001
Recipient							
Age, y, mean (SD)	1301	51.23 (13.36)	815	48.14 (12.77)	486	56.43 (12.72)	<0.001
Male sex, n (%)	1300	975 (75)	815	632 (77.55)	485	343 (70.72)	0.006
White ethnicity, n (%)	1300	933 (71.77)	815	619 (75.95)	485	314 (64.74)	<0.001
Ischemic cardiomyopathy, n (%)	1298	453 (34.90)	815	265 (32.52)	483	188 (38.92)	0.019
Long-term MCS, n (%)	1300	268 (20.61)	815	150 (18.40)	485	118 (24.33)	0.009
Previous history of hypertension, n (%)	1211	430 (35.51)	797	219 (27.48)	486	211 (50.97)	<0.001
Diabetes mellitus, n (%)	1281	261 (20.37)	813	109 (13.41)	468	152 (32.48)	<0.001
BMI ≥ 25 kg/m², n (%)	1296	564 (43.52)	815	327 (40.12)	481	237 (49.27)	0.001
Transplant baseline s							
Combined transplantation, n (%)	1300	83 (6.38)	815	33 (4.05)	485	50 (10.31)	<0.001
Cold ischemic time, min, mean (SD)	1282	177.5 (58.6)	815	183.0 (55.3)	467	167.8 (62.8)	<0.001
Sex mismatch (female D – male R), n (%)	1299	185 (15.38)	815	146 (17.91)	486	55 (11.36)	0.002
CMV mismatch (D+/R–), n (%)	1266	247 (19.51)	815	164 (20.27)	486	83 (18.16)	0.36
Immunosuppressive therapies							
ATG induction therapy, n (%)	1282	991 (77.30)	815	773 (94.85)	467	218 (46.68)	<0.001
1-year immunosuppressive regimen							
Cyclosporine	1297	505 (38.86)	815	465 (76.35)	482	27 (5.60)	<0.001
Tacrolimus	1297	792 (61.06)	815	144 (23.65)	482	455 (94.40)	<0.001
MMF	1297	1,113 (85.81)	815	732 (89.82)	482	381 (79.05)	<0.001
mTOR-inhibitors	1297	212 (16.35)	815	132 (16.20)	482	80 (16.60)	0.85
1-year posttransplant cardiovascular risk profile							
Treated hypertension, n (%)	813	592 (72.82)	813	592 (72.82)		–	–
Diabetes mellitus, n (%)	813	177 (21.77)	813	177 (21.77)		–	-
Statins, n (%)	1275	1,178 (92.39)	789	692 (87.71)	486	470 (96.70)	<0.001
LDL-c ≥1 g/L, n (%)	1126	536 (45.19)	794	386 (48.61)	392	150 (38.27)	0.001
Tobacco, n (%)	813	47 (5.78)	813	47 (5.78)		–	–
Immunology and histology							
Anti-HLA DSA, preexisting and 1-y (MFI ≥500), n (%)	1242	307 (24.72)	799	218 (27.28)	443	89 (20.09)	0.005
MFI of immunodominant DSA, preexisting & 1-y	1241		798		443		
None		935 (75.34)		581 (72.81)		354 (79.91)	
MFI: 500–2999		151 (12.17)		135 (16.92)		16 (3.61)	<0.001
MFI: ≥3000		155 (12.49)		82 (10.28)		73 (16.48)	
Class II anti-HLA DSA, preexisting and 1-y, n (%)	1241	215 (17.32)	798	150 (18.80)	443	65 (14.67)	0.07
Acute cellular rejection ≥2R, n (%)	1301	140 (10.76)	815	108 (13.25)	486	32* (6.58)	<0.001
Antibody-mediated rejection ≥ pAMR1, n (%)	1094	104 (9.51)	608†	76 (12.48)	486	28* (5.76)	<0.001
Follow-up							
Follow-up, y, median (IQR)	1301	6.56 (4.72)	815	7.73 (5.14)	486	4.84 (3.23)	<0.001

AMR indicates antibody-mediated rejection; ATG, antithymocyte globulins; BMI, body mass index; CMV, cytomegalovirus; DSA, donor-specific antibodies; HLA, human leukocyte antigen; IQR, interquartile range; LDL-c, low-density lipoprotein cholesterol; MCS, mechanical circulatory support; MFI, mean fluorescence intensity; MMF: mycophenolate mofetil; and mTOR, mammalian target of rapamycin.

*Only the information treated rejection was available in the US independent cohort.

†The retrospective analysis of the histological criteria of antibody-mediated rejection pAMR1(H+) was only performed in the 2 French centers (Pitié-Salpêtrière and Georges Pompidou European Hospital, n=609).

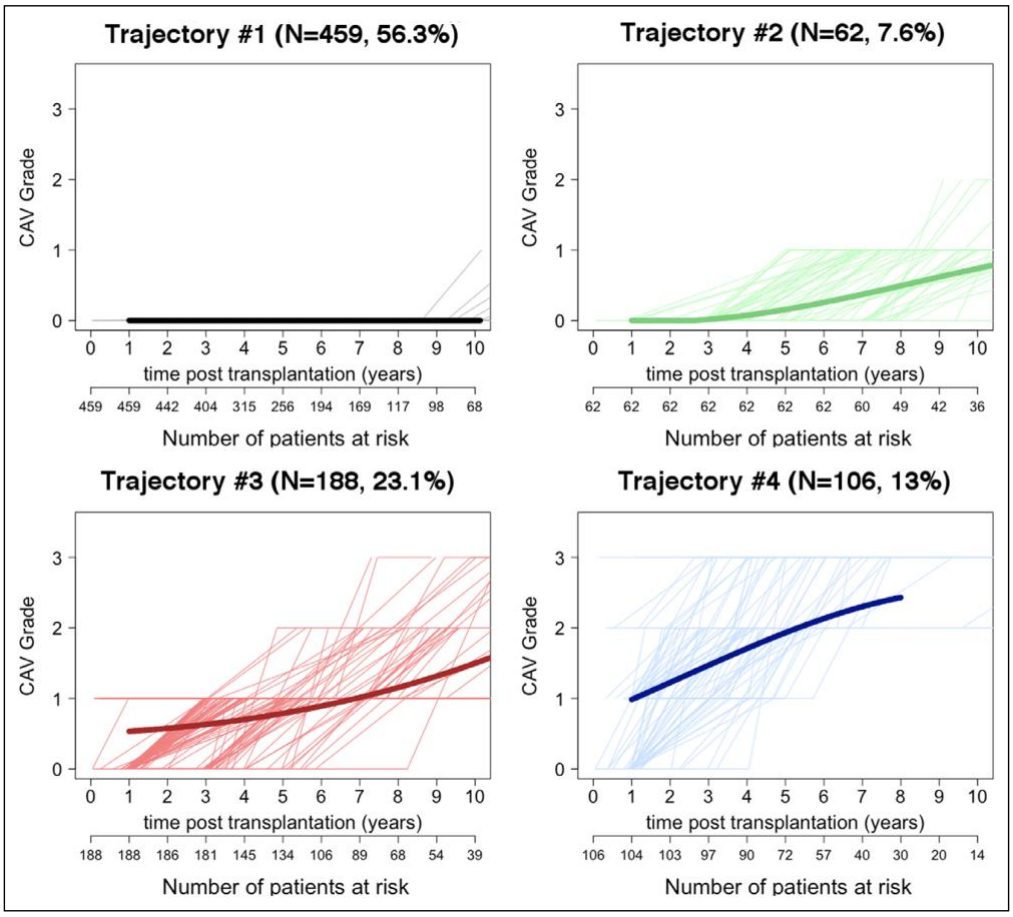

Figure 1. Distinct profiles of CAV trajectories identified after transplantation in the European derivation cohort (n=815).
This figure represents the main profile CAV grades identified with latent class mixed models. Each patient, represented by an individual CAV trajectory, was assigned to the class for which the membership probability was the highest. Discrimination=0.92. CAV trajectory 1 was composed of patients with no CAV at 1 year that remained stable over time; CAV trajectory 2 was composed of patients with no CAV at 1 year, with a slight increase in CAV over time starting ≈4years after transplantation; CAV trajectory 3 was composed of patients with intermediate CAV grade at 1 year who experienced a moderate increase during follow-up; and patients from CAV trajectory 4 presented with a pattern of intermediate CAV at 1 year and acceleration over time. Thick lines represent latent class trajectory; thin lines represent CAV individual patient trajectory. CAV indicates cardiac allograft vasculopathy.

among the 823 and the corresponding 2792 coronary angiographies analyzed in trajectory 1, only 6 (0.07%) patients had an increase of CAV grade over the 10 years of observation time.

CAV trajectory 2 was composed of patients with no CAV at 1 year, with a late-onset increase of CAV starting at ≈4 years after transplantation (n=79, 6.07%, overall CAV slope per year=0.11±0.12). CAV trajectory 3 was composed of patients with intermediate CAV grade at 1 year who experienced a moderate increase during follow-up (n=261, 20.06%, CAV slope per year=0.18±0.16). Patients from CAV trajectory 4 presented with a pattern of intermediate CAV at 1 year and acceleration over time (n=138, 10.61%, CAV slope per year=0.40±0.50).

Clinical, Functional, Structural, and Immunologic Candidate Predictive Variables of CAV Trajectories

Donors, recipients, transplant, immunosuppression, and immunologic characteristics according to CAV trajectory are detailed in Table VIII in the Data Supplement.

A total of 60 clinical, functional, structural, and immunologic factors of CAV trajectories were

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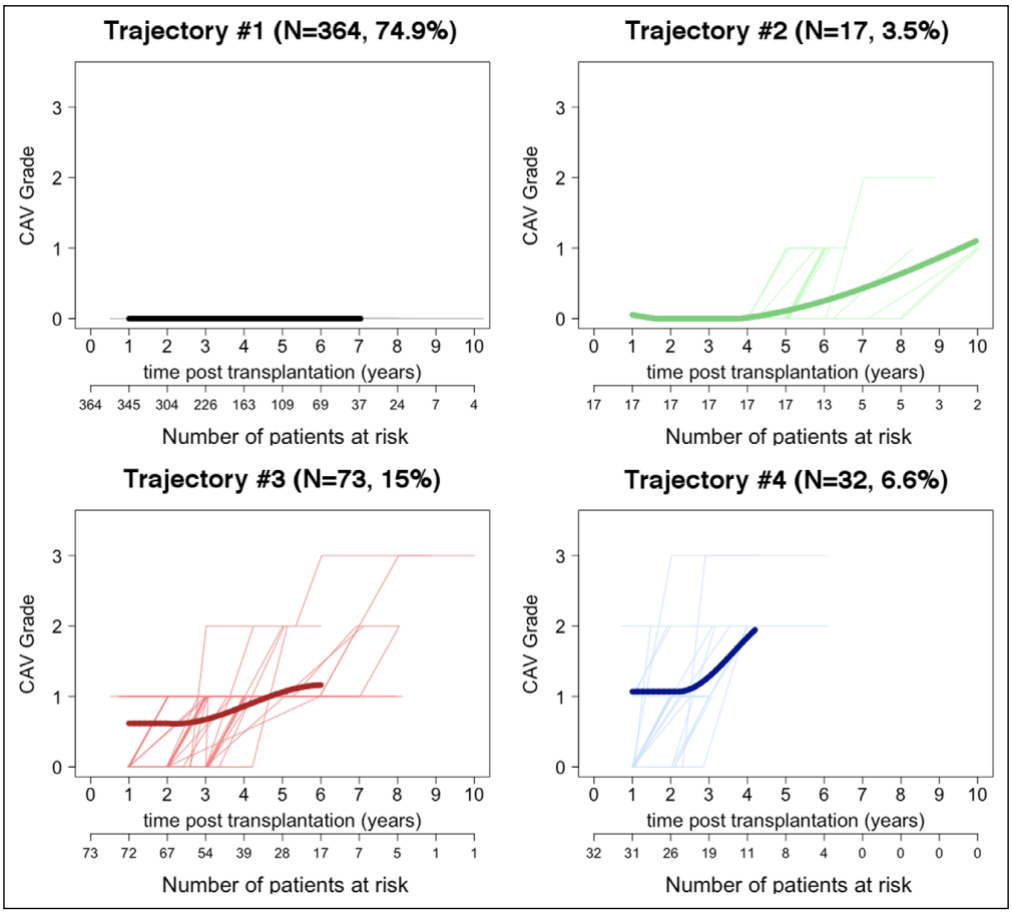

Figure 2. Cardiac allograft vasculopathy trajectories: robustness of the 4-trajectory pattern in the US independent cohort.
Latent class mixed models were applied to the US independent cohorts. CAV profiles identified in these independent analyses were similar to those identified in the derivation cohort with an excellent discrimination of 0.97. Thick lines represent latent class trajectory; thin lines represent CAV individual patient trajectory. CAV indicates cardiac allograft vasculopathy.

investigated. The main results of the univariate analysis conducted in the derivation cohort are reported in Table 2. We identified 17 significant variables associated with the trajectories: 8 donor-related risk factors (age: $P<0.001$; sex: $P=0.002$; hypertension: $P=0.035$; diabetes mellitus: $P=0.003$; tobacco consumption: $P=0.004$; body mass index ≥25 kg/m^2: $P=0.002$; creatinine clearance ≤60 mL/min: $P<0.001$; vascular cause of death: $P=0.013$), 4 pretransplant recipient variables (sex: $P=0.081$; ischemic cardiomyopathy: $P=0.022$; hypertension: $P=0.081$; body mass index ≥25 kg/m^2: $P=0.031$), 1 immunosuppressive therapy variable (type of calcineurin inhibitor: $P<0.001$), 4 recipient cardiovascular profile variables assessed at 1 year after transplantation (diabetes mellitus: $P=0.07$; statin therapy: $P=0.09$; low-density lipoprotein cholesterol ≥1 g/L: $P=0.002$; creatinine clearance: $P=0.02$), 4 immunologic parameters (presence of preexisting or de novo in the first year anti-HLA DSA: $P=0.007$; class II immunodominant DSA: $P=0.025$; cellular rejection grade ≥2R occurring during the first year after transplantation: $P=0.042$; episode of antibody-mediated rejection occurring during the first year: $P=0.104$).

After the multivariable analysis, the following independent candidate predictive variables of CAV trajectories were identified: (1) donor age ($P<0.001$), (2) donor sex ($P<0.001$), (3) donor tobacco consumption ($P=0.001$), (4) recipient low-density lipoprotein cholesterol ≥1 g/

Table 2. Candidate Predictive Variables of CAV Trajectories in the Derivation Cohort

Parameters	n	Trajectory 1 (n=459)	Trajectory 2 (n=62)	Trajectory 3 (n=188)	Trajectory 4 (n=106)	*P* Value
Donor						
Age (10-y increment)	815	–	1.23 (1.00–1.52)	1.80 (1.54–2.10)	1.91 (1.57–2.33)	<0.001
Sex (ref=female)	815	–	1.50 (0.83–2.70)	1.30 (0.90–1.88)	2.59 (1.52–1.88)	0.002
Hypertension	788	–	1.42 (0.70–2.88)	1.56 (0.99–2.49)	2.08 (1.23–3.53)	0.035
Diabetes mellitus	790	–	1.02 (0.12–8.42)	2.87 (1.03–8.05)	3.11 (0.97–10.00)	0.003
Tobacco consumption	783	–	1.32 (0.77–2.26)	1.55 (1.09–2.20)	2.00 (1.30–3.09)	0.004
BMI >25 kg/m^2	815	–	1.61 (0.94–2.74)	1.64 (1.17–2.32)	1.92 (1.26–2.94)	0.002
Creatinine clearance ≤60 (mL·min^{-1}·1.73 m^{-2})	815	–	1.57 (0.75–3.29)	1.08 (0.64–1.85)	0.95 (0.48–1.89)	<0.001
Vascular cause of death	815	–	1.11 (0.65–1.88)	1.56 (1.11–2.19)	1.75 (1.14–2.68)	0.013
Recipient						
Age (10-y increment)	815	–	0.98 (0.96–1.00)	1.01 (0.99–1.02)	1.01 (0.99–1.03)	0.153
Sex (ref=female)	815	–	1.17 (0.62–2.21)	1.50 (0.98–2.28)	1.79 (1.02–3.13)	0.081
Ischemic cardiomyopathy	815	–	0.57 (0.30–1.08)	1.00 (0.70–1.45)	1.64 (1.07–2.53)	0.022
Previous history of hypertension	797	–	0.77 (0.40–1.47)	1.19 (0.81–1.75)	1.71 (1.08–2.70)	0.081
BMI >25 kg/m^2	815	–	1.11 (0.64–1.92)	1.43 (1.01–2.01)	1.77 (1.15–2.70)	0.031
Transplant baseline						
Cold ischemic time (per 1-h increment)	815	–	1.08 (0.81–1.45)	0.99 (0.82–1.18)	0.87 (0.69–1.09)	0.565
Combined transplantation	815	–	0.66 (0.15–2.89)	0.77 (0.32–1.83)	0.38 (0.09–1.65)	0.500
CMV mismatch (D+/R–)	809	–	1.15 (0.61–2.18)	1.07 (0.71–1.63)	0.82 (0.47–1.42)	0.800
Immunosuppressive therapies						
Interleukin-2 receptor inhibitor induction therapy (ref=ATG)	815	–	1.18 (0.34–1.10)	1.72 (0.83–1.56)	1.64 (0.67–4.00)	0.467
Tacrolimus at 1 y (ref=cyclosporine)	815	–	0.51 (0.26–1.01)	0.47 (0.30–0.72)	0.36 (0.20–0.66)	<0.001
Everolimus therapy at 1 y	815	–	1.54 (0.81–2.94)	1.00 (0.63–1.60)	0.87 (0.48–1.59)	0.557
Cardiovascular risk factor 1-y post-HTx						
Treated hypertension	813	–	0.78 (0.44–1.36)	1.10 (0.75–1.61)	1.71 (1.01–2.90)	0.123
Diabetes mellitus	813	–	1.04 (0.53–2.03)	1.52 (1.02–2.27)	1.70 (1.05–2.76)	0.070
Statins	789	–	2.86 (0.87–9.43)	0.79 (0.49–1.30)	1.38 (0.68–2.81)	0.090
LDL-c ≥1 g/L	815	–	1.39 (0.82–2.37)	1.76 (1.25–2.49)	1.84 (1.20–2.82)	0.002
Tobacco	813	–	2.02 (0.79–5.18)	1.06 (0.49–2.27)	1.54 (0.67–3.55)	0.462
Creatinine clearance >60 mL·min^{-1}·1.73 m^{-2}	813	–	1.30 (0.76–2.21)	1.10 (0.78–1.54)	0.55 (0.35–0.86)	0.020
Immunology and histology						
Anti–HLA DSA (preexisting +1-y post-HTx)	799	–	0.45 (0.21–0.97)	1.49 (1.03–2.16)	1.31 (0.82–2.10)	0.007
Anti-HLA DSA (preexisting+1-y post-HTx	798					0.025
Class I		–	0.51 (0.15–1.71)	1.08 (0.57–2.02)	1.37 (0.67–2.80)	
Class II		–	0.42 (0.16–1.10)	1.72 (1.13–2.61)	1.30 (0.75–2.25)	
Acute cellular rejection ≥2R during the 1st y	815	–	2.39 (1.23–4.63)	1.25 (0.75–2.10)	1.79 (1.00–3.18)	0.042
Antibody-mediated rejection ≥ pAMR1 during the 1st y	608	–	1.78 (0.82–3.84)	1.21 (0.69–2.14)	0.53 (0.22–1.31)	0.104

This table shows the association of clinical, immunologic, functional, and structural parameters associated with CAV trajectories in univariate multinomial regression analysis. The trajectory of reference was trajectory 1, including patients with no CAV at 1 year and who were stable over time. AMR indicates antibody-mediated rejection; ATG, antithymocyte globulins; BMI, body mass index; CAV, cardiac allograft vasculopathy; CMV, cytomegalovirus; DSA, donor-specific antibodies; HLA, human leukocyte antigen; HTx, heart transplantation; LDL-c, low-density lipoprotein cholesterol; and MCS, mechanical circulatory support.

dL 1 year after transplantation (*P*=0.009), (5) recipient immunologic profile as defined by the presence of preexisting or de novo circulating class II anti–HLA donor-specific antibodies (*P*=0.004), and (6) allograft injury defined by acute cellular rejection ≥2R occurring in the first year after transplantation (*P*=0.028; Table 3).

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Projection of Patient Individual 10-Year CAV Trajectories Based on Risk Factors Assessed in the First Year After Transplantation

Based on the candidate variables independently associated with CAV trajectories identified in previous analyses, we built an online interface to provide clinicians with a ready-to-use tool that projects the CAV trajectories (https://transplant-prediction-system.shinyapps.io/CAV_trajectories/). Clinicians can enter the individual parameters of 1 patient, and 4 likelihoods of belonging for each trajectory are provided, corresponding to the personalized likely future CAV progression of the patient. A patient who is projected to belong to trajectory 1 at 1 year has a probability of 0.07% of having a coronary angiography showing a CAV grade increase within 10 years of follow-up. Examples on the clinical application of trajectory in real-life patients is provided in Table IX in the Data Supplement.

Association Between CAV Trajectories and Overall-Cause Mortality

The trajectories were also associated with mortality. During the follow-up, a total of 198 patients died. We found that CAV trajectories 3 and 4 were associated with higher mortality rates (10-year patient survival of 73.43% [95% CI, 65.18–80.02] and 51.89% [95% CI, 38.76–63.51], respectively), in comparison with trajectories 1 and 2 that were characterized by 10-year patient survival of 80.01% (95% CI, 76.38–84.82) and 83.49% (95% CI, 71.34–90.80), respectively (log-rank test: $P<0.001$; Figure 3).

Sensitivity Analyses

Various sensitivity analyses were performed to test the robustness and generalizability of the CAV trajectories and candidate predictive variables in different subpopulations and clinical scenarios.

CAV Trajectories and Center Effect

To take into account a possible bias in the assessment of the candidate variables associated with the CAV trajectories, the center was also entered in the final multivariable model and did not modify the set of independent parameters associated with trajectories (Table X in the Data Supplement). Also, when the multivariable model was performed adding the US cohort to the derivation cohort, the 6 independent candidate predictive variables that dominated in primary analyses remained unchanged (Table XI in the Data Supplement).

Immune Candidate Predictive Variables of CAV Trajectory

When histological antibody-mediated rejection was forced in the final multivariable model, it showed a trend for association ($P=0.07$) with CAV trajectory, but was outperformed by the circulating anti-HLA DSA status.

Consistency of CAV Trajectories According to Timing of First CAV Assessment

We tested and confirmed the robustness of the profiles of CAV trajectories when the CAV evaluation started before 1 year after transplantation (discrimination=0.89). We also confirmed the consistency of the trajectories when the CAV was first assessed at 2 years after transplantation (discrimination=0.90).

Last, a similar 4-trajectory pattern was found when we performed latent class mixed model analyses stratified by countries in the derivation cohort (France: Figure I in the Data Supplement; Belgium: Figure II in the Data Supplement).

Cytomegalovirus Status and CAV

We did not find an association between donor (D) and recipient (R) cytomegalovirus status at the time of transplantation (ie, D–/R–, R+, D+/R–) with CAV trajectories. The occurrence of cytomegalovirus infection during the first year after transplantation (2 viral load thresholds tested: ≥10 000 UI/mL and ≥1000 UI/mL) was not associated with the CAV trajectories.

Proliferation Signal Inhibitors and CAV

We did not find any association between the use of proliferation signal inhibitors at 1 year after transplantation and CAV trajectories. The use of proliferation signal inhibitors did not significantly differ between trajectories (Table 1; $P=0.53$). Multinomial logistic regression did not find associations between proliferation signal inhibitor use at 1 year and CAV ($P=0.56$). Last, when the use of proliferation signal inhibitors was forced in the final multivariate multinomial regression model, the set of parameters independently associated with CAV found in primary analyses was not changed.

DISCUSSION

In this international study of 1301 carefully phenotyped HTx recipients with protocol-based repeated assessment of CAV over 10 years (4710 coronary angiographies), combined with histology (12 803 biopsies) and immune profiling, we identified 4 distinct trajectories of long-term CAV progression for the first time by using unsupervised approach. We demonstrated that the 4 trajectories were consistent in geographically distinct cohorts recruited in Europe and the United States. We found that these trajectories were quite varied for several different conditions related to donor and recipient

Table 3. Factors Associated With CAV Trajectories in Multivariate Analyses in the Derivation Cohort

Parameters	Trajectory 1 (n=459)	Trajectory 2 (n=62)	Trajectory 3 (n=188)	Trajectory 4 (n=106)	*P* Value
Donor					
Age (10-y increment)	–	1.27 (1.02–1.58)	1.90 (1.62–2.24)	2.17 (1.75–2.70)	<0.001
Sex (ref=female)	–	1.66 (0.90–3.06)	1.82 (1.23–1.71)	3.76 (2.14–6.60)	<0.001
Tobacco	–	1.36 (0.79–2.34)	1.72 (1.19–2.48)	2.23 (1.41–3.53)	0.001
Cardiovascular risk factor 1-y posttransplant					
LDL-c ≥1 g/L	–	1.37 (0.80–2.35)	1.71 (1.19–2.46)	1.79 (1.14–2.82)	0.009
Immunology and histology					
Anti-HLA DSA class II, preexisting + 1-y post-HTx (ref=none)	–	0.47 (0.18–1.22)	1.95 (1.25–3.04)	1.47 (0.82–2.62)	0.004
Acute cellular rejection ≥2R during the 1st y	–	2.39 (1.22–4.68)	1.2 9(0.75–2.21)	1.98 (1.07–3.65)	0.028

This table shows the association of clinical, immunologic, functional, and structural parameters associated with CAV trajectories in multivariate multinomial regression analysis. The trajectory of reference was trajectory 1, including patients with no CAV at 1 year and a stable CAV grade over time. CAV indicates cardiac allograft vasculopathy; DSA, donor-specific antibodies; HLA, human leukocyte antigen; HTx, heart transplantation; and LDL-c, low-density lipoprotein cholesterol.

characteristics, ongoing disease processes, and immunologic profiles that can be determined at an early stage after transplantation, identifying potential triggers for treatment. In addition, the patient trajectory assessment that can be performed at an early stage after transplantation may inform the design and optimize end point definition of next-generation clinical trials.

Study Strengths and Novelties

In this study, we applied the following 3-step development process: identification of different CAV trajectories, identification of predictive variables associated with each trajectory, and development of a new risk-stratification tool.

Despite the importance of coronary angiography evaluation as standard of care after HTx, no study has characterized long-term trajectories using large unselected transplant cohorts with a prespecified longitudinal CAV monitoring together with a patient deep-level phenotyping, including donor and recipient characteristics, histology, immunology and treatment based on multiple post-transplant evaluations. Beyond the novel study design, the original advantage of our trajectory approach over traditional analysis is its ability to map the CAV course and classify individuals into distinct groups. Hence, this approach not only helped to conceptualize the long-term trajectories of CAV, but also allowed us to probe the population heterogeneity and the susceptibility of change in CAV over the life course. Furthermore, we believe that identifying the profiles of evolution in time of a chronic disease with an unsupervised approach and investigating whether these profiles manifest consistently across centers and countries may provide important guidance on the potential universality of the disease and its determinants, which has great considerable implications for future research, in particular, for counseling patients, and also for choosing therapies. Our holistic approach allowed for the development of an integrated individual risk-stratification tool aimed at improving clinical management and follow-up.

Clinical Significance of the CAV Trajectories

The 4 distinct trajectories identified represent different profiles of CAV evolution over time. CAV trajectory 1 is characterized by the absence of CAV over time, trajectory 2 by a mild and late onset of CAV, trajectory 3 by an early onset with progressive evolution of CAV, and trajectory 4 by an early onset with rapid evolution of CAV. From a clinical perspective, those findings might help to refine CAV management. However, the coronary angiography monitoring protocol could be adapted to the evolving risk of CAV and, therefore, to the likelihood of belonging to each trajectory. Patients with a high likelihood of belonging to trajectory 1 might be monitored less intensively, resulting in cost savings and avoiding procedural risks. In contrast, patients with a high likelihood of belonging to trajectories 3 and 4, at risk of CAV progression, might benefit from closer invasive follow-up and early stratification for use of proliferation signal inhibitors that have been demonstrated to reduce progression of CAV.[19] These trajectories may also improve prognosis stratification after heart transplantation because trajectories 3 and 4 are associated with a significantly higher risk of overall mortality.

Significance of the Immune Predictive Characteristics Associated With CAV Trajectories

This study also emphasizes the interplay between donor and recipient characteristics, the allograft immune

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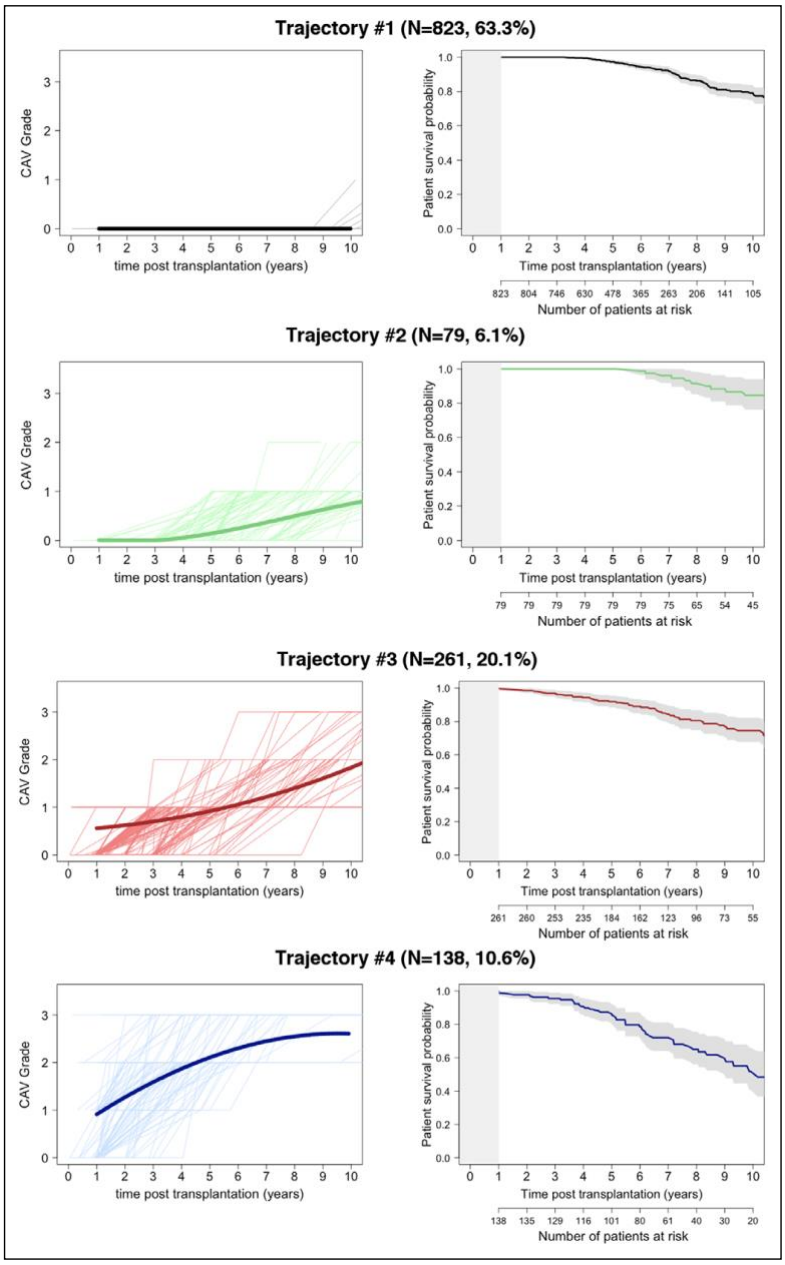

Figure 3. Overall 10-year survival probability according to the CAV trajectory in the overall cohort (n=1301).
Trajectories 3 and 4 were associated with higher mortality rates (10-year patient survival of 73.43% [95% CI, 65.18–80.02] and 51.89% [95% CI, 38.76–63.51], respectively) in comparison with trajectories 1 and 2 that were characterized by 10-year patient survival of 80.01 (95% CI, 76.38–84.82) and 83.49% (95% CI, 71.34–90.80), respectively ($P<0.001$).

profile and existing allograft injury, and the long-term CAV trajectories. The associations between these characteristics and the CAV trajectories provide mechanistic insight. Class II DSA appears to be an important trigger of CAV in our cohort. Both experimental and clinical studies support our findings.[8,20–25] The expression of class II HLA antigens by the endothelial cells requires their activation. Traditional cardiovascular risk factors associated with trajectory 3, both derived from the donor and from the recipient, promote endothelial inflammation and activation, and increasing data suggest that the natural-killer cells play a critical role in the development of immunologic atherosclerosis.[22,26,27]

We found that acute cellular rejection ≥2R components is an independent risk factor for CAV progression. On the one hand, severe cellular rejection might acutely accelerate CAV by promoting local inflammation and the recruitment of other immune cells. On the other hand, cellular rejection has been recognized as a risk factor for the development of de novo DSA.[28] In the French derivation cohort, patients with ≥1 episode of acute cellular rejection ≥2R were twice as likely to develop de novo DSA as patients without acute cellular rejection (17/60 [25.3%] in comparison with 55/315 [14.9%]; P=0.01).

We found marginal associations between antibody-mediated rejection and CAV trajectories in our cohort, contrasting with a robust association with the presence of preexisting or de novo anti-HLA DSA. DSA may be a more sensitive marker of allosensitization than antibody-mediated rejection. Although acute and severe antibody-mediated rejection has been associated with fulminant forms of CAV,[29] this entity is rare, and chronic allograft inflammation induced by allosensitization may be a trigger of CAV at the population level. Chronic antibody-mediated rejection has not been properly identified in heart allografts in contrast to kidney transplantation. This subclinical disease process might not be captured by 1-year histology.

We did find not an association between cytomegalovirus status and CAV. Because the present study gives a contemporary picture of HTx, it might be that prophylaxis strategies have modified the clinical expression and thereby the associations between cytomegalovirus and CAV.

Robustness of the 4 Trajectory Profiles and Prospects for Patient Risk Stratification and Patient Monitoring

It is remarkable that, despite the identification without any preconceptions of 4 CAV trajectories in the derivation cohort, very similar trajectories were also detected in the US cohort. This robustness of the same set of trajectories and predictive variables for patients in different healthcare systems promotes the idea that the same independent factors drive the evolution of CAV across the world. Although the proportions of patients in each trajectory differed between the cohorts, reflecting intrinsic variability in the demographics and HTx practices across nations, our results suggest using these profiles with HTx recipients first and then tailor the plan for future allograft monitoring and therapy based on the category. Consequently, to make trajectory-based monitoring of patients feasible in contemporary practice, we developed an easy-to-use online interface that allows clinicians to predict the personalized likely future of CAV trajectory of any given patient.

This approach to determining patient trajectories brings a wider dimension to the traditional approaches that are either derived from 1 single coronary angiography result and selected but limited parameters, or are instead based on a few measurements in non–protocol-based cohorts. Taking into account the evolution of CAV in the long term could therefore take advantage of more information about subtle changes and could be an important complement to current medical practices.

Although not validated by drug regulatory authorities, CAV is a major clinical end point for past and ongoing clinical trials in heart transplantation.[7,19,30] Endocoronary imaging modalities, either intravascular ultrasound or optical coherence tomography, have the ability to detect early coronary lesions while the coronary angiography remains normal. The change in maximal intimal thickness from baseline to 1 year or from 1 to 5 years after transplantation has been associated with cardiovascular outcomes.[31,32] All ongoing CAV-focused studies registered on clinicaltrials.gov (n=18) have an proliferation signal inhibitors/optical coherence tomography end point. However, endocoronary imaging procedures are invasive, have specific complications, and are not available in all centers.[33] Moreover, coronary angiography maintains the highest level of evidence for CAV monitoring, although the diagnosis is usually made after several years of the disease process.[12] The latent class trajectory approach also holds promise as an outcome measure. For most of trials, the duration of follow-up is too brief to expect a large change in CAV. This approach could also be used as a recruitment tool for prospective studies to enrich a population at high risk for CAV.

Study Limitations

Several limitations of the study should be noted. First, a limited number of trajectories were derived that may not accurately reflect every possible CAV profile. However, the good discrimination of our trajectory-building model indicates that these trajectories can parsimoniously summarize the predominant features of patient allografts in our population without a significant loss of information. Second, there are unmeasured characteristics of the recipients and allografts such as non-HLA antibodies or inflammatory

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circulatory biomarkers that may well affect CAV trajectories and could be explored in future studies. Third, the lack of an early angiogram in the European cohort might be a limitation to interpreting the origin of coronary artery lesions. However, we found strong correlations between donor cardiovascular risk factors and 1-year angiograms, suggesting that donor-transmitted coronary artery disease accounts for a significant part of coronary lesions observed 1 year after transplantation. Fourth, although performed by an expert interventional cardiologist, coronary angiograms may lack the sensitivity to detect early signs or diffuse patterns of CAV. The present study was specifically designed based on angiography assessment, because it is broadly available and standard of practice with the advantage of having an international grading scheme. However, we do agree that assessing CAV by angiogram may be less sensitive than proliferation signal inhibitors. Fifth, because of the study design, we considered candidate risk factors assessed at the time of transplant, during the first year or at 1 year after transplantation. We acknowledge that the analysis of the impact of risk/protective factors beyond the first year after transplantation, such as the use of proliferation signal inhibitors, remains an important question that deserves specific studies. Last, low-density lipoprotein levels and rejection processes were identified at 1 year after transplantation as strong, independent, and potentially modifiable factors associated with the CAV development. However, our study was observational and not designed as a clinical trial.

In conclusion, this analysis takes an original approach to analyzing and characterizing, for the first time, trajectories of long-term CAV after HTx associated with overall mortality. We also found that the identified CAV trajectories and their immune and nonimmune predictive variables could be generalizable and transportable across centers in different continents. Our results provide an important new tool for improving the approach to monitoring and risk stratifying heart transplant recipients, potentially paving the way toward a rationalization of the use of coronary angiograms and therapeutic interventions.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

Expanded Methods and Materials
Data Supplement Figures I–IV
Data Supplement Tables I–XI
Appendix

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II.C.3. Synthèse & Perspectives

Nous avons phénotypé la CAV par une approche machine learning non supervisée en utilisant les données de 2 centres européens comme bases d'apprentissage et les données d'un seul centre américain pour la validation. L'étude inclut 1301 patients (815 européens, 486 américains) pour identifier 4 trajectoires distinctes de CAV allant du profil 1 (pas de CAV sans progression) au profil 4 (développement précoce de la CAV avec progression significative). En utilisant une régression multinominale standard, nous avons identifié 6 facteurs de risque pour ces trajectoires de CAV : l'âge du donneur, le sexe du donneur, le tabagisme du donneur, le taux de LDL du receveur >1 g/L, des DSA de classe II et la présence d'un rejet cellulaire modéré ≥2R à 1 an. À la suite de ce travail, nous fournissons un outil de stratification du risque en ligne qui peut informer les cliniciens en pratique quotidienne sur la probabilité d'un profil de risque de CAV. Les points forts de l'étude comprennent la nature clinique, histologique et immunologique robuste et bien caractérisée des ensembles de données. Les patients ont été suivis pendant une durée médiane de 7 ans avec très peu de données manquantes.
Les courbes de survie commencent à diverger à 7 ans, mais il y a peu de différence entre les profils 1 à 3, malgré le développement potentiel d'une CAV assez sévère dans le profil 3 par rapport au profil 1. Par conséquent, même si un patient peut être classé dans le profil 3 à 1 an, les implications pour la surveillance et le traitement restent incertaines. Même pour les patients à qui l'on attribue une catégorie de risque faible lors de la première visite annuelle, un rejet tardif et le développement ultérieur d'anticorps spécifiques du donneur peuvent conduire à une CAV d'apparition rapide, ce qui n'est pas pris en compte dans la trajectoire initiale. Pour fournir une prédiction plus personnalisée, il pourrait être utile de permettre la saisie de données au cours du temps pour permettre de ré-adapter la surveillance à la trajectoire spécifique du patient. Ce défi des données longitudinales pour réactualiser le risque personnalisé de CAV est aussi un défi méthodologique dont une approche statistique par les modèles joints pourrait être une piste de réflexion.

Notre étude s'appuie également sur le classement consensuel de l'International Society of Heart and Lung Transplantation, qui est insensible au développement

d'une CAV précoce. Par définition, la CAV1 est une sténose de <50% dans l'artère coronaire principale gauche ou de 70% dans un vaisseau primaire. Même à ce stade, il peut déjà y avoir une implication vasculaire diffuse qui peut par la suite limiter l'efficacité potentielle des interventions thérapeutiques. À l'avenir, les modèles de prédiction pourraient être renforcés en intégrant une évaluation initiale et à un an par échographie intravasculaire pour tenir compte de la maladie athéromateuse « transmise » du donneur et de l'impact connu des changements précoces de l'épaisseur de l'intima, qui peuvent être graves même en présence d'une angiographie d'apparence normale.[41] En outre, le modèle actuel classe le receveur en fonction du profil ayant la probabilité la plus élevée, mais il convient de prendre en compte le pourcentage précis d'appartenance au profil de trajectoire. Par exemple, un receveur ayant des antécédents de LDL élevées, de rejet cellulaire modéré à un an et d'absence d'anticorps spécifiques du donneur, qui reçoit un cœur de donneur de sexe masculin âgé de 40 ans, a une probabilité de 28,5 % pour le profil 1, de 34 % pour le profil 2, de 15 % pour le profil 3 et de 22 % pour le profil 4. Bien qu'il soit considéré comme ayant le profil 2, il existe une probabilité de 66 % que le receveur ne soit pas de ce phénotype. Par conséquent, le modèle n'apporte pas une réponse dichotomique, mais bien des pourcentages d'appartenance personnalisés à chaque trajectoire, car il parait parfois impossible de définir de façon certaine lequel des 4 profils de progression de la CAV est définitivement celui du patient. Il parait important de concevoir que certains patients présentent des formes « frontières » d'évolution mettant à l'épreuve les outils de stratification du risque.

Dans ce contexte où la CAV, un épaississement intimal diffus entraînant un rétrécissement progressif des artères coronaires, a une prévalence de 50 % dix ans après la transplantation, c'est la troisième cause de mortalité tardive et la principale cause de dysfonctionnement tardif des allogreffes.[9,97,98] Le gold-standard actuel pour la surveillance de la CAV après une HTx repose sur les coronarographies protocolaires, qui guident la gestion clinique des patients, y compris les stratégies de prévention, les changements thérapeutiques, et également le critère d'évaluation potentiel pour les essais cliniques.[99,100] La CAV est une maladie fibroproliférative chronique ; sa pathophysiologie est liée à l'interaction complexe de l'immunologie et des facteurs de risque traditionnels de la coronaropathie, ce qui entraîne des

modifications vasculaires panartérielles.[101] Contrairement à de nombreuses comorbidités post-transplantation, les patients peuvent rester asymptomatiques malgré la progression sévère de la CAV. Compte tenu de la nature diffuse et concentrique des modifications vasculaires, la coronarographie conventionnelle est d'un intérêt limité pour le diagnostic précoce de la CAV, car elle sous-estime souvent le degré d'atteinte de la maladie. Des tests complémentaires à l'angiographie, tels que l'échographie intra-coronaire ou la tomographie en cohérence optique (OCT), ont amélioré la détection précoce, mais ces options de test ne sont pas universellement disponibles et ne sont pas applicables de la même manière aux enfants et aux adultes.[102,103] En outre, les évaluations angiographiques sont souvent limitées par la présence d'une insuffisance rénale post-transplantation. Enfin, alors que les statines améliorent la mortalité post-transplantation et que les inhibiteurs du signal de prolifération peuvent ralentir la progression de la CAV, les programmes peuvent développer un nihilisme diagnostique pour les évaluations invasives continues pour les patients qui sont soit intolérants, soit déjà sous ces thérapies en raison du manque d'alternatives. Lorsque nous prenons des décisions concernant la CAV, nous nous préoccupons souvent trop de la dernière angiographie, « en nous concentrant sur l'endroit où le palet a été », au lieu de pouvoir intégrer une évaluation plus complète centrée sur le patient pour comprendre le risque individuel de CAV et « mieux concentrer nos efforts sur l'endroit où le palet va se trouver ». Cette métaphore avec le Hockey a été formulée dans l'éditorial associé à notre publication.[104]

Notre approche non supervisée et méthodologique s'inscrit dans une dimension plus large qu'est le machine learning. Ces approches sont apparues comme un moyen potentiel d'évaluer de grands ensembles de données complexes en appliquant des algorithmes analytiques qui apprennent de manière itérative les données pour révéler de nouveaux modèles qui peuvent améliorer les méthodes statistiques traditionnelles de détermination du risque.[105,106] Bien que les programmes de transplantation reposent sur des protocoles qui sont appliqués à l'ensemble d'une cohorte de patients, l'utilisation de machine learning peut permettre aux médecins de mieux comprendre le risque et de passer à des stratégies diagnostiques et thérapeutiques plus individualisées. Dans l'approche machine learning classique, les

ensembles de données sont divisés en une cohorte d'apprentissage et une cohorte de test pour construire et ensuite évaluer la performance d'un modèle. Une approche machine learning non supervisée évalue les modèles sans étiquettes prédéfinies pour « mettre de l'ordre » dans l'ensemble des données. Cependant, la qualité d'un modèle prédictif dépend de celle des données d'entrée. Les analyses précédentes utilisant le machine learning dans les registres du United Network of Organ Sharing pour les transplantations cardiaques n'ont pas dépassé les performances des modèles linéaires.[19] Bien que ces bases de données soient avantagées par le grand nombre de patients, elles manquent souvent de détails et de mesures répétées que l'on trouve dans les bases de données institutionnelles relativement plus petites. Nous sommes une fois de plus face à l'enjeu majeur des nouvelles approches algorythmiques en santé : la qualité des bases de données. Les approches innovantes doivent être au service d'une vision, d'une hypothèse prédéfinie, et fondées sur des bases de données comprenant de l'hétérogénéité, du volume, de la véracité, de la granularité, jusqu'à des marqueurs nouveaux, par exemple immunologiques.

Bien que ces trajectoires de la maladie aient des limites, l'étude apporte un éclairage unique sur la CAV en fournissant la première description de modèles potentiellement distincts de progression de la maladie. A l'avenir, nous espérons que de telles collaborations continueront à fournir la base de l'application des techniques algorythmiques innovantes pour mieux comprendre les processus pathologiques complexes tels que la CAV.

Conclusion

Dans un contexte où la prédiction post-transplantation est imparfaite, le développement de modèles prédictifs spécifiques pour chaque type d'assistance circulatoire a eu un impact limité sur la performance statistique des modèles prédictifs.

L'allosensibilisation et le rejet médié par les anticorps sont des facteurs de risque majeurs pour le développement de pathologies spécifiques du greffon, qui constituent la principale cause de mortalité tardive après transplantation cardiaque.

Les transplantés cardiaques, en particulier les plus jeunes, présentaient un risque très élevé de mort subite par rapport à la population générale. La prise en compte de facteurs de risque spécifiques peut aider à identifier les sous-groupes à haut risque.

Nous avons identifié 4 trajectoires de coronaropathie du greffon et leurs variables prédictives indépendantes respectives. Nos résultats fournissent la base d'une évaluation basée sur les trajectoires des patients ayant bénéficié d’une transplantation cardiaque pour la stratification précoce du risque et le suivi des patients.

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